ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2016 February 4; 5(1): 1-110

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

Contents Quarterly Volume 5 Number 1 February 4, 2016

EDITORIAL

FRONTIER

REVIEW

MINIREVIEWS

World Journal of Critical Care Medicine
Volume 5 Number 1 February 4, 2016

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
February 4, 2016

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1949-8462/g_info_20100316161927.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.1

World J Crit Care Med 2016 February 4; 5(1): 1-6
ISSN 2220-3141 (online)

EDITORIAL

New pharmacological approaches against chronic bowel and bladder problems in paralytics

Pierre A Guertin

Pierre A Guertin, Department of Psychiatry and Neurosciences, Laval University, Pavillon Vandry, Québec, QC G1V 0A6, Canada

Pierre A Guertin, Laval University Medical Center (CHU de Québec - CHUL), Québec, QC G1V 4G2, Canada

Author contributions: Guertin PA solely contributed to all aspects of this editorial paper.

Conflict-of-interest statement: The author is also president and chief executive officer of Nordic Life Science Pipeline.

Correspondence to: Pierre A Guertin, PhD, Professor, Laval University Medical Center (CHU de Québec - CHUL), 2705 Laurier Boulevard, RC-9800 (Neuroscience), Québec, QC G1V 4G2, Canada. pierre.guertin@crchul.ulaval.ca
Telephone: +1-418-5254444-48831
Fax: +1-418-6542753

Received: May 13, 2015
Peer-review started: May 20, 2015
First decision: July 6, 2015
Revised: September 15, 2015
Accepted: November 10, 2015
Article in press: November 11, 2015
Published online: February 4, 2016

Abstract

Spinal cord injury (SCI) leads generally to an irreversible loss of sensory functions and voluntary motor control below injury level. Cures that could repair SCI and/or restore voluntary walking have not been yet developed nor commercialized. Beyond the well-known loss of walking capabilities, most SCI patients experience also a plethora of motor problems and health concerns including specific bladder and bowel dysfunctions. Indeed, chronic constipation and urinary retention, two significant life-threatening complications, are typically found in patients suffering of traumatic (*e.g.*, falls or car accidents) or non-traumatic SCI (*e.g.*, multiple sclerosis, spinal tumors). Secondary health concerns associated with these dysfunctions include hemorrhoids, abdominal distention, altered visceral sensitivity, hydronephrosis, kidney failure, urinary tract infections, sepsis and, in some cases, cardiac arrest. Consequently, individuals with chronic SCI are forced to regularly seek emergency and critical care treatments when some of these conditions occur or become intolerable. Increasing evidence supports the existence of a novel experimental approach that may be capable of preventing the occurrence or severity of bladder and bowel problems. Indeed, recent findings in animal models of SCI have revealed that, despite paraplegia or tetraplegia, it remains possible to elicit episodes of micturition and defecation by acting pharmacologically or electrically upon specialized lumbosacral neuronal networks, namely the spinal or sacral micturition center (SMC) and lumbosacral defecation center (LDC). Daily activation of SMC and LDC neurons could potentially become, new classes of minimally invasive treatments (*i.e.*, if orally active) against these dysfunctions and their many life-threatening complications.

Key words: Prevention of intensive care problems; Quality of care; Temporary recovery of vital functions; Micturition; Defecation; Spinal networks; Central pattern generators

Core tip: This editorial is one of the first to describe

clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for those suffering chronically of constipation and urinary retention or detrusor-sphincter dyssynergia. Products combining several already known and safe active ingredients for new or synergistic effects acting upon specific central networks of neurons that normally control these functions are of particular interest.

Guertin PA. New pharmacological approaches against chronic bowel and bladder problems in paralytics. *World J Crit Care Med* 2016; 5(1): 1-6 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/1.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.1

INTRODUCTION

Spinal cord injury (SCI) either traumatically (*e.g.*, falls, car or sport accidents) or non-traumatically induced (*e.g.*, multiple sclerosis, angioma, *etc.*) generally leads to an irreversible loss of sensory functions and voluntary motor control below injury level. In the United States and Canada, 1.3 million people (approximately 20-25 million worldwide) currently live with a traumatic SCI[1,2] which is a 5-fold increase (*i.e.*, attributed to improvements in acute emergency care) compared with prevalence values assessed previously. As such, SCI has thus progressively become the 2nd most important neurological problem in North America after Alzheimer's disease (*i.e.*, approximately 5 million patients)[2,3]. No therapy can repair SCI *per se*, cure paralysis or even significantly prevent related chronic complications, dysfunctions, multiple debilitating diseases and life-threatening problems (*i.e.*, cardiovascular problems, osteoporosis, muscular atrophy, anemia, spasticity, urinary tract infections, bed sores, pneumonia, sepsis, bladder and bowel problems, *etc.*)[4]. Only symptomatic drugs and biologics are currently used to minimize consequences (*e.g.*, aspirin for pain, antibiotics for infections, *etc.*)[5].

Urination, also called micturition or voiding, is the process of disposing urine from the urinary bladder through the urethra to the outside of the body. When urinary retention (UR) occurs, the bladder remains full which may cause complete anuria that is a medical emergency as the bladder distend (stretch) to enormous sizes. If the bladder distends enough it may become painful and tear. The increase in bladder pressure can also prevent urine entering from the ureters or even cause urine to back up and get into the kidneys, causing hydronephrosis, pyonephrosis, and kidney failure. It has been associated also with urinary tract infections, sepsis and cardiac arrest[6,7]. In chronic cases, UR may cause bladder stones, atrophy of the detrusor muscle, diverticula in the bladder wall and related infections. In cervical injured patients, bladder problems also impact autonomic responses that are affected by SCI, *e.g.*, a full bladder leads to autonomic dysreflexia, hypertension, severe headaches, stroke or cardiovascular failure.

Bowel problems such as diarrhea, fecal incontinence, irritable bowel syndrome (IBS) or constipation typically occur when the gastrointestinal (GI) tract does not work properly. More specifically, constipation is characterized clinically as difficult or infrequent (*i.e.*, < 3 times/wk) passage of stools[8]. In the general population, constipation is often caused by diet problems (*e.g.*, low fiber), lack of exercise, dairy products, stress, pregnancy, medicines such as laxatives, antacids, antidepressants, iron, pain killers or by structural abnormalities (*e.g.*, colon polyps, cancer, diverticula, anal problems, *etc.*)[9,10]. Related-secondary complications include fissures, fecal impaction, ulceration, abdominal distension, hemorrhoids, bleeding, pain and, occasionally, septic shock and death[11]. Chronic constipation is experienced overall by 60 M North Americans[10].

PATHOPHYSIOLOGY OF BLADDER AND BOWEL DYSFUNCTIONS IN PATIENTS WITH SCI

Normally, the process of urination (also called micturition) involves coordination between the central, autonomic and somatic nervous systems that is under voluntary control (brain). Specifically, muscles involved in micturition (*i.e.*, those activating bladder, urethra and pelvic floor) are essentially controlled by coordinated inputs from spinal or sacral micturition center (SMC) neurons[12]. Brain structures (*e.g.*, pontine micturition center) provide additional inputs mediated by SMC for facilitation or inhibition[13-15]. In brief, as the bladder fills, sensory receptors in the bladder wall trigger the micturition motor behaviour - a coordinated contraction of the detrusor and relaxation of the urethral and periurethral muscles[13]. When control over urination is abnormal, urinary incontinence generally occurs. However, for incompletely understood reasons, in patients with SCI and other related pathologies, the opposite problem occurs - that is UR and detrusor-sphincter dyssynergia that lead to improper capacity to empty bladder content is expressed in absence of descending brain inputs.

The gastrointestinal system is a 20 foot-long system comprising the stomach and intestine (bowel) that essentially releases hormones (*e.g.*, gastrin, secretin, melatonin, ghrelin, *etc.*) for local regulation of digestion, absorption and elimination[16]. However, to achieve that, it critically depends also on food transit (> 24 h/meal) that is ensured by rhythmic muscle contractions, *i.e.*, peristalsis, defined as cyclic rostrocaudal series of coordinated contractions and relaxations of GI smooth muscles mediated locally by two main sensorimotor reflexes using acetylcholine, noradrenaline, substance P, adenosine triphosphate, *etc.*[17-19]. In clear contrast with

causes and mechanisms underlying constipation in the general population, bowel problems after SCI (typically chronic constipation, *i.e.*, more than 12 wk/year) is specifically attributed to a dysfunctional control by the CNS of peristalsis and colorectal motility[20-24]. Defecation requires interactions between the somatic, autonomic and central nervous systems. Specifically, supraspinal networks (*e.g.*, pontine defecation center) that send inputs to lumbosacral defecation center (LDC) neurons and corresponding motoneurons (Onuf's nucleus) for control of autonomic and somatic systems (smooth muscles, sphincters) involved in colorectal motility and defecation[16,23,25,26]. Consequently, a failure of supraspinal inputs to modulate LDC neurons (*e.g.*, due SCI) may lead to reduced colorectal motility and increased constipatory problems[16,23,25].

CURRENTLY USED APPROACHES ARE UNACCEPTABLE OR UNSAFE

As of now, there are five (5) main approaches or tools used to control bladder problems after SCI[27-30]: (1) bladder drainage with chronic indwelling catheters or intermittent catheters but frequent hospitalizations, urinary tract infections, bladder and kidney damage and sepsis can be induced when chronically used; (2) drugs (sedatives, anticholinergic, alpha-adrenergic, cholinergic) with peripheral actions on the contraction of bladder muscles or relaxation of sphincters but constipation, dry mouth, blurred vision can also be induced; (3) electrostimulation of sacral anterior roots but it also impairs sexual function and is generally not considered as user-friendly; (4) diapers or condom sheaths can also be used although generally poorly accepted by patient mainly for self-esteem reasons; or (5) *Botox* injection (in bladder, *e.g.*, detrusor muscle) is sometime recommended but only for those specifically experiencing related mild incontinence rather than UR. In other words, UR remains considered as a poorly addressed medical need.

Regarding chronic constipation, SCI patients are currently bound to use nonspecific approaches to reduce the severity of this debilitating problem: (1) stool softeners and laxatives (*e.g.*, Fleet, Senokot, Metamucil, Dulcolax, Colace, Diocto, Exlax); (2) digital rectal stimulation or sacral root stimulation of reflexes; (3) digital evacuation by professionals; or (4) surgery (*e.g.*, ileostomy)[17,31-35]. Although some of the above-mentioned approaches may be suitable for occasional constipation, they are generally not recommended for repeated use. Indeed, when chronically used, they are associated with significantly reduced efficacy and increased side effects such as bloating, cramps, nausea, fever, vomiting, breathing trouble, fainting, flatulence, dependency, diarrhea, electrolyte imbalance, rectal bleeding, pain, nerve lesion, intestinal paralysis, IBS, renal failure, hernia, seizure, arrhythmia, and sepsis[35-39]. Therefore, chronic constipation after SCI or related disorders is still considered as a poorly addressed medical need that would benefit from novel, innovative and potent medicines[39].

EVIDENCE OF A NOVEL NON-INVASIVE AND SAFER APPROACH

Given the problematic described above, it is imperative that scientists attempt rapidly to identify user-friendly, safe and well-tolerated treatments that could specifically and selectively prevent and reduce SCI-related chronic constipation, UR/detrusor sphincter dyssynergia and related health concerns. In fact, some researchers have recently begun to obtain promising results towards that goal. Indeed, a few laboratories in France, Japan, United States, China and Canada have been exploring the feasibility and potential of modulating either SMC neurons or LDC neurons for acute induction of on-demand episodes of micturition or defecation after SCI.

In a rat model of paraplegia (spinal transection at thoracic level T10), Chinese and Americans found that serotonergic agonists of the 5-HT7 subclass, administered intravenously (*iv*) can augment voiding reflex efficacy suggesting SMC-facilitating actions (also called external urethral sphincter central pattern generator by some researchers) given the well-known expression of 5-HT7 receptors in that sacral area of the spinal cord[40]. This mechanism of action is also supported by similar effects obtained following intrathecal administration of 5-HT agonists[41]. Other receptors may be involved since activation (*iv* administration) of the 5-HT1A receptors in these conditions also induced similar effects[42].

A few years prior to those pharmacological studies, a promising role for specific sacral networks in micturition had been clearly shown by Americans who after stimulation at or immediately dorsal to the dorsal gray commissure at S(1) level observed strong (at least 20 mmHg) bladder contractions as well as strong (at least 40 mmHg) external urethral sphincter relaxation, resulting in bladder voiding in cats either intact or spinal cord-injured at the thoracic level[43].

In parallel, my own laboratory in Canada has undertaken extensive drug screening studies aimed at identifying brain permeable drugs that could powerfully elicit, within minutes, some episodes of voiding in chronic paraplegic mice. A few families of ligands including 5-HT1A, 5-HT2 and 5-HT1A/7 agonists were found to elicit within 30 min some significant micturition effects. However, among all tests performed, it was a drug combination composed of buspirone (5-HT1A agonist) and 8-OH-DPAT (5-HT1A/7 agonist) that ended up producing the best micturition-inducing effects upon subcutaneous (*sc*) administration[44]. Comparable effects were found also upon oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever SMC-activating drug treatment against bladder dysfunction and related-secondary complications in patients with SCI and

comparable neurological disorders[45].

A comparable approach has been explored in recent years to determine the role of electrical stimulation or pharmacological ligands in LDC-mediated potent reflex defecation[46]. Japanese found that ghrelin receptor agonists such as capromorelin or CP464709 administered *sc* or *iv* (lumbosacral level) can increase fecal pellet production in SCI rats[47,48]. Indirectly, electrical stimulation of the pudendal nerve or of sacral roots can also trigger reflex defecation presumably by afferent-induced activation of LDC neurons given that comparable effects were found with intraspinal stimulation at S2 level[49-51].

As performed for micturition-inducing effects, we also conducted drug screening studies aimed at identify brain permeable drugs capable, within minutes, of inducing episodes of defecation in chronic paraplegic mice. Although, a few families of ligands were found to elicit some defecatory effects, it is a drug combination composed of buspirone (5-HT1A agonist) and neostigmine at low doses (cholinesterase inhibitor) that displayed the best defecation-inducing effects upon *sc* administration[52]. Again, comparable effects were found following oral gavage suggesting that an orally active tablet comprising both active ingredients could become the first ever LDC-activating drug treatment against chronic constipation and related-secondary complications in patients with SCI and comparable neurological disorders[53].

Since both technologies identified in our laboratory are already being developed, under contractual agreement, by a pharmaceutical company called Nordic Life Science Pipeline, it may be reasonably to expect that at least one of these therapies may be granted approval for commercialization in Canada, United States and Europe by 2022[54].

CONCLUSION

SCI is an increasing problem worldwide. It has recently become the second most important neurological problem after Alzheimer's disease. Beyond paralysis and loss of locomotion, several dysfunctions and life-threatening secondary complications associated with bladder and bower problems are often experienced by patients with SCI. Unfortunately, no safe or acceptable treatments have been found to control the occurrence or severity of these significant health concerns which, in turn, forces patients to seek emergency and critical care treatment on a regular basis. Pharmacological or electrical modulation of spinal command centers involved in controlling micturition and defecation behaviors may eventually constitute rather selective, specific and hence safe treatments against chronic constipation and UR after SCI.

REFERENCES

1 **Christopher and Dana Reeve Foundation**. One Degree of Separation: Paralysis and Spinal Cord Injury in the United States. Available from: URL: http://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.5091685/k.58BD/One_Degree_of_Separation.htm

2 **Rouleau P**, Ayoub E, Guertin PA. Traumatic and non-traumatic spinal cord-injured patients in Quebec, Canada: Part 1 – Epidemiological, clinical and functional characteristics. *Open Epidemiol J* 2011; **4**: 131-137 [DOI: 10.2174/1874297101104010133]

3 **Alzheimer's Association**. 2014 Alzheimer's disease facts and figures. *Alzheimers Dement* 2014; **10**: e47-e92 [PMID: 24818261]

4 **Rouleau P**, Guertin PA. Traumatic and non-traumatic spinal cord-injured patients in Quebec, Canada. Part 2: biochemical profile. *Spinal Cord* 2010; **48**: 819-824 [PMID: 20458326 DOI: 10.1038/sc.2010.42]

5 **Rouleau P**, Guertin PA. Traumatic and nontraumatic spinal-cord-injured patients in Quebec, Canada. Part 3: pharmacological characteristics. *Spinal Cord* 2011; **49**: 186-195 [PMID: 20548322 DOI: 10.1038/sc.2010.70]

6 **Hellström A**, Hanson E, Hansson S, Hjälmås K, Jodal U. Association between urinary symptoms at 7 years old and previous urinary tract infection. *Arch Dis Child* 1991; **66**: 232-234 [PMID: 2001110 DOI: 10.1136/adc.66.2.232]

7 **Hull RA**, Rudy DC, Wieser IE, Donovan WH. Virulence factors of Escherichia coli isolates from patients with symptomatic and asymptomatic bacteriuria and neuropathic bladders due to spinal cord and brain injuries. *J Clin Microbiol* 1998; **36**: 115-117 [PMID: 9431932 DOI: 10.1016/s0022-5347(01)62670-3]

8 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

9 **Staats PS**, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: a comparative study. *South Med J* 2004; **97**: 129-134 [PMID: 14982259 DOI: 10.1097/01.SMJ.0000109215.54052.D8]

10 **Higgins PD**, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* 2004; **99**: 750-759 [PMID: 15089911]

11 **Blok BF**, De Weerd H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. *J Comp Neurol* 1995; **359**: 300-309 [PMID: 7499530 DOI: 10.1002/cne.903590208]

12 **Belsey J**, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. *Aliment Pharmacol Ther* 2010; **31**: 938-949 [PMID: 20180788 DOI: 10.1111/j.1365-2036.2010.04273.x]

13 **Beckel JM**, Holstege G. Neurophysiology of the lower urinary tract. *Handb Exp Pharmacol* 2011; **(202)**: 149-169 [PMID: 21290226]

14 **Yoshimura N**, Chancellor MB, Andersson KE, Christ GJ. Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy. *BJU Int* 2005; **95**: 733-738 [PMID: 15794773 DOI: 10.1111/j.1464-410X.2005.05392.x]

15 **Miller H**, Simpson CA, Yeates WK. Bladder dysfunction in multiple sclerosis. *Br Med J* 1965; **1**: 1265-1269 [PMID: 14278814 DOI: 10.1136/bmj.1.5445.1265]

16 **Palit S**, Lunniss PJ, Scott SM. The physiology of human defecation. *Dig Dis Sci* 2012; **57**: 1445-1464 [PMID: 22367113 DOI: 10.1007/s10620-012-2071-1]

17 **Izzo AA**, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther* 2010; **126**: 21-38 [PMID: 20117132 DOI: 10.1016/j.pharmthera.2009.12.005]

18 **Grider JR**, Foxx-Orenstein AE. Mediators and regulation of peristalsis. *Curr Opin Gastroenterol* 1999; **15**: 22-25 [PMID: 17023913 DOI: 10.1097/00001574-199901000-00005]

19 **de Groat WC**, Krier J. An electrophysiological study of the sacral parasympathetic pathway to the colon of the cat. *J Physiol*

1976; **260**: 425-445 [PMID: 185366 DOI: 10.1113/jphysiol.1976.sp011523]
20 **Lynch AC**, Frizelle FA. Colorectal motility and defecation after spinal cord injury in humans. *Prog Brain Res* 2006; **152**: 335-343 [PMID: 16198711 DOI: 10.1016/S0079-6123(05)52022-3]
21 **Schaller BJ**, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. *Am J Gastroenterol* 2006; **101**: 1655-1665 [PMID: 16863574 DOI: 10.1111/j.1572-0241.2006.00540.x]
22 **Gillis RA**, Dias Souza J, Hicks KA, Mangel AW, Pagani FD, Hamilton BL, Garvey TQ, Pace DG, Browne RK, Norman WP. Inhibitory control of proximal colonic motility by the sympathetic nervous system. *Am J Physiol* 1987; **253**: G531-G539 [PMID: 2889367]
23 **Nagano M**, Ishimizu Y, Saitoh S, Okada H, Fukuda H. The defecation reflex in rats: fundamental properties and the reflex center. *Auton Neurosci* 2004; **111**: 48-56 [PMID: 15109938 DOI: 10.1016/j.autneu.2004.02.002]
24 **Brading AF**, Ramalingam T. Mechanisms controlling normal defecation and the potential effects of spinal cord injury. *Prog Brain Res* 2006; **152**: 345-358 [PMID: 16198712 DOI: 10.1016/S0079-6123(05)52023-5]
25 **Drake MJ**, Fowler CJ, Griffiths D, Mayer E, Paton JF, Birder L. Neural control of the lower urinary and gastrointestinal tracts: supraspinal CNS mechanisms. *Neurourol Urodyn* 2010; **29**: 119-127 [PMID: 20025025 DOI: 10.1002/nau.20841]
26 **De Groat WC**, Krier J. The sacral parasympathetic reflex pathway regulating colonic motility and defaecation in the cat. *J Physiol* 1978; **276**: 481-500 [PMID: 650474 DOI: 10.1113/jphysiol.1978.sp012248]
27 **Fowler CJ**. Neurological disorders of micturition and their treatment. *Brain* 1999; **122** (Pt 7): 1213-1231 [PMID: 10388789 DOI: 10.1093/brain/122.7.1213]
28 **Andersson KE**, Chapple C, Wein A. The basis for drug treatment of the overactive bladder. *World J Urol* 2001; **19**: 294-298 [PMID: 11760776 DOI: 10.1007/PL00007101]
29 **Andersson KE**. Treatment-resistant detrusor overactivity--underlying pharmacology and potential mechanisms. *Int J Clin Pract Suppl* 2006; **151**: 8-16 [PMID: 17169005 DOI: 10.1111/j.1742-1241.2006.01184.x]
30 **Buckley BS**, Lapitan MC. Drugs for treatment of urinary retention after surgery in adults. *Cochrane Database Syst Rev* 2010; **6**: CD008023 [PMID: 20927768 DOI: 10.1002/14651858.cd008023.pub2]
31 **Coggrave M**, Norton C, Wilson-Barnett J. Management of neurogenic bowel dysfunction in the community after spinal cord injury: a postal survey in the United Kingdom. *Spinal Cord* 2009; **47**: 323-330; quiz 331-333 [PMID: 19015665 DOI: 10.1038/sc.2008.137]
32 **Furlan JC**, Urbach DR, Fehlings MG. Optimal treatment for severe neurogenic bowel dysfunction after chronic spinal cord injury: a decision analysis. *Br J Surg* 2007; **94**: 1139-1150 [PMID: 17535012 DOI: 10.1002/bjs.5781]
33 Gastrointestinal Disorders Therapeutics Market to 2018 - Novel Agents Targeting Irritable Bowel Syndrome (IBS), Chronic Constipation (CC) and Ulcerative Colitis (UC) to Reinvigorate the Market. Published by GBI Research, 2012: 171. Available from: URL: http://www.gbiresearch.com/report-store/market-reports/archive/gastrointestinal-disorders-therapeutics-market-to-2018-novel-agents-targeting-irritable-bowel-syndrome-(ibs)-chronic-constipa
34 **Creasey GH**, Craggs MD. Functional electrical stimulation for bladder, bowel, and sexual function. *Handb Clin Neurol* 2012; **109**: 247-257 [PMID: 23098717 DOI: 10.1016/B978-0-444-52137-8.00015-2]
35 **Rasmussen MM**, Clemmensen D, Rawashdeh YF, Tankisi H, Christensen P, Krogh K. [Surgical reinnervation with nerve anastomosis technique for neurogenic bladder and bowel dysfunction]. *Ugeskr Laeger* 2011; **173**: 2412-2415 [PMID: 21958483]
36 **Awad RA**. Neurogenic bowel dysfunction in patients with spinal cord injury, myelomeningocele, multiple sclerosis and Parkinson's disease. *World J Gastroenterol* 2011; **17**: 5035-5048 [PMID: 22171138 DOI: 10.3748/wjg.v17.i46.5035]
37 **Stone JM**, Nino-Murcia M, Wolfe VA, Perkash I. Chronic gastrointestinal problems in spinal cord injury patients: a prospective analysis. *Am J Gastroenterol* 1990; **85**: 1114-1119 [PMID: 2389723]
38 **De Looze D**, Van Laere M, De Muynck M, Beke R, Elewaut A. Constipation and other chronic gastrointestinal problems in spinal cord injury patients. *Spinal Cord* 1998; **36**: 63-66 [PMID: 9471141 DOI: 10.1038/sj.sc.3100531]
39 **Prather CM**. Subtypes of constipation: sorting out the confusion. *Rev Gastroenterol Disord* 2004; **4** Suppl 2: S11-S16 [PMID: 15184810]
40 **Gang W**, Hongjian T, Jasheng C, Jiemin S, Zhong C, Yuemin X, Baojun G, Andersson KE. The effect of the 5-HT7 serotonin receptor agonist, LP-44, on micturition in rats with chronic spinal cord injury. *Neurourol Urodynam* 2013; **33**: 1165-1170 [DOI: 10.1002/nau.22463]
41 **Lecci A**, Giuliani S, Santicioli P, Maggi CA. Involvement of 5-hydroxytryptamine1A receptors in the modulation of micturition reflexes in the anesthetized rat. *J Pharmacol Exp Ther* 1992; **262**: 181-189 [PMID: 1352548]
42 **Dolber PC**, Gu B, Zhang X, Fraser MO, Thor KB, Reiter JP. Activation of the external urethral sphincter central pattern generator by a 5-HT(1A) receptor agonist in rats with chronic spinal cord injury. *Am J Physiol Regul Integr Comp Physiol* 2007; **292**: R1699-R1706 [PMID: 17204596 DOI: 10.1152/ajpregu.00142.2006]
43 **Pikov V**, Bullara L, McCreery DB. Intraspinal stimulation for bladder voiding in cats before and after chronic spinal cord injury. *J Neural Eng* 2007; **4**: 356-368 [PMID: 18057503 DOI: 10.1088/1741-2560/4/4/002]
44 **Guertin PA**. Methods and uses for inducing or facilitating micturition in a patient in need thereof. USPTO, No. 61946097, 2014. Available from: URL: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015127558
45 **Guertin PA**. Methods and uses for inducing or facilitating micturition in a patient in need thereof. PCT, No. PCT/CA2015/050146, 2015. Available from: URL: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015127558
46 **Sessenwein JL**, Lomax AE. Ghrelin receptors as targets for novel motility drugs. *Neurogastroenterol Motil* 2015; **27**: 589-593 [PMID: 25903396 DOI: 10.1111/nmo.12562]
47 **Naitou K**, Shiina T, Sugita R, Nakamori H, Shimizu Y. Characterization of ghrelin-sensitive neurons in the lumbosacral defecation center in rats. *Neurogastroenterol Motil* 2015; **27**: 147-155 [PMID: 25557226 DOI: 10.1111/nmo.12492]
48 **Shimizu Y**, Chang EC, Shafton AD, Ferens DM, Sanger GJ, Witherington J, Furness JB. Evidence that stimulation of ghrelin receptors in the spinal cord initiates propulsive activity in the colon of the rat. *J Physiol* 2006; **576**: 329-338 [PMID: 16873401 DOI: 10.1113/jphysiol.2006.116160]
49 **Chancellor MB**, Changfeng T. Methods and systems for achieving a physiological response by pudendal nerve stimulation and blockade. USPTO patent no. US8805510. Available from: URL: https://www.google.ca/patents/US8805510?dq=patent no. US8805510&hl=fr&sa=X&ved=0CBwQ6AEwAGoVChMIpofA1ov3xwIViGWSCh1wrw58
50 **Vallès M**, Rodríguez A, Borau A, Mearin F. Effect of sacral anterior root stimulator on bowel dysfunction in patients with spinal cord injury. *Dis Colon Rectum* 2009; **52**: 986-992 [PMID: 19502867 DOI: 10.1007/DCR.0b013e31819ed459]
51 **Tai C**, Booth AM, de Groat WC, Roppolo JR. Colon and anal sphincter contractions evoked by microstimulation of the sacral spinal cord in cats. *Brain Res* 2001; **889**: 38-48 [PMID: 11166684 DOI: 10.1016/S0006-8993(00)03095-X]
52 **Guertin PA**. Methods and uses for inducing or facilitating defecation in a patient in need thereof. USPTO application no. 61/946, 113, Feb 2014. Available from: URL: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015127556

53 **Guertin PA**. Methods and uses for inducing or facilitating defecation in a patient in need thereof. PCT application no. PCT/CA2015/050143. 2015. Available from: URL: https//patentscope.wipo.int/search/en/detail.jsf?docId=WO2015127556
54 **Nordic**. Available from: URL: http://www.nordiclifesciencepipeline.com/

P- Reviewer: Bener A **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.7

World J Crit Care Med 2016 February 4; 5(1): 7-11
ISSN 2220-3141 (online)

EDITORIAL

Optimizing the value of measuring inferior vena cava diameter in shocked patients

Fikri M Abu-Zidan

Fikri M Abu-Zidan, Department of Surgery, College of Medicine and Health Sciences, UAE University, PO Box 17666, Al-Ain, United Arab Emirates

Author contributions: Abu-Zidan FM had the idea, critically read the literature, supplied the images, wrote the paper, and approved its final version.

Conflict-of-interest statement: None declared by the author.

Correspondence to: Fikri M Abu-Zidan, MD, FACS, FRCS, PhD, Dip Applied Statistics Professor, Acute Care Surgeon, Point-of-care Sonographer, Statistical Consultant, Department of Surgery, College of Medicine and Health Sciences, UAE University, Tawam Roundabout, Tawam Street, PO Box 17666, Al-Ain, United Arab Emirates. fabuzidan@uaeu.ac.ae
Telephone: +971-50-8335390
Fax: +971-3-7672067

Received: July 15, 2015
Peer-review started: July 16, 2015
First decision: September 28, 2015
Revised: October 22, 2015
Accepted: December 8, 2015
Article in press: December 11, 2015
Published online: February 4, 2016

Abstract

Point-of-care ultrasound has been increasingly used in evaluating shocked patients including the measurement of inferior vena cava (IVC) diameter. Operators should standardize their technique in scanning IVC. Relative changes are more important than absolute numbers. We advise using the longitudinal view (B mode) to evaluate the gross collapsibility, and the M mode to measure the IVC diameter. Combining the collapsibility and diameter size will increase the value of IVC measurement. This approach has been very useful in the resuscitation of shocked patients, monitoring their fluid demands, and predicting recurrence of shock. Pitfalls in measuring IVC diameter include increased intra-thoracic pressure by mechanical ventilation or increased right atrial pressure by pulmonary embolism or heart failure. The IVC diameter is not useful in cases of increased intra-abdominal pressure (abdominal compartment syndrome) or direct pressure on the IVC. The IVC diameter should be combined with focused echocardiography and correlated with the clinical picture as a whole to be useful.

Key words: Inferior vena cava diameter; Point-of-care ultrasound; Measurement

Core tip: Bedside measurement of inferior vena cava is useful in evaluating and resuscitating shocked patients. To achieve that, the operator should be well-trained, use standardized techniques, understand ultrasound limitations, and finally correlate the findings with the clinical picture as a whole.

Abu-Zidan FM. Optimizing the value of measuring inferior vena cava diameter in shocked patients. *World J Crit Care Med* 2016; 5(1): 7-11 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/7.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.7

INTRODUCTION

Point-of-care ultrasound has been increasingly used in

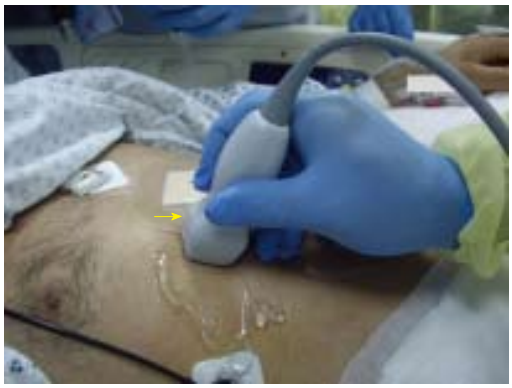


Figure 1 A figure demonstrating the technique to measure the inferior vena cava diameter longitudinally. A small print convex array probe with a frequency of 3-5 MHZ is located in the mid-clavicular line at 90 degrees perpendicular to the skin. The marker is pointing proximally towards the head (arrow).

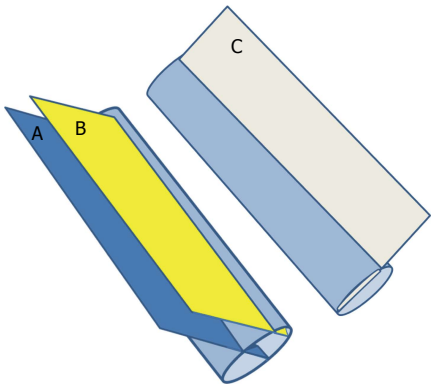


Figure 2 Three dimensional diagram showing the longitudinal ultrasound measurement of the antero-posterior diameter. Measurements depend on the site and angle at which it crosses the IVC. Section A is the proper one as it crosses the IVC vertically at the midpoint. Section B crosses the IVC vertically but peripherally and gives a false low measurement of the IVC diameter. Section C crosses the IVC obliquely and gives a false high measurement of the IVC diameter. IVC: Inferior vena cava.

evaluating shocked patients including the measurement of inferior vena cava diameter (IVC)[1-3]. Nevertheless, there have been conflicting results regarding its value[4-6]. It is important to highlight the technical and clinical difficulties that may be encountered in measuring the IVC diameter as these limit its use. There are four components that affect the outcome of ultrasound studies. These are the effectiveness and technical limitations of the ultrasound machine, the experience of the operator, the body built of the patient, and the pathology studied.

TECHNICAL CONSIDERATIONS

Operators should standardize their technique in scanning the IVC. IVC can be measured through different approaches including the subxiphoid or subcostal approach[7,8]. We prefer to measure the IVC directly through a transhepatic approach using a portable machine and a small print convex array probe with a frequency of 3-5 MHZ

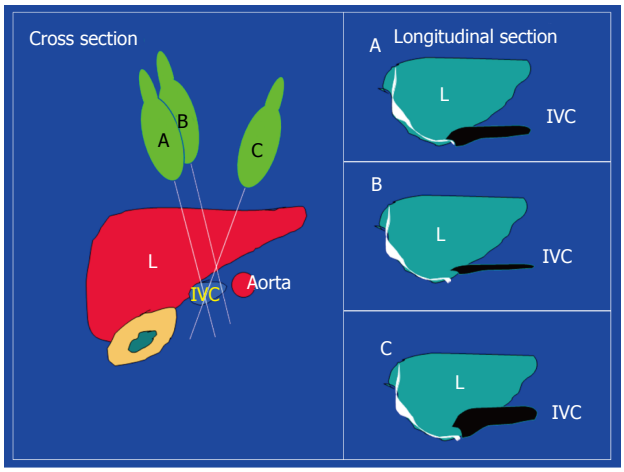


Figure 3 Cross section of the abdomen on the left side of the figure showing the liver, inferior vena cava, and aorta. The B mode longitudinal ultrasound image will depend on the angle between the plane of the ultrasound section and the IVC. Three different planes are shown on the cross section (A-B-C) and the corresponding longitudinal IVC images are shown to the right. Longitudinal section A is the proper one as it crosses the IVC vertically at the midpoint. Section B crosses the IVC vertically but peripherally and gives a false low measurement of the IVC diameter. Section C crosses the IVC obliquely and gives a false high IVC diameter measurement. IVC: Inferior vena cava.

while the patient is in supine position. The probe is located in the mid-clavicular line between the ribs of the right lower chest wall at 90 degrees perpendicular to the skin. The marker points proximally towards the head (Figure 1). The probe may be slightly directed towards the right to be parallel to the IVC. The probe is then shifted slowly transversely to get the best longitudinal perpendicular view. We think that this is better than the subxiphoid approach[7] as the IVC is located slightly to right and the diameter of the IVC may be overestimated by getting an oblique section (Figure 2).

The ultrasound cross section should be vertical to the IVC. Common pitfalls in measurement include measuring the IVC obliquely or peripherally (Figures 2 and 3). In general, it is advised to use the B mode to evaluate the gross collapsibility of the IVC and the M mode to accurately measure the changes in IVC diameter. The IVC can be measured in both longitudinal and transverse sections.

Pitfalls in measuring IVC include increased intra-thoracic pressure resulting from mechanical ventilation or increased right atrial pressure resulting from heart failure or pulmonary embolism. These conditions will increase the diameter of the abdominal IVC[3]. We have recently reported that IVC diameter was not useful in guiding resuscitation, and was even misleading in abdominal compartment syndrome[9]. The increased pressure in abdominal compartment syndrome will compress the IVC and reduce its antero-posterior diameter. The unexperienced clinician may increase the fluid resuscitation which would further decrease the diameter. Furthermore, direct pressure on the IVC as in late pregnancy and acute gastric dilatation[10] can affect the measurement. The IVC diameter should be combined with focused

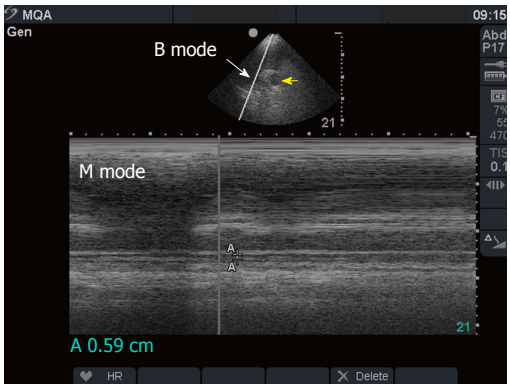


Figure 4 Inferior vena cava measurements in a 39-year-old man who was in septic shock and complete renal failure. The upper image is a transverse cross sectional B mode showing the aorta (yellow arrow) and the IVC (white arrow). The lower image is an M mode showing the IVC measurement (A-A) which is 59 mm indicating that the patient was hypovolemic. IVC: Inferior vena cava.

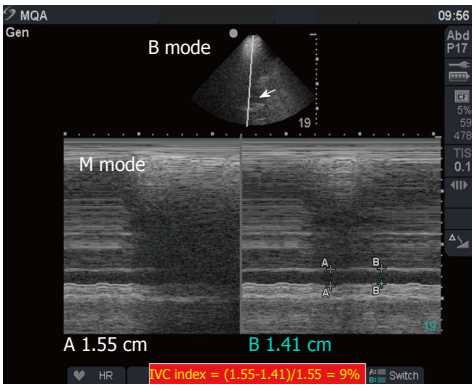


Figure 5 Two point five liters of crystalloids were given to the previous patient over 35 min and repeated measurements of the inferior vena cava diameter were performed. The upper image is a transverse cross sectional B mode showing the IVC (white arrow). The lower image is an M mode showing that the IVC increased to a maximum 1.55 cm with an IVC index of 9% [(1.55-1.41)/1.55]. A-A in the M mode represents the maximum IVC diameter while B-B represents the minimum IVC diameter. IVC: Inferior vena cava.

echocardiography and correlated with the clinical picture as a whole to be useful.

VALUE OF MEASURING IVC DIAMETER IN SHOCKED PATIENTS

IVC measurement can be used as part of defined protocols in diagnosing shocked patients to optimize its value. These protocols evaluate the heart, IVC, chest, and the abdomen to try defining the cause of the shock. Our group follows the RUSH protocol which examines the pump (heart), tubes (great vessels) and reservoir (free intra-peritoneal or intra-thoracic fluid)[2]. Vegas *et al*[7] use the same principles but in a different approach, whereby they classify the shocked patients into those with (1) reduced mean systemic venous pressure; (2) increased right atrial pressure; and (3) increased resistance to the venous return. They study the size of IVC, respiratory variation of the IVC, and the hepatic venous flow to define the type of shock[7].

In a study of 47 patients having septic shock, Coen *et al*[11] used the variability of IVC diameter to decide the volume of fluid resuscitation. They gave boluses of 500 mL of crystalloids as needed to reach an IVC index of 30%-50% which was defined as [(maximum IVC diameter - minimum IVC diameter)/maximum IVC diameter] × 100. IVC measurement was feasible in 92% of the cases and central venous catheter was avoided in more than one third of the patients. The IVC index was significantly higher in shocked patients compared with non shocked patients[12].

The IVC diameter was negatively correlated with the lactate level and positively correlated with the base excess level during hemorrhagic shock resuscitation indicating its good clinical value[8]. Furthermore, Yanagawa *et al*[13] prospectively studied 30 trauma patients and found that the relative change of IVC diameter is effective in differentiating stable resuscitation responders from transient responders who develop recurrent shock. These findings were supported by Feissel *et al*[14] who found the same results in ventilated septic patients. Furthermore, Schefold *et al*[15] found that IVC diameter was highly correlated with the central venous pressure and extravascular lung water index in septic ventilated intensive care unit (ICU) patients. This may be helpful in avoiding unnecessary volume expansion in these sick patients. In contrast, Corl *et al*[5] found that measuring the IVC index was not a good marker for proper fluid responsiveness in the emergency department and questioned its value.

Weekes *et al*[4] prospectively evaluated the gross appearance of IVC and correlated it with the actual measured size in 24 hypotensive patients. They developed a three point scale of visual appearance of IVC as follows: (1) decreased IVC index of $\leqslant$ 0.3; (2) normal range (0.31-0.69); and (3) increased index $\geqslant$ 0.7. Serial gross evaluation of IVC agreed with the actual measured IVC during fluid resuscitation. This study supports the opinion that relative changes are more important than absolute numbers. Gross collapsibility is a more useful marker for hypovolemia than IVC collapsibility index[3]. We advise using the longitudinal view (B mode) to evaluate the gross collapsibility, and the M mode to measure the diameter of IVC. Combining the collapsibility and diameter will increase the value of IVC measurement. This approach has been very useful in our hands (Figures 4-6).

EVIDENCED-BASED APPROACH

There is no doubt that this area needs more evidence based approach. Dipti *et al*[6] in a meta-analysis that was published in 2012, studied the value of IVC diameter in estimating volume status in adults. They searched 5 major databases and combined 5 prospective studies on this topic. The meta-analysis included 86 hypovolemic

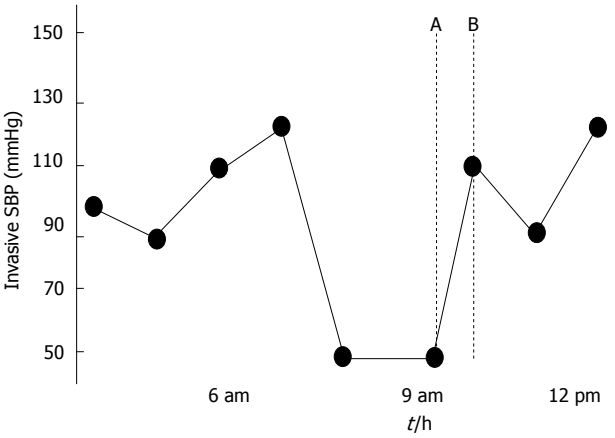


Figure 6 The patient's blood pressure quickly improved without evidence of pulmonary oedema. Point A is when images in Figure 4 were taken while point B is when images in Figure 5 were taken.

patients and 189 controls. IVC diameter was significantly less in hypovolemic patients compared with controls. These studies stemmed from 4 countries having good external validity and a spectrum of different disease severity. Nevertheless, the analysis had a very high heterogeneity (I^2 = 99%), no randomized controlled study was included, and the sample size was small.

A recent prospective randomized controlled trial in injured patients having hypotension or tachycardia treated in a level I trauma center in United States has just been published[16]. It compared transthoracic limited echocardiography including measuring IVC (106 patients) with usual care (134 patients). The outcome variables were fluid requirement, time to surgery, percentage of ICU admission, and mortality. This study shows that limited echocardiography significantly reduced the IV fluid requirements (average of 1.5 L compared with 2.5 L) and significantly reduced the time to the operating theatre (by 50%). It also alerted the physicians to the seriousness of some cases and increased the likelihood of ICU admission of such cases (from 67% to 80%).

It may be argued that the statements expressed in this editorial are biased. I have been interested in and passionate about point of care ultrasound for a quarter of a century, since time when it was not yet commonly used by surgeons or intensivists. I have observed the dramatic improvement in this field over time including the huge progress in point-of-care ultrasound and the development of acute care surgery as a special entity. I have been measuring the IVC diameter in critically-ill and trauma shocked patients as an acute care surgeon over the last 8 years and using it in making very critical decisions in a busy acute care hospital. From personal experience, I am confident that bedside measurement of IVC is to stay. It is useful in evaluating and resuscitating shocked patients. To achieve that, the operator should be well-trained, use standardized techniques, understand ultrasound limitations, and finally correlate the findings with the clinical picture as a whole.

ACKNOWLEDGMENTS

The author thanks Ms. Geraldine Kershaw, Lecturer, Medical Communication and Study Skills, Department of Medical Education, College of Medicine and Health Sciences, UAE University for language and grammar corrections.

REFERENCES

1 **Abu-Zidan FM**. Point-of-care ultrasound in critically ill patients: Where do we stand? *J Emerg Trauma Shock* 2012; **5**: 70-71 [PMID: 22416159 DOI: 10.4103/0974-2700.93120]
2 **Seif D**, Perera P, Mailhot T, Riley D, Mandavia D. Bedside ultrasound in resuscitation and the rapid ultrasound in shock protocol. *Crit Care Res Pract* 2012; **2012**: 503254 [PMID: 23133747 DOI: 10.1155/2012/503254]
3 **Seif D**, Mailhot T, Perera P, Mandavia D. Caval sonography in shock: a noninvasive method for evaluating intravascular volume in critically ill patients. *J Ultrasound Med* 2012; **31**: 1885-1890 [PMID: 23197540]
4 **Weekes AJ**, Tassone HM, Babcock A, Quirke DP, Norton HJ, Jayarama K, Tayal VS. Comparison of serial qualitative and quantitative assessments of caval index and left ventricular systolic function during early fluid resuscitation of hypotensive emergency department patients. *Acad Emerg Med* 2011; **18**: 912-921 [PMID: 21906201 DOI: 10.1111/j.1553-2712.2011.01157.x]
5 **Corl K**, Napoli AM, Gardiner F. Bedside sonographic measurement of the inferior vena cava caval index is a poor predictor of fluid responsiveness in emergency department patients. *Emerg Med Australas* 2012; **24**: 534-539 [PMID: 23039295 DOI: 10.1111/j.1742-6723.2012.01596.x]
6 **Dipti A**, Soucy Z, Surana A, Chandra S. Role of inferior vena cava diameter in assessment of volume status: a meta-analysis. *Am J Emerg Med* 2012; **30**: 1414-1419.e1 [PMID: 22221934 DOI: 10.1016/j.ajem.2011.10.017]
7 **Vegas A**, Denault A, Royse C. A bedside clinical and ultrasound-based approach to hemodynamic instability - Part II: bedside ultrasound in hemodynamic shock: continuing professional development. *Can J Anaesth* 2014; **61**: 1008-1027 [PMID: 25274122 DOI: 10.1007/s12630-014-0231-9]
8 **Akilli B**, Bayir A, Kara F, Ak A, Cander B. Inferior vena cava diameter as a marker of early hemorrhagic shock: a comparative study. *Ulus Travma Acil Cerrahi Derg* 2010; **16**: 113-118 [PMID: 20517763]
9 **Abu-Zidan FM**, Idris K. Sonographic Measurement of the IVC Diameter as an Indicator for Fluid Resuscitation: Beware of the Intra-abdominal Pressure. *World J Surg* 2015; **39**: 2608-2609 [PMID: 26126424 DOI: 10.1007/s00268-015-3142-1]
10 **Abu-Zidan FM**, Hefny AF, Saadeldinn YA, El-Ashaal YI. Sonographic findings of superior mesenteric artery syndrome causing massive gastric dilatation in a young healthy girl. *Singapore Med J* 2010; **51**: e184-e186 [PMID: 21140106]
11 **Coen D**, Cortellaro F, Pasini S, Tombini V, Vaccaro A, Montalbetti L, Cazzaniga M, Boghi D. Towards a less invasive approach to the early goal-directed treatment of septic shock in the ED. *Am J Emerg Med* 2014; **32**: 563-568 [PMID: 24666743 DOI: 10.1016/j.ajem.2014.02.011]
12 **Sefidbakht S**, Assadsangabi R, Abbasi HR, Nabavizadeh A. Sonographic measurement of the inferior vena cava as a predictor of shock in trauma patients. *Emerg Radiol* 2007; **14**: 181-185 [PMID: 17541661]
13 **Yanagawa Y**, Sakamoto T, Okada Y. Hypovolemic shock evaluated by sonographic measurement of the inferior vena cava during resuscitation in trauma patients. *J Trauma* 2007; **63**: 1245-1248; discussion 1248

[PMID: 18212645 DOI: 10.1097/TA.0b013e318068d72b]
14 **Feissel M**, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med* 2004; **30**: 1834-1837 [PMID: 15045170]
15 **Schefold JC**, Storm C, Bercker S, Pschowski R, Oppert M, Krüger A, Hasper D. Inferior vena cava diameter correlates with invasive hemodynamic measures in mechanically ventilated intensive care unit patients with sepsis. *J Emerg Med* 2010; **38**: 632-637 [PMID: 18385005 DOI: 10.1016/j.jemermed.2007.11.027]
16 **Ferrada P**, Evans D, Wolfe L, Anand RJ, Vanguri P, Mayglothling J, Whelan J, Malhotra A, Goldberg S, Duane T, Aboutanos M, Ivatury RR. Findings of a randomized controlled trial using limited transthoracic echocardiogram (LTTE) as a hemodynamic monitoring tool in the trauma bay. *J Trauma Acute Care Surg* 2014; **76**: 31-37; discussion 37-38 [PMID: 24368354 DOI: 10.1097/TA.0b013e3182a74ad9]

P- Reviewer: Boucek C, Inaba H, Lin J, Willms D
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.12

World J Crit Care Med 2016 February 4; 5(1): 12-16
ISSN 2220-3141 (online)

FRONTIER

Advanced trauma life support training: How useful it is?

Fikri M Abu-Zidan

Fikri M Abu-Zidan, Department of Surgery, College of Medicine and Health Sciences, UAE University, PO BOX 17666, Al-Ain, United Arab Emirates

Author contributions: Abu-Zidan FM had the idea, critically read the literature, drew the images, wrote the paper, and approved its final version.

Conflict-of-interest statement: None declared by the author.

Correspondence to: Fikri M Abu-Zidan, MD, FACS, FRCS, PhD, Dip Applied Statistics, Professor, Acute Care Surgeon, Point-of-Care Sonographer, Statistical Consultant, Department of Surgery, College of Medicine and Health Sciences, UAE University, Tawam Roundabout, Tawam Street, PO BOX 17666, Al-Ain, United Arab Emirates. fabuzidan@uaeu.ac.ae
Telephone: +971-50-8335390
Fax: +971-50-7672067

Received: July 22, 2015
Peer-review started: July 24, 2015
First decision: September 28, 2015
Revised: October 7, 2015
Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: February 4, 2016

Abstract

We have tried in a recently published systematic review (*World J of Surg* 2014; 38: 322-329) to study the educational value of advanced trauma life support (ATLS) courses and whether they improve survival of multiple trauma patients. This Frontier article summarizes what we have learned and reflects on future perspectives in this important area. Our recently published systematic review has shown that ATLS training is very useful from an educational point view. It significantly increased knowledge, and improved practical skills and the critical decision making process in managing multiple trauma patients. These positive changes were evident in a wide range of learners including undergraduate medical students and postgraduate residents from different subspecialties. In contrast, clear evidence that ATLS training reduces trauma death is lacking. It is obvious that it is almost impossible to perform randomized controlled trials to study the effect of ATLS courses on trauma mortality. Studying factors predicting trauma mortality is a very complex issue. Accordingly, trauma mortality does not depend solely on ATLS training but on other important factors, like presence of well-developed trauma systems including advanced pre-hospital care. We think that the way to answer whether ATLS training improves survival is to perform large prospective cohort studies of high quality data and use advanced statistical modelling.

Key words: Advanced trauma life support; Education; Course; Training; Death

Core tip: We recommend teaching advanced trauma life support (ATLS) courses for doctors who may treat multiple trauma patients in their setting. Large prospective cohort studies of high quality data are needed to evaluate the impact of ATLS training on trauma death rates and disability.

Abu-Zidan FM. Advanced trauma life support training: How useful it is? *World J Crit Care Med* 2016; 5(1): 12-16 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/12.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.12

BIOGRAPHY

Professor Fikri M Abu-Zidan (Figure 1) is a Consultant Trauma and Acute Care Surgeon who gained his MD from Aleppo University, Syria, in 1981. He was awarded the Fellowship of Royal College of Surgeons of Glasgow, Scotland in 1987. He achieved his PhD in Trauma and Disaster Medicine from Linkoping University, Sweden in 1995 and then obtained his Postgraduate Diploma of Applied Statistics from Massey University, New Zealand, in 1999. He worked as a surgeon at Mubarak Al-Kabeer Teaching Hospital in Kuwait from 1983-1993, as a Trauma Research Fellow at Linkoping University, Sweden, from 1993-1995, as a Senior Research Fellow at Auckland University, New Zealand from 1996-2001; and as a Trauma Fellow at Royal Perth Hospital, Perth, Australia, during 2001. He is at present a Professor of Surgery at the Department of Surgery, College of Medicine and Health Sciences, United Arab Emirates (UAE) University, United Arab Emirates. He has contributed to more than 270 publications in refereed international journals. Professor Abu-Zidan is a well-respected international Judge, invited speaker, and visiting Professor at numerous international meetings with more than 350 presentations and invited lectures. At present, Professor Abu-Zidan is serving as the Statistical Consultant for *World Society of Emergency Surgery*, Statistical Consultant for *World Journal of Emergency Surgery*, Statistics Editor of *Hamdan Medical Journal*, and as an Invited Editor, member of Editorial board, and reviewer for several international journals. His clinical experience includes treating war injured patients during the Second Gulf War (1990). He has been promoting the use of Point-of-Care Ultrasound for more than twenty five years and he is considered a World Leader in this area. Furthermore, he is an international expert on trauma experimental methodology with particular expertise in developing novel clinically relevant animal models. He played an important role in establishing experimental surgical research in Auckland University, New Zealand which subsequently developed into a strong successful PhD Program. Professor Abu-Zidan has received numerous national and international awards for clinical, research and educational activities.

INTRODUCTION

Trauma is a leading cause of death and disability all over the world. Trauma management can be improved by implementing a trauma system that includes injury prevention, education, pre-hospital care, transportation, hospital care, and rehabilitation[1]. If properly implemented, trauma systems can reduce mortality of severe trauma patients by at least 15%[2]. Training physicians to manage multiple trauma patients is an essential part of developing proper trauma systems. The primary end point of any clinical educational activity is its impact on improving health care. Our trauma group has been extensively involved in teaching advanced trauma life support (ATLS) and focused assessment sonography courses for the last 15 years[3-6]. These courses are time consuming and need extensive resources and manpower. ATLS is one of the most common courses taught worldwide. In an evidenced-based era, it is legitimate to question the educational and clinical value of these courses. We tried in a recently published systematic review to study the educational value of ATLS courses and whether they improved survival of multiple trauma patients[7]. This article summarizes what we have learned and reflects on future perspectives in this area.

Figure 1 Fikri M Abu-Zidan, MD, FACS, FRCS, PhD, Dip Applied Statistics; Professor, Acute Care Surgeon, Point-of-Care Sonographer, and Statistical Consultant; Department of Surgery, College of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates.

ATLS COURSE

The ATLS course was established in 1976 by Dr James Styner in United States after a tragic private family plane crash. Dr Styner was not happy with the level of health care given to his family members. He developed ATLS so as to improve the management of multiple trauma patients in rural areas. This course was adopted by the American College of Surgeons and quickly spread worldwide[8,9]. To date it has been taught to more than one million doctors in more than 60 countries[10]. It is accepted as a standard protocol for the initial care of trauma patients in many trauma centers worldwide[11,12].

ATLS is a very demanding two/three full days course that uses different adult learning approaches[13] including interactive didactic teaching, simulated clinical cases (Figures 2 and 3), practical skill stations (Figure 4), and group discussions[14]. Following ATLS training, non-surgical physicians should be able to successfully manage severe trauma patients[15]. The interactive approach for teaching ATLS improves clinical assessment of trauma patients. It is more enjoyable and rewarding compared with classical teaching[16,17]. It actively involves students in discussions, encourages them to ask more questions, and gives direct feedback. ATLS simulations place candidates under stress in clinical scenarios so that they can later make critical decisions in a real world environment. ATLS aims high to reach the top layer of Miller's educational pyramid

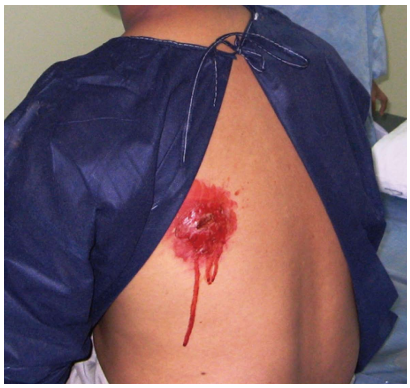


Figure 2 A moulaged simulated patient having a stab wound to the left chest wall with tension pneumothorax.

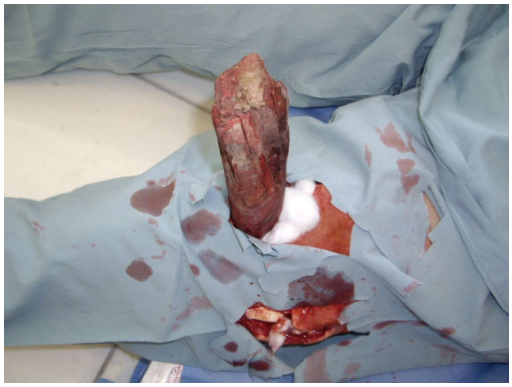


Figure 3 A moulaged simulated trauma patient with a penetrating impalement injury to the left thigh with left femur fracture and superficial femoral artery injury caused by a piece of wood.

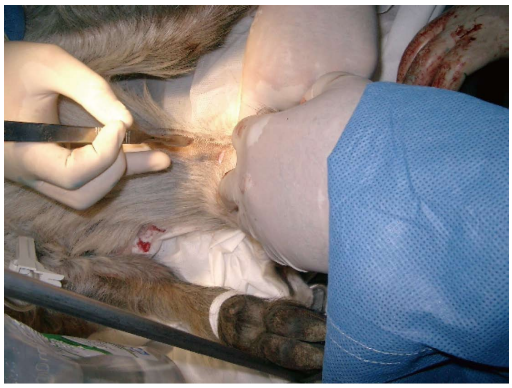


Figure 4 Practical training on performing diagnostic peritoneal lavage on anaesthetized goats using the open technique and a transverse sub-umbilical incision.

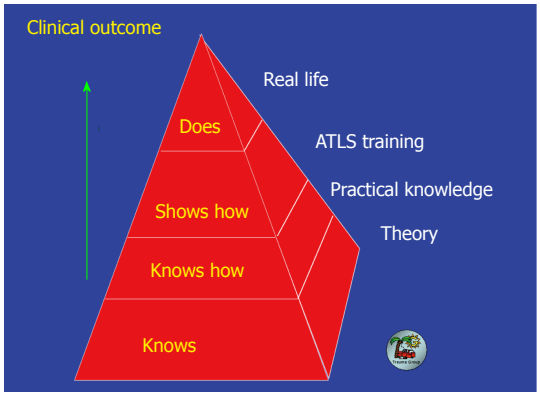


Figure 5 Miller's pyramid for gaining clinical skills in Advanced Trauma Life Support courses. ATLS: Advanced Trauma Life Support.

("does") (Figure 5)[18,19]. Physicians are observed performing certain procedures and applying them in simulated clinical scenario. It is important to stress that the real value of any educational medical activity is measured by its clinical benefit for patients in real life.

We started teaching ATLS in UAE in 2004. More than 2000 doctors have taken this course in UAE[20]. The majority of participants in UAE were residents (44.8%), and specialists (43.7%). Critical care physicians and anaesthetists constituted 11% of all participants of ATLS courses in UAE. Interestingly, critical care physicians showed similar theoretical (P = 0.89) and practical knowledge (P = 0.99) when compared with surgeons during ATLS courses in UAE[4].

METHODS USED

We searched MEDLINE, PubMed, and the Cochrane databases for articles studying the educational outcomes of ATLS courses and their impact on trauma death. Articles published during the period 1966-2012 were studied. Out of 384 papers, 23 met our selection criteria. Ten original papers investigated the effects of ATLS courses on knowledge and practical skills, six original papers studied the time needed to lose practical skills gained by ATLS courses, and seven original papers studied the impact of ATLS courses on trauma death. I critically appraised these papers regarding their research methodology and statistical analysis in this systematic review[7]. We used The Scottish Intercollegiate Guidelines Network handbook to grade the level of evidence of the papers[21]. Furthermore, we used the United States preventive Services Task Force grading system to grade overall quality of evidence[22].

WHAT IS THE EDUCATIONAL IMPACT OF ATLS?

ATLS significantly increases knowledge of trauma management, improves practical skills, organization of trauma management, and identification of management priorities (level Ⅰ evidence: Evidence obtained from at least one properly randomized controlled trial). The gained knowledge and skills start to decline gradually 6 mo after the course (level Ⅱ-1 evidence: Evidence obtained from well-designed controlled trials without randomization) and reach maximum decline after 2 years. Participants keep the gained organizational skills and identification of management priorities up to 8

years after taking the course. Teaching ATLS courses using the interactive approach significantly improved the practical skills compared with the old classical teaching (Level I evidence)[7].

Knowledge and practical skills gained by ATLS participants decline over time if these skills are not utilized. This supports the need for re-certification. We are of the opinion that ATLS re-certification should be under taken every four years so as to update candidates with recent advances in trauma management. Trauma management continuously changes depending on new scientific evidence that leads to modification of recommendations and guidelines.

DOES ATLS TRAINING IMPROVE SURVIVAL OF TRAUMA PATIENTS?

Medical literature does not show accumulative evidence that ATLS training reduces trauma death. All seven studies addressing the effects of ATLS training on trauma death were retrospective except one which was a prospective cohort study. Five of these studies did not show any effect of ATLS training on trauma death, one study showed significant improvement, while another showed a worse outcome of trauma patients who were managed by ATLS certified doctors[7].

LIMITATIONS OF OUR REVIEW

It is recommended that at least two independent researchers should do the literature search in systematic reviews and at least two methodologists should critically appraise the selected papers. This would reduce both search bias and evaluator bias. What worked for us during the search stage is that ATLS or "Advanced Trauma Life Support" is a very specific term. Furthermore, MEDLINE and PubMed have the ability to automatically search for alternative terms. This would have reduced the search bias. One of the major limitations in performing systematic reviews in developing countries is lack of research methodologists. The systematic review discussed[7] was critically appraised by only one evaluator which is definitely a limitation.

What assured us that our evaluation was proper is that a very recent Cochrane database systematic review that was published a few months after our paper had the same research question. This systematic review produced exactly the same results and conclusions as ours[23].

SUMMARY OF THE SYSTEMATIC REVIEW

Our recently published systematic review has shown that ATLS training is very useful from an educational point view. It significantly increased knowledge, and improved both practical skills and the critical decision making process in managing multiple trauma patients. These positive changes were evident in a wide range of learners including undergraduate medical students and postgraduate residents from different subspecialties. In contrast, clear evidence that ATLS training reduces trauma death is lacking. We recommend teaching ATLS courses for those doctors who may treat multiple trauma patients in their setting. Large prospective cohort studies of high quality data are needed to evaluate the impact of ATLS training on trauma death rates and disability.

PERSPECTIVE

It is obvious that it is almost impossible to perform randomized controlled trials to study the effect of ATLS courses on trauma mortality simply because all conditions cannot be standardized. Studying factors predicting trauma mortality is a very complex issue. There are multiple confounders and logistics that prevent such experimental design. Accordingly, trauma mortality does not depend solely on ATLS training but on other important factors, like presence of well-developed trauma systems with advanced pre-hospital care. In a population based study from different counties in United States, Rutledge *et al*[24] found that the effects of ATLS training differed between different county clusters. This indicates that factors affecting mortality are more complex and pertain not only to ATLS training[24]. We think that the way to answer whether ATLS training improves survival is to perform large prospective cohort studies of high quality data and use advanced statistical modelling for that.

ACKNOWLEDGMENTS

The author thanks Ms. Geraldine Kershaw, Lecturer, Medical Communication and Study Skills, Department of Medical Education, College of Medicine and Health Sciences, UAE University for language and grammar corrections.

REFERENCES

1 **Hoyt DB**, Coimbra R. Trauma systems. *Surg Clin North Am* 2007; **87**: 21-35, v-vi [PMID: 17127121]
2 **Celso B**, Tepas J, Langland-Orban B, Pracht E, Papa L, Lottenberg L, Flint L. A systematic review and meta-analysis comparing outcome of severely injured patients treated in trauma centers following the establishment of trauma systems. *J Trauma* 2006; **60**: 371-378; discussion 378 [PMID: 16508498]
3 **Abu-Zidan FM**, Dittrich K, Czechowski JJ, Kazzam EE. Establishment of a course for Focused Assessment Sonography for Trauma. *Saudi Med J* 2005; **26**: 806-811 [PMID: 15951874]
4 **Abu-Zidan FM**, Mohammad A, Jamal A, Chetty D, Gautam SC, van Dyke M, Branicki FJ. Factors affecting success rate of Advanced Trauma Life Support (ATLS) courses. *World J Surg* 2014; **38**: 1405-1410 [PMID: 24368574]
5 **Abu-Zidan FM**, Freeman P, Mandavia D. The first Australian workshop on bedside ultrasound in the Emergency Department. *N Z Med J* 1999; **112**: 322-324 [PMID: 10493445]
6 **Abu-Zidan FM**, Siösteen AK, Wang J, al-Ayoubi F, Lennquist S. Establishment of a teaching animal model for sonographic diagnosis of trauma. *J Trauma* 2004; **56**: 99-104 [PMID:

14749574]
7 **Mohammad A**, Branicki F, Abu-Zidan FM. Educational and clinical impact of Advanced Trauma Life Support (ATLS) courses: a systematic review. *World J Surg* 2014; **38**: 322-329 [PMID: 24136720]
8 **Collicott PE**. Advanced Trauma Life Support (ATLS): past, present, future--16th Stone Lecture, American Trauma Society. *J Trauma* 1992; **33**: 749-753 [PMID: 1464926]
9 **Gwinnutt CL**, Driscoll PA. Advanced trauma life support. *Eur J Anaesthesiol* 1996; **13**: 95-101 [PMID: 8829950]
10 **Drimousis PG**, Theodorou D, Toutouzas K, Stergiopoulos S, Delicha EM, Giannopoulos P, Larentzakis A, Katsaragakis S. Advanced Trauma Life Support certified physicians in a non trauma system setting: is it enough? *Resuscitation* 2011; **82**: 180-184 [PMID: 21122975 DOI: 10.1016/j.resuscitation.2010.10.005]
11 **Baker MS**. Advanced trauma life support: is it adequate stand-alone training for military medicine? *Mil Med* 1994; **159**: 587-590 [PMID: 7800171]
12 **van Olden GD**, Meeuwis JD, Bolhuis HW, Boxma H, Goris RJ. Advanced trauma life support study: quality of diagnostic and therapeutic procedures. *J Trauma* 2004; **57**: 381-384 [PMID: 15345989]
13 **Carley S**, Driscoll P. Trauma education. *Resuscitation* 2001; **48**: 47-56 [PMID: 11162882]
14 **Carmont MR**. The Advanced Trauma Life Support course: a history of its development and review of related literature. *Postgrad Med J* 2005; **81**: 87-91 [PMID: 15701739]
15 **Ben Abraham R**, Stein M, Kluger Y, Rivkind A, Shemer J. The impact of advanced trauma life support course on graduates with a non-surgical medical background. *Eur J Emerg Med* 1997; **4**: 11-14 [PMID: 9152689]
16 **Ali J**, Adam RU, Josa D, Pierre I, Bedaysie H, West U, Winn J, Haynes B. Comparison of performance of interns completing the old (1993) and new interactive (1997) Advanced Trauma Life Support courses. *J Trauma* 1999; **46**: 80-86 [PMID: 9932687]
17 **Ali J**, Adam R, Pierre I, Bedaysie H, Josa D, Winn J. Comparison of performance 2 years after the old and new (interactive) ATLS courses. *J Surg Res* 2001; **97**: 71-75 [PMID: 11319883]
18 **Miller GE**. The assessment of clinical skills/competence/performance. *Acad Med* 1990; **65**: S63-S67 [PMID: 2400509]
19 **Schuwirth LW**, van der Vleuten CP. The use of clinical simulations in assessment. *Med Educ* 2003; **37** Suppl 1: 65-71 [PMID: 14641641]
20 **Advanced Trauma Life Support**. Advanced Trauma Life Support for Doctors, UAE Chapter. Available from: URL: http://www.traumauae.com/
21 **Scottish Intercollegiate Guidelines Network**. Key to evidence statements and grades of recommendations. SIGN 50: A Guideline Developer's Handbook, Revised Edn, January 2008. Edinburgh, 2011: 51. Available from: URL: http://www.sign.ac.uk/pdf/sign50.pdf
22 **Berg AO**, Allan JD. Introducing the third US Preventive Services Task Force. *Am J Prev Med* 2001; **20**: 3-4 [PMID: 11306224]
23 **Jayaraman S**, Sethi D, Chinnock P, Wong R. Advanced trauma life support training for hospital staff. *Cochrane Database Syst Rev* 2014; **8**: CD004173 [PMID: 25146524 DOI: 10.1002/14651858.CD004173.pub4]
24 **Rutledge R**, Fakhry SM, Baker CC, Weaver N, Ramenofsky M, Sheldon GF, Meyer AA. A population-based study of the association of medical manpower with county trauma death rates in the United States. *Ann Surg* 1994; **219**: 547-563; discussion 563-567 [PMID: 8185404]

P- Reviewer: Cotogni P, Lee TS, Mashreky SR, Trohman RG
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.17

World J Crit Care Med 2016 February 4; 5(1): 17-26
ISSN 2220-3141 (online)

REVIEW

Antithrombin in the treatment of burn trauma

Areta Kowal-Vern, Bruce A Orkin

Areta Kowal-Vern, Bruce A Orkin, Department of General Surgery, Rush University Medical Center, Chicago, IL 60612, United States

Author contributions: Kowal-Vern A designed the review, acquired the literature and drafted the article; Kowal-Vern A and Orkin BA analysed and interpreted the data and literature, made critical revisions related to important intellectual content of the manuscript, and approved the final version of the article to be published.

Conflict-of-interest statement: None.

Correspondence to: Areta Kowal-Vern, MD, FCAP, FASCP, CTBS, Assistant Professor, Department of General Surgery, Rush University Medical Center, Professional Building, Suite 1138, 1725 Harrison Street, Chicago, IL 60612, United States. akvern@comcast.net
Telephone: +1-312-9427088
Fax: +1-312-9427081

Received: July 29, 2015
Peer-review started: July 29, 2015
First decision: October 8, 2015
Revised: October 28, 2015
Accepted: November 24, 2015
Article in press: November 25, 2015
Published online: February 4, 2016

Abstract

Antithrombin (AT) is a natural anticoagulant with anti-inflammatory properties that has demonstrated value in sepsis, disseminated intravascular coagulation and in burn and inhalation injury. With high doses, AT may decrease blood loss during eschar excision, reducing blood transfusion requirements. There are no human randomized, placebo-controlled studies, which have tested the true benefit of this agent in these conditions. Two main forms of AT are either plasma-derived AT (phAT) and recombinant AT (rhAT). Major ovine studies in burn and smoke inhalation injury have utilized rhAT. There have been no studies which have either translated the basic rhAT research in burn trauma, or determined the tolerance and pharmacokinetics of rhAT concentrate infusions in burn patients. Advantages of rhAT infusions are no risk of blood borne diseases and lower cost. However, the majority of human burn patient studies have been conducted utilizing phAT. Recent Japanese clinical trials have started using phAT in abdominal sepsis successfully. This review examines the properties of both phAT and rhAT, and analyzes studies in which they have been utilized. We believe that it is time to embark on a randomized placebo-controlled multi-center trial to establish the role of AT in both civilian and military patients with burn trauma.

Key words: Antithrombin; Burn trauma; Burn injury; Inhalation injury; Recombinant antithrombin

Core tip: Based on ovine and rat research, and civilian population studies, antithrombin (AT) therapy with either human plasma-derived AT or recombinant AT (rhAT) may be a valuable adjunct treatment in patients with ⩾ 25% total body surface area burn. AT has anticoagulant and anti-inflammatory properties, a positive effect on cardiopulmonary function, and wound healing, with concomitant decreases in pneumonia and mortality. Studies in human volunteers with endotoxemia have shown that rhAT doses as high as 200% and 500% are tolerated safely. With adequate high doses, AT may decrease blood loss during eschar excision, and reduce blood transfusion requirements.

Kowal-Vern A, Orkin BA. Antithrombin in the treatment of burn

trauma. *World J Crit Care Med* 2016; 5(1): 17-26 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/17.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.17

BACKGROUND

World-wide, there are an estimated 265000 deaths per year attributed to burns and inhalation injury, mainly in countries with lower incomes, especially in the World Health Organization South-East Asia area[1]. In the United States alone, the American Burn Association 2015 Fact Sheet compiled data estimates that there have been 3240 deaths from fire and smoke inhalation, 486000 burn injuries requiring medical treatment, and 40000 requiring hospitalization with a survival rate of 96.7%[2]. In spite of major improvements in burn care during the past 30 years, inhalation injury has not been adequately addressed, and is often the main reason patients die even when they have recovered from their burns. Currently, there are no definitive clinical trials for agents that would reverse or improve the inflammatory response, cytokine release, capillary leakage, pulmonary edema, and cellular influx into the lung parenchyma in these patients. It has been well documented in the literature that burn and inhalation injury patients have varying degrees of disseminated intravascular coagulation (DIC), hypercoagulability with thromboembolism, and systemic inflammatory response syndrome (SIRS). Current beneficial relevance of antithrombin (AT) to burn trauma has not been proven[3-6]. Human and ovine studies have shown that AT can have an impact on the morbidity and mortality associated with burn trauma[7,8]. In this review we will examine the utility of AT as a natural anticoagulant and anti-inflammatory agent in the treatment of ≥ 25% total body surface area (TBSA) burns and inhalation injury. The review will describe the status quo of overall research in the field and problems that have been resolved.

Human plasma-derived AT

Paul Morawitz[9] was the first to coin the word "anti-thrombin" (as an inhibitor of thrombin) in his review in 1904. AT was then identified in 1939 as a co-factor of heparin in preventing thrombin formation and inactivating thrombin by forming the thrombin-AT complex[10].

Plasma-derived AT (phAT) is a 58200 kDa serine protease inhibitor of the serpin family which, as a natural anticoagulant: Neutralizes activated serine proteases like factors Ⅹ, Ⅸ, Ⅺ, Ⅻ; complexes with and deactivates thrombin (factor Ⅱ); and increases the rate of dissociation of factor Ⅶa-tissue factor complex to reduce factor Ⅶa activity[11,12]. Since the anticoagulant activity of phAT is potentiated by interactions with endothelial heparin sulfates, this effect is localized to the blood vessels where it competes with heparin for the glycosaminoglycans through thrombomodulin to activate the release of prostacyclin[11,12]. phAT also has anti-inflammatory properties: It complexes with thrombin, removes it from circulation, and decreases production of tumor necrosis factor (TNF)-α which plays a major role in the SIRS syndrome initiated cytokine proliferation[13,14]. phAT may improve wound healing in a hypercoagulable system by reducing thrombosis and maintaining a more vascularized subcutaneous tissue[15,16]. If there is a decrease of thrombosis and microthrombi under the burned skin due to AT-treatment, there would be increased intensity of heat shock protein (hsp) expression in the underlying tissue of the burned area, leading to more viable cells expressing the *hsp* genes[16]. phAT-treated burned skin had a significantly increased intensity of expression of hps70 ($P < 0.02$) and of grp78 ($P < 0.01$) compared to controls[16].

AT plasma levels in healthy blood donors are age-related; between the ages of 25-30 years, women have lower phAT levels compared to men; between the ages of 35 and 50 years, the levels are the same; and over 50 years of age, women have higher phAT levels and increased levels of factor Ⅶ and fibrinogen[17,18]. phAT was used successfully in patients with hereditary AT deficiency[19].

In the past 20 years, published human studies and case reports have documented benefit from the use of phAT in patients with DIC and sepsis[20-23]. The Kybersept study of 2314 septic patients (multi-national, randomized, placebo controlled) was undertaken to determine if there was decreased mortality in patients with phAT treatment (30000 units over 4 d); there was no significant benefit of AT in 28 d mortality rates[24]. In addition, the subset of patients who received heparin with phAT had increased risk of bleeding episodes[24]. However, in this study, there was no adjustment of the AT dose for weight, and burn trauma patients were not included. In a subset of the Kybersept septic patients who had clinical DIC, Kienast *et al*[25] found that patients treated only with phAT did not have increased bleeding compared to controls. These results had a negative and cautionary impact on further investigations of phAT in critically ill patients with DIC and sepsis[25].

Recombinant AT

Recombinant AT (rhAT) as a sterile lyophilized powder became available in the 1990s. As a recombinant product, it eliminates the morbidity of blood borne pathogens and is less expensive than phAT[26]. It is currently FDA approved for hereditary AT deficient patients[26]. A detailed biochemical analysis found that rhAT transgenically produced from goat milk is comparable to clinical grade human plasma-derived AT with respect to specific activity, purity, amount of aggregates, primary sequence, secondary and tertiary structure[26]. Recombinant AT has a shorter half- life than phAT (10.16 ± 1.28 h *vs* 2.8-3.8 d)[26,27]. rhAT also has a greater affinity for heparin than phAT, which may be due to differences in glycosylation[26]. Because rhAT is cleared faster from the circulation compared to phAT, it is usually

Table 1 Literature review of plasma-derived antithrombin studies in human burn patients

Ref.	# phAT patients	# controls	Age (yr) mean	%TBSA	# doses	Admit AT % levels	phAT dose units	AT % level desired	AT % level achieved	AT Level predict mortality	Other
[1]Danielsson *et al*[31], 1997	6	8	37 (20-56)	49 (26-75)	9 d	< 50	333-3800	> 70	50-75	None	Heparin also
[3]Kowal-Vern *et al*[7,15], 2000-2001	9	9	45-30	40-45	9 q 8 h	45 (35-55)	97 U/kg per dose	175	120 (95-145)	None	Pneumonia↓ in AT-treated
[3]Kowal-Vern *et al*[40], 2003	2	0	1.8	70	9 q 8 h	25-66	1000 U/ dose	200	173 (114-224)	None	None
Del Principe[32], 2003	50	0	< 16	> 30	9 q 8 h	--	--	100	105 (85-125)	$P = 0.0005$	None
[2]Niedermayr *et al*[33], 2007	108	93	53 (30-76)	36 (12-60)	--	85 (63-107)	--	70-120	70-120	$P = 0.003$	Heparin also (APTT-50 s)
[4]Lavrentieva *et al*[34], 2008	15	16	22-66	44 (22-66)	3 d	44 (28-81)	65 U/kg per day	> 150	124 (106-148)	None	AT-treated ↑ survival $P = 0.004$

In age, %TBSA. [1]AT-treated group received continuous unfractionated heparin from day 3. One thousand six hundred and sixty-seven U/patient daily as did the controls; [2]The controls had less inhalation injury (14% *vs* 50%) and the %TBSA was much lower (17 ± 17 *vs* 36 ± 24); [3]Calculations for the loading dose were 97 U/kg per loading dose and the next 9 doses were at 2/3 of the loading dose; [4]Unknown if AT given q 8 h or as a continuous infusion. AT: Antithrombin; phAT: Plasma-derived antithrombin; TBSA: Total body surface area; U: Units.

administered as a continuous intravenous infusion. It has been studied in an ovine model of burn and inhalation injury. Other rhAT formulations are produced from the Chinese hamster ovary cells, baby hamster kidney cells and a methylotropic yeast, Pichia pastoris[28]. The primary available rhAT product is Atryn™ (GTC BioTherapeutics, Framingham, MA, United States). It is approved for use in patients with congenital AT deficiency, and is well tolerated and effective[29]. Leitner *et al*[30] studied the effects of rhAT in 30 healthy volunteers. rhAT was infused to increase AT plasma levels to 200% and 500% of normal in a randomized, double-blind, placebo-controlled fashion[30]. Then endotoxin (LPS), 2 ng/kg was administered. Infusion of rhAT dose-dependently decreased coagulation activation ($P < 0.01$), and interleukin-6 (IL-6) levels ($P < 0.01$)[30]. rhAT also decreased peak IL-6 levels by 40% in both study groups, 222 pg/mL and 216 pg/mL *vs* 357 pg/mL in the placebo group, ($P < 0.001$)[30]. In summary, rhAT dose-dependently inhibited tissue factor-triggered coagulation[30]. While rhAT has been used in normal volunteers and in patients with hereditary AT deficiency, there have been no human studies in patients with burn and inhalation injuries.

phAT studies in burn trauma

Table 1 is a compendium of six studies using phAT in human subjects. Of these, 5 reported patient benefits in terms of either pulmonary function, wound healing or mortality. All the studies used different treatment methods and could not be compared to each other. The results in the Danielsson *et al*'s[31] study were compromised by the use of very low doses of phAT, which were continued for 3-4 d. The study had a total of only 6 patients, with small and large burns in one cohort, each of whom were administered a different dose of phAT, without achieving levels above the "normal"[31]. In addition, the authors started heparin on day 3 in both the phAT-treated and non-treated patients, further complicating the clinical picture and data analysis[31]. Therefore, the study conclusion that phAT was not of benefit in burn trauma was based on inadequate numbers, low AT levels, and overall inconclusive evidence[31].

In contrast, Del Principe[32] reported a significant decrease in mortality with the use of infused phAT to > 100% of normal in an Italian pediatric population.

In the Niedermayr *et al*[33] study, burn and inhalation patients were followed by daily AT plasma levels and received AT concentrates to correct any deficiencies to physiologic levels of 70%-120%. Controls had less inhalation injury (14% *vs* 50%) and the %TBSA was much lower (17 ± 17 *vs* 36 ± 24); one might, therefore, expect the control arm with less injury severity to have a significantly lower mortality (7% *vs* 36%)[33]. In this study, all patients received heparin to maintain an APTT of 50 s[33]. Pharmacokinetics of bolus *vs* continual infusion of phAT revealed that continual infusion consumed less drug over time and sustained fewer unintentional decreases in plasma once the steady state was reached; this also provided a cost benefit for the patient[33].

Lavrientieva *et al*[34] published a prospective, randomized study of 31 severely burned patients comparing phAT-treated patients with controls. AT administration was started from the 1st post-burn day and continued for the next 3 d[34]. The AT dose was titrated to the target value of plasma AT activity > 150%[34]. The baseline AT in controls was 54.7% ± 26% on admission and increased to 70.4% ± 19% on day 4; the baseline AT in the phAT-treated patients was 44.3% ± 16% and increased to 121.2% ± 18%[34]. On the basis of specific coagulation markers for DIC such as thrombin-AT complex (TAT) and D-dimer, 19 (61.3%) of patients had non-overt DIC on admission and 9 (29%) had overt DIC on admission[34]. The study did not provide subset analyses of their patients, separating the less injured %TBSA from the more severely injured ones[34].

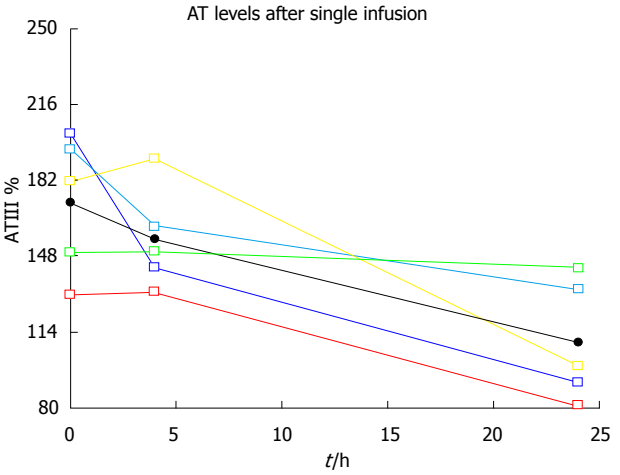


Figure 1 AT levels after calculations for bolus single infusions to attain > 175% plasma antithrombin levels (personal file AKV). AT: Antithrombin.

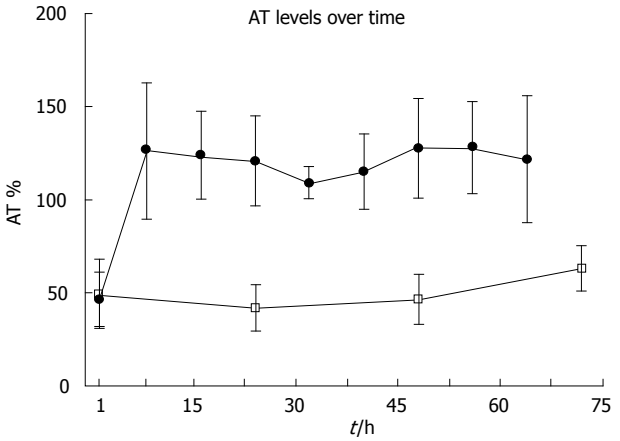


Figure 2 A 72 h depiction of q 8 h dosage coefficient of variations for the antithrombin-treated burn patients (black dots) compared to control plasma antithrombin levels (white squares) (personal file AKV). AT: Antithrombin.

Kowal-Vern *et al*[15] prospectively studied 18 patients with ⩾ 20% TBSA burns ± inhalation injury to assess phAT concentrate infusions for safety and efficacy, and impact on pulmonary function. Since phAT had not been previously utilized in burn trauma, patients were consented on the basis of their decision to either receive the concentrate or to enter as a control patient, not randomized. Nine patients received q 8 h phAT concentrate infusions to raise the plasma level in the first 72 h of hospitalization[15]. The empiric choice, to maintain a high level at > 175% plasma levels was not adequate in treating these patients, to prevent thrombosis of blood vessels, DIC, and stymie the SIRS response that was initiated by release of the thrombin into the circulation (Figure 1)[15].

The loading dose and q 8 h dosing strategy showed variable levels of phAT in patients over the course of 3 d, (Figure 2)[15].

Changes in coagulation activation, fibrinolysis, and anti-inflammatory effects did not extend past the last phAT concentrate dose[15]. More than likely, the half-life of phAT was decreased due to the consumption and loss during the acute resuscitative period. By day 5, control patient AT levels were returning to normal in the less severe cases; liver production of AT was, therefore, intact in most cases unless liver failure developed during treatment[15,35]. Aspartate aminotransferase levels are markedly elevated in burn patients compared to other liver enzymes most likely as a reaction to the inflammation that is occurring rather than liver disease or failure on admission[35].

Several investigators recommended that phAT concentrates be given to achieve > 200% plasma level for adequate anticoagulation and anti-inflammatory activity[36-39]. One patient with 80% TBSA and inhalation injury received the higher recommended doses of phAT concentrate and the four extremity eschar was easily separated from the viable subcutaneous tissues with no blood loss and no excision[40]. Figure 3 shows the severity of the burn with a well-defined escharotomy scar on the lower extremity. Figure 4 shows how easily the eschar is peeled back off the viable subcutaneous tissue below. Histopathology showed viable sebaceous glands and a vascular bed at the separation edge beneath the burnt non-viable skin[40].

Human and ovine studies of AT concentrates for pulmonary injury in burn trauma

Utilizing AT concentrates as replacement therapy for burn trauma, there has been one human study assessing pulmonary function and a number of ovine model studies evaluating burn trauma and specifically lung pathophysiology. Although a small study, the Loyola group compared nine phAT-treated burn patients to 23 control patients[7]. Forty-three percent of controls and 23% of phAT-treated patients developed pneumonia, $P < 0.01$[7]. With potential decreased airway resistance and increased oxygenation, phAT-treated patients had significantly fewer episodes of pneumonia compared to controls[7]. AT concentrate infusions were judged safe and a good option to shorten hospital stay, promote graft viability and survival, and improve pulmonary function in burn injury[7,15].

In a later comparison study of 11 Inhalation injury patients to 11 inhalation + burn injury patients, the inhalation group had a significantly lower 5% ± 4% TBSA compared to 37% ± 24% TBSA in the inhalation+burn group, $P < 0.001$[41]. phAT plasma levels were significantly decreased in inhalation ± burn injury patients (41% + 16% of normal) compared to those with inhalation injury (81% ± 26%), $P < 0.003$[41]. The bronchoalveolar lavage (BAL) did not show any AT levels in the inhalation only patients, but the inhalation + burn injury patients had 1% ± 3% phAT in the lavage[41]. TNF-α levels were significantly increased in BAL compared to plasma on admission and days 3-6 in both groups, $P < 0.001$[41]. BAL IL-6 levels increased in severity through days 3-6, in contrast to plasma levels which decreased in intensity

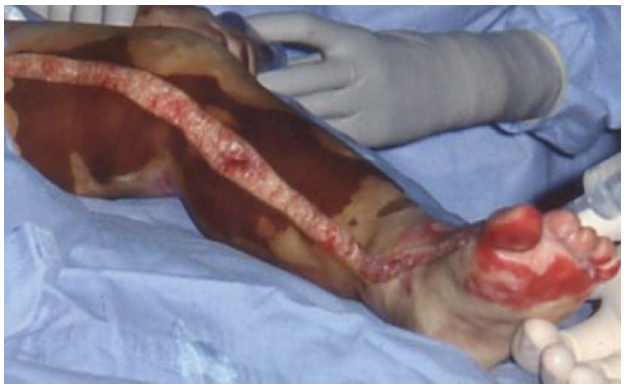


Figure 3 The severity of injury requiring an escharotomy in a burn patient with 80% total body surface area (personal file AKV).

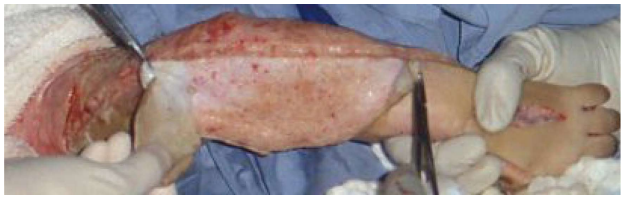


Figure 4 The "peeling off" of the eschar, not requiring knife excision with exposed viable subcutaneous tissue and minimal bleeding (personal file AKV).

by days 3-6[41]. This increase and persistence of BAL TNF-α and IL-6 may have contributed to the pulmonary perturbations of these patients.

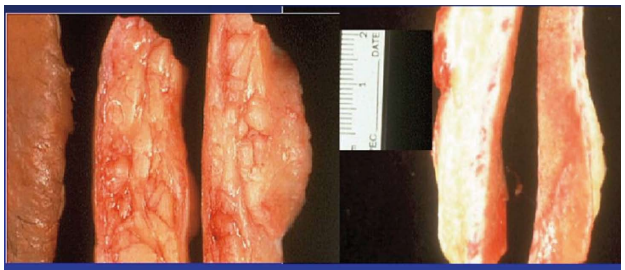
The major work on lung pathophysiology in burn trauma and smoke inhalation injury has been performed at the University of Texas Medical Branch in Houston, Texas[8,42-44]. They have shown therapeutic benefits of rhAT on burn injury and pulmonary function in their well-established ovine burn and smoke inhalation-induced model of acute lung injury/acute respiratory distress syndrome (ARDS)[8,42-44]. The ovine model is a 48 h protocol of burn and smoke inhalation injury in sheep with different medication regimens[8,42-44]. Murakami *et al*[8] investigated the treatment impact of rhAT on sepsis after smoke inhalation in sheep and found that rhAT attenuated the septic shock and the acute lung injury and maintained platelet counts at baseline. Enkhbaatar *et al*[42] were able to prevent the formation of airway fibrin clots causing airway obstruction and Acute Lung Injury and ARDS, with aerosolized anticoagulants (rhAT and heparin) and attenuated all the expected pulmonary pathophysiology.

In contrast to the Kybersept trial where the combination of phAT and heparin increased bleeding episodes, there was no increased bleeding noted by the combination of intravenous rhAT and aerosolized heparin[42]. This may possibly be a result of the increased affinity of rhAT to heparin, and less competition for attachment to the endothelial surfaces of blood vessels. The other explanation may be that the mode of agent delivery by separate intravenous and aerosolized routes results in different modes of interaction with the coagulation cascade and fibrinolysis. Rehberg *et al*[43] put together a useful compendium of their research with the ovine model and pulmonary pathophysiology in burn trauma. Two centers have described the phenomenon of leukocyte activation contributing to pulmonary vascular permeability and pulmonary edema in conjunction with inflammatory agents such as thrombin which promotes systemic capillary leakage and systemic interstitial edema[44,45].

DIC

DIC is defined by the International Society on Thrombosis and Hemostasis as an "acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes"[46]. It is a clinicopathologic diagnosis and requires the following laboratory diagnostic tests in an acute care setting: Platelets $\leqslant$ 100000/mm^3, increased fibrin related markers as D-dimer or fibrin degradation products, a prolonged prothrombin time (PT), a prolonged activated partial thromboplastin time (aPTT), and a fibrinogen (Fbg) < 1 g per liter[46]. Depending on the score, it can be diagnostic of either overt or non-overt DIC[46]. These required parameters for diagnosing DIC have not always been utilized by studies on burn in the literature. The clearest indication for use of AT replacement in trauma may be in the treatment of severe thermal burns. Hemostatic interactions are composed of the coagulation system, the fibrinolytic system, cellular elements (platelets, endothelium), and vasculature balanced in an intricate interrelationship to maintain homeostasis. Most of the global markers of hemostasis as PT, aPTT, and Fbg are not sensitive enough to detect a hypercoagulable state, changes in fibrinolysis, or non-overt DIC. Thus, PT, aPTT, and Fbg levels provide only a superficial impression of hemostasis and become abnormal only when severe coagulation-related disorders are established. Acute thermal injury initiates an activation of coagulation and fibrinolysis resulting in either an overt or non-overt DIC, which increases in severity with the severity of the injury (%TBSA/inhalation injury)[35,47,48]. These hemostatic abnormalities are a result of increased consumption of coagulation and fibrinolytic factors, dilution by the resuscitative fluids, and loss of plasma and fluids through the injured integument. AT concentrates have been used successfully in patients with DIC[20-23].

Significant coagulation abnormalities in burned patients have been demonstrated in the literature for the past 30 years. A detailed discussion of these would deserve a separate review. Prior to providing phAT concentrates to burn trauma patients, both Kowal-Vern *et al*[35] and Lavrentieva *et al*[47] investigated the coagulation and fibrinolytic markers in these burn patient populations to determine the extent of the coagulopathy present. Most pronounced was the decrease in AT, which was significantly suppressed on the first day of burn injury and correlated with the degree of burn injury; it was also the earliest to recover by day 5 to within normal



Comparison of AT(H)-treated skin on the left to the control burnt skin on the right of the ruler. There are more microthrombi in the control burnt skin beneath the surface. The under-surface of the burn is more vascular in the AT(H)-treated skin

Figure 5 A representation of the pathology in third degree burnt skin from a patient treated with plasma-derived antithrombin and in patient without plasma-derived antithrombin treatment. Whereas the skin beneath the control eschar is dead and non-viable with clotted and coagulated blood vessels, the skin and subcutaneous tissue beneath the phAT-treated skin is more viable in comparison with fewer thrombi (personal file AKV). phAT: Plasma-derived antithrombin.

levels[35]. These abnormalities caused an increased state of fibrinolysis and thrombogenicity in the patients, which was confirmed by specific markers of activation such as D-dimer, TAT complex, plasminogen activator inhibitor-1, and tissue plasminogen activator[35,47].

The DIC pathophysiology initiates coagulation and fibrinolysis through endothelial cells or tissue injury, with release of cytokines and other acute phase reactants. Once activated, the proteolytic enzymes, thrombin and plasmin, circulate systemically; their respective concentration determines either a bleeding or thrombotic tendency. AT protects the body against excess clotting by neutralizing thrombin; it is the most important physiological inhibitor of thrombin and factor Xa. In all instances of significant trauma, AT is consumed and plasma AT levels may rapidly decrease to levels at which the process of coagulation will proceed unchecked, quickly leading to deficits in oxygenation, organ failure and shock. There is a significant body of literature that correlates low levels of plasma AT following severe injury and trauma, with an increase of organ failure and death. AT replacement may affect the outcome of all of these conditions.

SIRS

The human body maintains homeostasis with all systems such as coagulation, inflammation, and innate immunity on a daily basis; any insult such as burn, inhalation, infection, sepsis induces a SIRS reaction to control and heal the injury imposed on the body[49]. The cytokine cascade initiates pulmonary inflammation even in the absence of smoke inhalation. AT is a key protagonist affecting not only the coagulation cascade, but also modulating the cytokine release and a major anti-inflammatory agent in plasma, counteracting the boundless SIRS release on the homeostasis of an acutely injured burn patient. AT promotes the release of prostacyclin on the endothelial surface which, as an anti-inflammatory agent, counteracts the production of monocytes and inhibits the release of cytokines such as TNF-α[13,14]. Hur *et al*[50] evaluated 67 burn patients with 27 cytokines and found that IL-1RA, IL-6, and MCP-1 may be used to predict mortality[50]. It appears that the presence and intensity of cytokines, chemokines and growth factors in the pulmonary bronchi and alveoli corresponds to the severity of the inhalation injury[51]. Neonatal rats receiving 100% oxygen for 9 d developed pulmonary edema and hypercellularity on days 1-3 which resolved by days 6-9; this condition was accompanied by the production of TNF-α and IL-6 in the bronchoalveolar lavage which were not present in the control rats[52]. Intra-alveolar TNF-α and IL-6 were also significantly increased in a rat model subjected to burn and inhalation injury[53].

Thrombosis and thromboembolism

There is an interrelationship between the degree of burn and the extent of thrombosis in burned tissue[54]. A second-degree burn has thrombi in the venules only, and a third-degree burn has thrombi in the venules and arterioles[55]. Cotran *et al*[56] have elegantly demonstrated by electron microscopy, in a rat model, that after a mild thermal injury and at the periphery of more severe burns, there is an increase in vascular permeability produced by gaps in the endothelium with no demonstration of endothelial damage[56]. As the severity of thermal injury increases, arterioles, small vessels, and capillaries undergo endothelial necrosis or stasis; larger vessels may continue to leak[56]. When stasis occurs, an amorphous material, chylomicra or thrombi of platelets, and necrotic debris clog the vascular lumen[56]. Animal studies have shown that the presence of infection and sepsis induces a significant increase in thrombosis and distant pyogenic abscesses[56-58]. Autopsy cases have shown pulmonary microthrombi and partially dissolved fibrin in vessels of burn patients contributing to sludging of cells in vessels[59]. However, there have been no prior published histopathological representations of "normal" and phAT-treated human third degree burnt skin, Figure 5 (unpublished data). Subcutaneous tissue vascular thrombi and debris are depicted in Figure 6 (unpublished data).

Cardiac function

Burn patients are known to have myocardial dysfunction which increases in severity with the severity of the injury and is worse if there are any cardiac co-morbidities present. In their ovine burn and smoke inhalation model, Rehberg *et al*[60] have noted that post injury infusion of 6 U/kg per hour of rhAT for 48 h improved myocardial contractility and decreased myocardial oxygen consumption. In addition, TNF-α and IL-6 were not released and the sheep did not accumulate as much systemic fluid[60].

Bacterial translocation

Many of the infections seen in burn patients appear to come from the bacteria transferred from the gut into the systemic circulation to provide the nidus for the infectious complications of burn patients[61]. The ovine model of

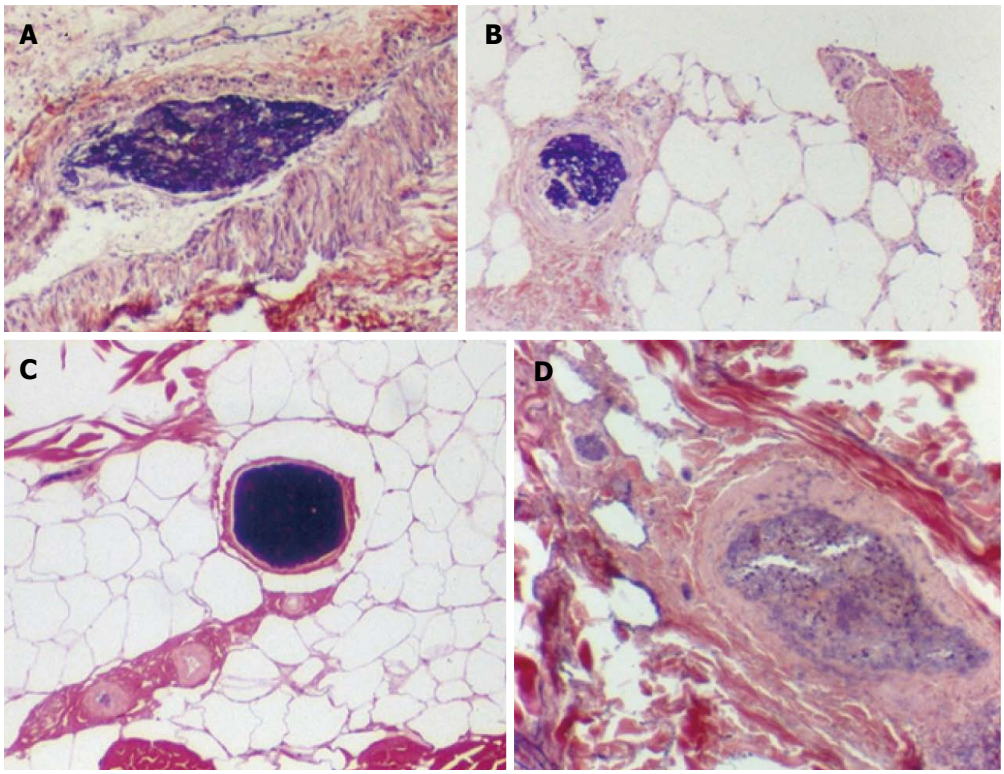


Figure 6 The thrombi, sludge and necrotic debris in burnt skin subcutaneous tissue blood vessels. A: Illustrates a blood vessel with sludge and fibrin debris; B: Depicts a small vessel with fibrin debris; C: Shows a clotted vessel; D: A larger vessel occluded with amorphous material. Magnification 40-100 ×, PTAH staining (personal file AKV).

burn and smoke inhalation injury documented that when the lung is injured, gut bacteria are transported systemically during acute injury because blood is shunted from the intestinal tract into the cardiopulmonary system, and through the systemic capillary leakage[43]. Using an Albino rat model, Herek infused the animals with phAT with 250 U/kg phAT prior to infecting them and creating a burned surface; phAT-treated rats had reduced intestinal villi degeneration and decreased bacterial translocation to mesenteric lymph nodes, spleen and liver compared to sham and control rat ($P < 0.02$)[62]. This study followed the work of Ozden *et al*[63] who showed that an infusion of phAT prevented an ischemic reperfusion injury in the rat.

DISCUSSION

There are two forms of AT used in these studies-rhAT and phAT. rhAT has been primarily used in basic/animal research studies, while phAT has been used in clinical studies. This may lead to questions about the relevance of the basic science studies to human care. The safety of the commercially produced phAT and rhAT concentrates in treating acquired and congenital AT (H) deficiencies has been well documented. High dose AT replacement has been supported in polytrauma and patients with septic shock and DIC[20,23,25].

AT use in disseminated intravascular coagulopathy and sepsis has been evaluated but has not yet been proven useful conclusively[3-6]. It is still worthwhile to pursue AT as a potential treatment in burn and inhalation injury[64]. AT would be of extreme value to the (3%-9% of burn patients with ⩾ 25% BSA) as well as to inhalation injury patients. With the research recommendations for high AT dosing (> 200%), the lack of bleeding during burn eschar removal may eliminate the need for blood transfusions, an intervention known to increase infectious complications and mortality in burn patients[65]. There are no new products in development with both anticoagulant and anti-inflammatory potential such as those possessed by phAT and rhAT to treat severe thermal burns. Not only do rhAT and phAT have the potential to inhibit thrombin and thrombin generation, they can also reduce the systemic inflammatory response that contributes to pulmonary and organ failure, and shock. The vast majority of products in active clinical development for the treatment of burns and inhalation injury does not address systemic injury and falls into the following categories: topical wound healing formulations, artificial skin products and temporary wound coverings, products for the control of bacterial colonization at wound sites, cultured skin and cells for dermal tissue repair, and proteolytic enzymes.

Future research to maximize the practical impact on the field

AT research requires a multicenter randomized placebo-controlled clinical trial. Accrual may be challenging because of smaller numbers (3%-9% of the burn population) than those of patients with sepsis or DIC, but 100-200

patients with reproducible and creditable results would likely determine the utility of AT therapy. This is certainly attainable.

Going forward, primary research objectives should be to determine whether rhAT can safely replace phAT and can maintain AT plasma levels between 200%-250% (normal AT plasma level = 80%-120%) in the first three days post-burn. Secondary objectives are to determine whether patients who receive rhAT or phAT realize significant reductions in pneumonia rates, extent of grafting needed, acute care stays, mechanical ventilation, the number of days of supplemental oxygen, positive end-expiratory pressure, and mortality. Decreases in the frequency of organ failure may also be found. It would also be quite worthwhile to assess the effect of high-dose AT on burn eschar "peeling off" to decrease the need for operative excision.

The lower cost of rhAT may also allow for dissemination of this treatment approach in lower income international communities, where burn injuries are prevalent, highly morbid and often fatal.

CONCLUSION

AT therapy for patients with major burn and inhalation injuries may be a very valuable adjunct to standard treatment. The current literature has shown, albeit in small studies in the civilian population and animal research, that AT therapy has a positive effect on pulmonary function, wound healing, with a decrease in pneumonia and mortality. rhAT may be a very viable option because the literature has shown that it is safe in humans and animals. AT infusions have shown a positive effect on capillary leakage, pulmonary function, wound healing, DIC, inflammation, cardiac function and decreasing bacterial translocation systemically, pneumonia and mortality. Human study volunteers, given endotoxin and rhAT concentrates in doses as high as 200% and 500% of normal AT levels, tolerated them safely. It is time for a multicenter, randomized, placebo-controlled. Standardization of burn trauma patients should include the DIC scoring system guidelines recommended by the International Society of Thrombosis and Hemostasis[46]. AT levels should be targeted to more than therapeutic levels (200%-250%) over a four day period after injury for the most beneficial clinical response in burn patients with $\geqslant$ 25% TBSA. rhAT pharmacokinetics should be initiated in burn and inhalation patients to determine the appropriate dosage for treatment response. Each of the proposal elements represents a significant technological challenge and medical advance. The development of this treatment modality has universal benefits for severe burn trauma patients, both on the battlefield or in the civilian sector. In addition, the broad benefits of AT treatment may be widely applicable in a variety of traumatic injuries and acute care settings.

REFERENCES

1 **WHO**. Burns, fact sheet N°365. Available from: URL: http://www.who.int/mediacentre/factsheets/fs365/en/

2 Burn Incidence and Treatment in the United States: 2015. Available from: URL: http: //www.ameriburn.org/resources_factsheet.php

3 **Afshari A**, Wetterslev J, Brok J, Møller AM. Antithrombin III for critically ill patients. *Cochrane Database Syst Rev* 2008; **(3)**: CD005370 [PMID: 18646125 DOI: 10.1002/14651858.CD005370.p002]

4 **Afshari A**, Wetterslev J, Brok J, Møller A. Antithrombin III in critically ill patients: systematic review with meta-analysis and trial sequential analysis. *BMJ* 2007; **335**: 1248-1251 [PMID: 18037615 DOI: 10.1136/bmj.39398.682500.25]

5 **LaRosa SP**, Opal SM. Clinical trials of Novel anticoagulants for severe sepsis: a tale of three molecules. *Adv Sepsis* 2004; **4**: 17-23

6 **Lavrentieva A**. Coagulopathy in burn patients: one part of a deadly trio. *Burns* 2015; **41**: 419-420 [PMID: 25681959]

7 **Kowal-Vern A**, Walenga JM, McGill V, Gamelli RL. The impact of antithrombin (H) concentrate infusions on pulmonary function in the acute phase of thermal injury. *Burns* 2001; **27**: 52-60 [PMID: 11164666]

8 **Murakami K**, McGuire R, Cox RA, Jodoin JM, Schmalstieg FC, Traber LD, Hawkins HK, Herndon DN, Traber DL. Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia in sheep. *Crit Care Med* 2003; **31**: 577-583 [PMID: 12576969]

9 **Morawitz P**. The Chemistry of Blood Coagulation. Originally published as Die Chemie der Blutgerinnung in Ergebnisse der Physiologie 4 307-423, 1905. A monograph in the Bannerstone Division of American lectures in hematology. IL: Springfield, 1958

10 **Brinkhous KM**, Smith HP, Warner ED, Seegers WH. The inhibition of clotting: an unidentified substance which acts in conjunction with heparin to prevent the conversion of prothrombin into thrombin. *Am J Physiol* 1939; **125**: 683-687

11 **Wada H**, Asakura H, Okamoto K, Iba T, Uchiyama T, Kawasugi K, Koga S, Mayumi T, Koike K, Gando S, Kushimoto S, Seki Y, Madoiwa S, Maruyama I, Yoshioka A. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. *Thromb Res* 2010; **125**: 6-11 [PMID: 19782389 DOI: 10.1016/j.thromres.2009.08.017]

12 **Milton BA**, Steineck A, Talavera F, Conrad ME, Besa EC. Antithrombin Deficiency: Background, Pathophysiology, Antithrombin Gene Structure. Available from: URL: http://emedicine.medscape.com/article/198573-overview

13 **Okajima K**. Regulation of inflammatory responses by natural anticoagulants. *Immunol Rev* 2001; **184**: 258-274 [PMID: 11918684]

14 **Wiedermann ChJ**, Römisch J. The anti-inflammatory actions of antithrombin--a review. *Acta Med Austriaca* 2002; **29**: 89-92 [PMID: 12168569 DOI: 10.1046/j.1563-2571.2002.02012.x]

15 **Kowal-Vern A**, McGill V, Walenga JM, Gamelli RL. Antithrombin(H) concentrate infusions are safe and effective in patients with thermal injuries. *J Burn Care Rehabil* 2000; **21**: 115-127 [PMID: 10752744 DOI: 10.1097/00004630-200021020-00007]

16 **Kowal-Vern A**, Goral J, Gamelli RL, McGill V, Clancy J. hsp70, hsp32, and grp78 are increased in thermally injured skin with and without antithrombin(human) concentrate infusion. *J Burn Care Rehabil* 2000; **21**: 213-219 [PMID: 10850902 DOI: 10.1097/00004630-200021030-00006]

17 **Meade TW**, Dyer S, Howarth DJ, Imeson JD, Stirling Y. Antithrombin III and procoagulant activity: sex differences and effects of the menopause. *Br J Haematol* 1990; **74**: 77-81 [PMID: 2310699 DOI: 10.1111/j.1365-2141.1990.tb02541.x]

18 **Tait RC**, Walker ID, Davidson JF, Islam SI, Mitchell R. Antithrombin III activity in healthy blood donors: age and sex related changes and prevalence of asymptomatic deficiency. *Br J Haematol* 1990; **75**: 141-142 [PMID: 2375917]

19 **Schwartz RS**, Bauer KA, Rosenberg RD, Kavanaugh EJ, Davies DC, Bogdanoff DA. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. The Antithrombin III Study Group. *Am J Med* 1989; **87**: 53S-60S [PMID: 2679072 DOI: 10.1016/0002-9343(89)80533

-9]
20 **Fuse S**, Tomita H, Yoshida M, Hori T, Igarashi C, Fujita S. High dose of intravenous antithrombin III without heparin in the treatment of disseminated intravascular coagulation and organ failure in four children. *Am J Hematol* 1996; **53**: 18-21 [PMID: 8813091]
21 **Wisecarver JL**, Haire WD. Disseminated intravascular coagulation with multiple arterial thromboses responding to antithrombin-III concentrate infusion. *Thromb Res* 1989; **54**: 709-717 [PMID: 2781511 DOI: 10.1016/0049-3848(89)90135-7]
22 **Gando S**, Kameue T, Nanzaki S, Nakanishi Y. Disseminated intravascular coagulation is a frequent complication of systemic inflammatory response syndrome. *Thromb Haemost* 1996; **75**: 224-228 [PMID: 8815564]
23 **Tagami T**, Matsui H, Fushimi K, Yasunaga H. Supplemental dose of antithrombin use in disseminated intravascular coagulation patients after abdominal sepsis. *Thromb Haemost* 2015; **114**: 537-545 [PMID: 25948492 DOI: 10.1160/TH15-01-0053]
24 **Warren BL**, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Pénzes I, Kübler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001; **286**: 1869-1878 [PMID: 11597289 DOI: 10.1001/jama.286.15.1869]
25 **Kienast J**, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, Keinecke HO, Warren BL, Opal SM. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. *J Thromb Haemost* 2006; **4**: 90-97 [PMID: 16409457 DOI: 10.1111/j.1538-7836.2005.01697.x]
26 **Edmunds T**, Van Patten SM, Pollock J, Hanson E, Bernasconi R, Higgins E, Manavalan P, Ziomek C, Meade H, McPherson JM, Cole ES. Transgenically produced human antithrombin: structural and functional comparison to human plasma-derived antithrombin. *Blood* 1998; **91**: 4561-4571 [PMID: 9616152]
27 **Thrombate III**. Available from: URL: http://www.thrombate.com/en/web/thrombate/home
28 **Kuwae S**, Ohyama M, Ohya T, Ohi H, Kobayashi K. Production of recombinant human antithrombin by Pichia pastoris. *J Biosci Bioeng* 2005; **99**: 264-271 [PMID: 16233787 DOI: 10.1263/jbb.99.264]
29 **Paidas MJ**, Forsyth C, Quéré I, Rodger M, Frieling JT, Tait RC. Perioperative and peripartum prevention of venous thromboembolism in patients with hereditary antithrombin deficiency using recombinant antithrombin therapy. *Blood Coagul Fibrinolysis* 2014; **25**: 444-450 [PMID: 24686101 DOI: 10.1097/MBC.0000000000000076]
30 **Leitner JM**, Firbas C, Mayr FB, Reiter RA, Steinlechner B, Jilma B. Recombinant human antithrombin inhibits thrombin formation and interleukin 6 release in human endotoxemia. *Clin Pharmacol Ther* 2006; **79**: 23-34 [PMID: 16413239]
31 **Danielsson P**, Nilsson L, Nettelblad H, Sjöberg F. Is there a need for antithrombin III substitution early after burn injury? *Burns* 1997; **23**: 300-305 [PMID: 9248638 DOI: 10.1016/S0305-4179(96)00135-0]
32 **Del Principe D**. [Antithrombin III in burned children]. *Minerva Anestesiol* 2003; **69**: 376-380 [PMID: 12768170]
33 **Niedermayr M**, Schramm W, Kamolz L, Andel D, Römer W, Hoerauf K, Zimpfer M, Andel H. Antithrombin deficiency and its relationship to severe burns. *Burns* 2007; **33**: 173-178 [PMID: 17118562 DOI: 10.1016/j.burns.2006.06.011]
34 **Lavrentieva A**, Kontakiotis T, Bitzani M, Parlapani A, Thomareis O, Scourtis H, Tsotsolis N, Lazaridis L, Giala MA. The efficacy of antithrombin administration in the acute phase of burn injury. *Thromb Haemost* 2008; **100**: 286-290 [PMID: 18690349 DOI: 10.1160/TH07-11-0684]
35 **Kowal-Vern A**, Gamelli RL, Walenga JM, Hoppensteadt D, Sharp-Pucci M, Schumacher HR. The effect of burn wound size on hemostasis: a correlation of the hemostatic changes to the clinical state. *J Trauma* 1992; **33**: 50-56; discussion 56-57 [PMID: 1635106 DOI: 10.1097/00005373-199207000-00011]
36 **Penner J**. Antithrombin deficiency in special clinical syndromes--Part II: trauma/burns. *Semin Hematol* 1995; **32**: 42-47; discussion 48 [PMID: 8821209]
37 **Uchiba M**, Okajima K, Murakami K. Effects of various doses of antithrombin III on endotoxin-induced endothelial cell injury and coagulation abnormalities in rats. *Thromb Res* 1998; **89**: 233-241 [PMID: 9645917 DOI: 10.1016/S0049-3848(98)00012-7]
38 **Dickneite G**. Antithrombin III in animal models of sepsis and organ failure. *Semin Thromb Hemost* 1998; **24**: 61-69 [PMID: 9515781 DOI: 10.1055/s-2007-995824]
39 **Fourrier F**, Chopin C, Huart JJ, Runge I, Caron C, Goudemand J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. *Chest* 1993; **104**: 882-888 [PMID: 8365305 DOI: 10.1378/chest.104.3.882]
40 **Kowal-Vern A**, Latenser BA. Antithrombin (human) concentrate infusion in pediatric patients with & gt; 50% TBSA burns. *Burns* 2003; **29**: 615-618 [PMID: 12927992 DOI: 10.1016/S0305-4179(03)00138-4]
41 **Kowal-Vern A**, Bourdon P, Latenser BA, Wiley DE, Dennis AJ, Casey L. Comparison of plasma and bronchoalveolar lavage antithrombin and pro-inflammatory cytokine levels in burn patients. # 65 at the 37th Annual ABA Meeting, Chicago, IL May10-13, 2005. *J Burn Care Rehabil* 2005; (Suppl) **26**: S78
42 **Enkhbaatar P**, Cox RA, Traber LD, Westphal M, Aimalohi E, Morita N, Prough DS, Herndon DN, Traber DL. Aerosolized anticoagulants ameliorate acute lung injury in sheep after exposure to burn and smoke inhalation. *Crit Care Med* 2007; **35**: 2805-2810 [PMID: 18074480 DOI: 10.1097/01.CCM.0000291647.18329.83]
43 **Rehberg S**, Maybauer MO, Enkhbaatar P, Maybauer DM, Yamamoto Y, Traber DL. Pathophysiology, management and treatment of smoke inhalation injury. *Expert Rev Respir Med* 2009; **3**: 283-297 [PMID: 20161170 DOI: 10-1586/ERS.09.21]
44 **Rehberg S**, Yamamoto Y, Sousse LE, Jonkam C, Zhu Y, Traber LD, Cox RA, Prough DS, Traber DL, Enkhbaatar P. Antithrombin attenuates vascular leakage via inhibiting neutrophil activation in acute lung injury. *Crit Care Med* 2013; **41**: e439-e446 [PMID: 24107637 DOI: 10.1097/CCM.0b013e318298ad3a]
45 **Johansson J**, Steinvall I, Herwald H, Lindbom L, Sjöberg F. Alteration of Leukocyte Count Correlates With Increased Pulmonary Vascular Permeability and Decreased PaO2: FiO2 Ratio Early After Major Burns. *J Burn Care Res* 2015; **36**: 484-492 [PMID: 25501784 DOI: 10.1097/BCR.0000000000000211]
46 **Toh CH**, Hoots WK. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost* 2007; **5**: 604-606 [PMID: 17096704 DOI: 10.1111/j.1538-7836.2007.02313.x]
47 **Lavrentieva A**, Kontakiotis T, Bitzani M, Papaioannou-Gaki G, Parlapani A, Thomareis O, Tsotsolis N, Giala MA. Early coagulation disorders after severe burn injury: impact on mortality. *Intensive Care Med* 2008; **34**: 700-706 [PMID: 18193192 DOI: 10.1007/s00134-007-0976-5]
48 **García-Avello A**, Lorente JA, Cesar-Perez J, García-Frade LJ, Alvarado R, Arévalo JM, Navarro JL, Esteban A. Degree of hypercoagulability and hyperfibrinolysis is related to organ failure and prognosis after burn trauma. *Thromb Res* 1998; **89**: 59-64 [PMID: 9630308 DOI: 10.1016/S0049-3848(97)00291-0]
49 **Rehberg S**, Traber DL, Enkhbaatar P. Update on Antithrombin for the treatment of burn trauma and smoke inhalation. Yearbook of Intensive Care and Emergency Medicine. Germany: Springer, 2010: 285-296
50 **Hur J**, Yang HT, Chun W, Kim JH, Shin SH, Kang HJ, Kim HS. Inflammatory cytokines and their prognostic ability in cases of major burn injury. *Ann Lab Med* 2015; **35**: 105-110 [PMID: 25553289 DOI: 10.3343/alm.2015.35.1.105]
51 **Albright JM**, Davis CS, Bird MD, Ramirez L, Kim H, Burnham EL, Gamelli RL, Kovacs EJ. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. *Crit*

Care Med 2012; **40**: 1113-1121 [PMID: 22067627 DOI: 10.1097/CCM.0b013e3182374a67]
52 **Ben-Ari J**, Makhoul IR, Dorio RJ, Buckley S, Warburton D, Walker SM. Cytokine response during hyperoxia: sequential production of pulmonary tumor necrosis factor and interleukin-6 in neonatal rats. *Isr Med Assoc J* 2000; **2**: 365-369 [PMID: 10892391]
53 **Stromps JP**, Fuchs P, Demir E, Grieb G, Reuber K, Pallua N. Intraalveolar TNF-α in combined burn and inhalation injury compared with intraalveolar interleukin-6. *J Burn Care Res* 2015; **36**: e55-e61 [PMID: 25522155 DOI: 10.1097/BCR.0000000000000108]
54 **Order SE**, Mason AD, Walker HL, Lindberg RF, Switzer WE, Moncrief JA. The pathogenesis of second and third degree burns and conversion to full thickness injury. *Surg Gynecol Obstet* 1965; **120**: 983-991 [PMID: 14269849]
55 **Robb HJ**. Dynamics of the microcirculation during a burn. *Arch Surg* 1967; **94**: 776-780 [PMID: 4226075 DOI: 10.1001/archsurg.1967.01330120030007]
56 **Cotran RS**, Remensnyder JP. The structural basis of increased vascular permeabiligy after graded thermal injury--light and electron microscopic studies. *Ann N Y Acad Sci* 1968; **150**: 495-509 [PMID: 5248763]
57 **McLean NR**, Harrop-Griffiths K, Shaw HJ, Trott PA. Fine needle aspiration cytology in the head and neck region. *Br J Plast Surg* 1989; **42**: 447-451 [PMID: 2765739 DOI: 10.1016/0007-1226(89)90153-7]
58 **Allen KS**, Sawheny E, Kinasewitz GT. Anticoagulant modulation of inflammation in severe sepsis. *World J Crit Care Med* 2015; **4**: 105-115 [PMID: 25938026 DOI: 10.5492/wjccm.v4.i2.105]
59 **Wells S**, Sissons M, Hasleton PS. Quantitation of pulmonary megakaryocytes and fibrin thrombi in patients dying from burns. *Histopathology* 1984; **8**: 517-527 [PMID: 6735362 DOI: 10.1111/j.1365-2559.1984.tb02361.x]
60 **Rehberg S**, Yamamoto Y, Bartha E, Sousse LE, Jonkam C, Zhu Y, Traber LD, Cox RA, Traber DL, Enkhbaatar P. Antithrombin attenuates myocardial dysfunction and reverses systemic fluid accumulation following burn and smoke inhalation injury: a randomized, controlled, experimental study. *Crit Care* 2013; **17**: R86 [PMID: 23663695 DOI: 10.1186/cc12712]
61 **Magnotti LJ**, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. *J Burn Care Rehabil* 2005; **26**: 383-391 [PMID: 16151282 DOI: 10.1097/01.bcr.0000176878.79267.e8]
62 **Herek O**, Yılmaz M, Kaleli I, Cevahir N, Demirkan N. Antithrombin III Prevents Early Bacterial Translocation in Burn Injury. *Ann Burns Fire Disasters* 2006; **19**: 196-200 [PMID: 21991051]
63 **Ozden A**, Tetik C, Bilgihan A, Calli N, Bostanci B, Yis O, Düzcan E. Antithrombin III prevents 60 min warm intestinal ischemia reperfusion injury in rats. *Res Exp Med* (Berl) 1999; **198**: 237-246 [PMID: 10209759 DOI: 10.1007/s004330050107]
64 **Korte W**, Graf L. Burn injuries: is antithrombin back on stage in critical care? *Thromb Haemost* 2008; **100**: 177-178 [PMID: 18690333 DOI: 10.1160/TH08-07-0433]
65 **Palmieri TL**, Caruso DM, Foster KN, Cairns BA, Peck MD, Gamelli RL, Mozingo DW, Kagan RJ, Wahl W, Kemalyan NA, Fish JS, Gomez M, Sheridan RL, Faucher LD, Latenser BA, Gibran NS, Klein RL, Solem LD, Saffle JR, Morris SE, Jeng JC, Voigt D, Howard PA, Molitor F, Greenhalgh DG. Effect of blood transfusion on outcome after major burn injury: a multicenter study. *Crit Care Med* 2006; **34**: 1602-1607 [PMID: 16607231 DOI: 10.1097/01.CCM.0000217472.97524.0E]

P- Reviewer: Coban Y, Levine EM **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.27

World J Crit Care Med 2016 February 4; 5(1): 27-35
ISSN 2220-3141 (online)

REVIEW

Alcoholism and critical illness: A review

Ashish Jitendra Mehta

Ashish Jitendra Mehta, Division of Pulmonary Critical Care Medicine, Department of Medicine, Atlanta VA Medical Center, Emory University School of Medicine, Atlanta, GA 30322, United States

Author contributions: Mehta AJ contributed to the work in its entirety.

Supported by Ashish J Mehta is supported by a Career Development Award (1IK2CX000643) from the Department of Veterans Affairs (Clinical Science Research and Development).

Conflict-of-interest statement: Author declares no potential conflicts of interest for this article.

Correspondence to: Ashish Jitendra Mehta, MD, MSc, Division of Pulmonary Critical Care Medicine, Department of Medicine, Atlanta VA Medical Center, Emory University School of Medicine, Pulmonary 111, 1670 Clairmont Road, Atlanta, GA 30033, United States. ashish.mehta@emory.edu
Telephone: +1-404-3216111
Fax: +1-404-4171525

Received: July 29, 2015
Peer-review started: July 29, 2015
First decision: September 28, 2015
Revised: October 7, 2015
Accepted: December 3, 2015
Article in press: December 4, 2015
Published online: February 4, 2016

Abstract

Alcohol is the most commonly used and abused drug in the world, and alcohol use disorders pose a tremendous burden to healthcare systems around the world. The lifetime prevalence of alcohol abuse in the United States is estimated to be around 18%, and the economic consequences of these disorders are staggering. Studies on hospitalized patients demonstrate that about one in four patients admitted to critical care units will have alcohol-related issues, and unhealthy alcohol consumption is responsible for numerous clinical problems encountered in intensive care unit (ICU) settings. Patients with alcohol use disorders are not only predisposed to developing withdrawal syndromes and other conditions that often require intensive care, they also experience a considerably higher rate of complications, longer ICU and hospital length of stay, greater resource utilization, and significantly increased mortality compared to similar critically ill patients who do not abuse alcohol. Specific disorders seen in the critical care setting that are impacted by alcohol abuse include delirium, pneumonia, acute respiratory distress syndrome, sepsis, gastrointestinal hemorrhage, trauma, and burn injuries. Despite the substantial burden of alcohol-induced disease in these settings, critical care providers often fail to identify individuals with alcohol use disorders, which can have significant implications for this vulnerable population and delay important clinical interventions.

Key words: Alcoholism; Alcohol withdrawal delirium; Alcohol-related disorders critical illness; Intensive care; Pneumonia; Sepsis; Acute respiratory distress syndrome; Delirium; Trauma

Core tip: Alcohol abuse is a major problem among hospitalized patients, and alcoholics are predisposed to developing critical illness while also facing increased rates of complications and mortality compared to non-alcoholics. The objective of this review is to examine the literature and summarize specific disorders encountered in intensive care unit settings that are impacted by alcoholism. Since alcohol use disorders are poorly recognized in hospitalized patients, this effort aims to raise awareness for critical care practitioners who frequently manage these susceptible

patients.

Mehta AJ. Alcoholism and critical illness: A review. *World J Crit Care Med* 2016; 5(1): 27-35 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/27.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.27

INTRODUCTION

Social, pathological, and medicinal uses of alcohol have been a component of human tradition for thousands of years. While there are obvious therapeutic properties of alcohol, its excessive consumption poses a significant burden to healthcare systems in the United States and globally. Indeed, alcohol has become the most widely used and abused drug in the world[1]. A national survey illustrated that more than 50% of individuals above the age of 12 drink alcohol regularly on at least a social level, almost a quarter participate in binge drinking, and 7% described habitual heavy consumption, which translates into over 17 million Americans[2]. Epidemiological data report the lifetime prevalence of alcohol use disorders in the United States to be an astounding 18%[3]. The economic consequences of alcohol abuse have been estimated to be upwards of $200 billion annually, of which 11% is directly attributable to healthcare costs[4]. These figures are also likely underestimated as they fail to incorporate data from patients whose alcohol use disorders went unrecognized by their clinicians, a situation that occurs commonly in inpatient settings.

Driven by the widespread systemic effects of alcohol, multiple comorbidities, and poor nutrition, individuals with alcohol use disorders frequently require hospital admission for ailments both related and unrelated to alcoholism. Studies on hospitalized patients have suggested that between 20% to 40% of inpatients have alcohol-related conditions[5-7]. The effect is particularly felt in medical and surgical intensive care units (ICUs), which have been overwhelmingly impacted by the burden of unhealthy alcohol use. Alcoholics are not only at an increased risk for suffering critical illness, but they also experience a greater likelihood of complications, poorer outcomes, and increased healthcare utilization compared to those patients who do not have alcohol use disorders. Despite these observations, recognition of alcohol use disorders in hospitalized patients and particularly among individuals in the ICU is inadequate. This review will focus on specific conditions encountered in the critical care setting that are impacted by the considerable burden of pathologic alcohol consumption.

RECOGNITION OF ALCOHOL USE DISORDERS

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recognizes the potential benefits of moderate alcohol consumption. According to dietary guidelines, "moderate" is considered to be an average of no more than two standard drinks per day for men and one standard drink per day in women[8]. Research from the NIAAA shows that staying within these weekly limits as well as not exceeding more than 3 drinks in any given day for women and 4 drinks for men poses a very low risk for developing an alcohol use disorder (AUD). An AUD is an unhealthy pattern of alcohol use that causes significant clinical impairment and has been explicitly defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) to meet at least two of 11 specified criteria[9]. The total number of criteria that are satisfied determines the severity, with two the three symptoms denoting a mild AUD, four to five signifying a moderate disorder, and six or more representing a severe problem. The DSM-V has abandoned the categorizations of "alcohol abuse" and "alcohol dependence" that were previously defined in the earlier edition, DSM-IV[10]. While alcohol abuse and dependence represent different physiological effects of alcohol, for classification purposes these terms have been replaced with the single characterization of an alcohol use disorder.

Given that AUDs are common in critical illness and contribute significantly to morbidity and mortality, it is surprising that we are so poorly equipped to recognize the presence of these disorders in this population. Excessive alcohol use impacts one out of every four to five admissions to the ICU[11]. One review of the literature reported this frequency to be as high as 33%[12], and the rate of AUDs are even higher among patients admitted after traumatic injury[13]. In parallel, studies among hospitalized patients with alcohol use disorders revealed that clinicians correctly identified the diagnosis in only 25% of cases[14], and in critical care settings almost three quarters of surveyed ICUs used no tool to assess for alcohol use disorders and alcohol withdrawal syndromes[15]. Several explanations may support these findings. First, individuals with alcohol use disorders may not always be forthcoming about the extent of their drinking, and worse, may not recognize that they themselves have a problem. Second, during acute illness-and especially in the ICU setting-patients may be unable to provide history or suffer from alteration in mentation that either precludes the gathering of this information or renders it significantly more challenging. Finally, practitioners may fail to elicit this history for a variety of reasons, such as a perceived lack of relevance of this information to the acute presentation. Regardless of the rationale, failure to recognize the impact of alcohol-related disease during critical illness can have significant implications for this vulnerable patient population. Precisely, it is important for critical care providers to understand that the potential for complications from acute interventions is heightened, and possible therapeutic opportunities may be delayed if alcohol use disorders are not appropriately identified.

ALCOHOL, DELIRIUM AND WITHDRAWAL SYNDROMES

Delirium is an acute state of confusion that is characterized primarily by inattentiveness. While many risk factors have been identified, medical illness commonly precipitates as well as exacerbates delirium. Thus, it occurs with high prevalence among hospitalized patients. Experts reveal that delirium occurs in about 30% of older patients at some point in time during their hospitalization, and individuals who develop delirium during their hospital stay have greater morbidity and mortality than those who do not[16,17]. In the ICU, delirium may perhaps be the most commonly encountered diagnosis with its reported prevalence reaching as high as 70%-90% depending on the patient population and method of assessment[18,19].

In a recent study, Mehta *et al*[20] assessed different risk factors for the development of delirium among critically ill, mechanically ventilated patients and found that delirium was significantly more common among those with a history of alcohol use compared to those without this history. Importantly, in this same study, those individuals that developed delirium had a longer duration of mechanical ventilation, a greater likelihood of requiring tracheostomy, and an overall longer hospital stay compared to those who did not develop delirium. Alcohol abuse as a risk factor for the development of delirium was also confirmed in a recent meta-analysis[21]. In the multivariate analysis, alcohol use had the highest odds ratio for the development of delirium after advanced age and mechanical ventilation. This key finding suggests that an assessment for alcohol use is absolutely necessary in critical care settings to identify those individuals who have a greater propensity towards experiencing delirium and ultimately poor outcomes. While many risk factors cannot be modified, it would be valuable to identify those patients with the greatest threat of developing delirium so that clinicians acknowledge and readily act upon those factors that are modifiable.

Recognition and identification of alcohol use disorders in critically ill patients is essential for a variety of other reasons as well. Specifically, chronic alcohol consumption significantly increases possibility of developing alcohol withdrawal syndromes, which include withdrawal seizures, alcoholic hallucinosis, and delirium tremens. Withdrawal syndromes, and especially delirium tremens, can be life threatening and occur in about 20% of alcoholics who stop drinking acutely[22]. Given the prevalence of alcohol use disorders in ICUs, this represents a significant burden among critically ill patients. Further, treatment of alcohol withdrawal syndromes has been linked to greater morbidity and resource utilization particularly in the ICU[23]. Delirium tremens carries a mortality rate between 5% and 15%[24], and treatment guidelines underscore the importance of early identification to ensure better effectiveness of therapy in these individuals. Despite its life-threatening nature, there continues to be a relative lack of data on how best to identify, screen, and prevent patients with a history of alcohol abuse from developing withdrawal syndromes, but the awareness of alcohol use disorders during critical illness is paramount.

ALCOHOL, PNEUMONIA, AND ASPIRATION

The connection between alcohol use and respiratory infections can be traced back over a century. William Osler in his book Principles and Practice of Medicine noted that a tendency towards alcohol abuse was extremely important in predisposing individuals to developing pneumonia[25]. In the United States, pneumonia is the eighth most common cause of death overall and the leading cause of death from an infection. Given the high morbidity and mortality associated with pneumonia, it is a commonly encountered diagnosis in the ICU. Further, pneumonia not only often necessitates ICU admission, it can also occur as a complication critical illness after traumatic injury, post-operative status, and mechanical ventilation.

More recent studies have continued to uphold the finding that alcoholism is an important risk factor for the development of both "typical" pneumonias as well as more severe respiratory infections caused by more virulent and atypical organisms. In a study among patients with community-acquired pneumonia, de Roux *et al*[26] showed that *Streptococcus pneumoniae* was seen more frequently and occurred with higher severity scores in alcoholics compared to non-alcoholics. In another prospective study among patients admitted with community acquired pneumonia, Chalmers *et al*[27] performed multivariate regression analysis and found that a history of alcohol use was an independent risk factor for the development of complicated parapneumonic effusion and empyema, further illustrating that alcoholic subjects have a more complex disease course even with so-called typical infections[27]. Prior to these investigations, Marik[28] undertook a study to identify clinical, microbiological, and prognostic features of patients with septic shock from community-acquired pneumonia. He showed that patients who presented with infections secondary to *Pseudomonas* and *Acinetobacter* had a particularly high mortality greater than 80%. In his study, the only variable that identified patients who developed infections from these virulent organisms was a history of alcohol abuse. In parallel, a prospective study by Bochicchio *et al*[29] implicated alcohol abuse in both the severity and frequency of ventilator-associated pneumonias in trauma patients admitted to the ICU.

There are several mechanisms that predispose individuals with alcohol use disorders to the development of these more severe pneumonias. First, chronic alcohol consumption alters the oropharyngeal flora such that is colonized by more gram-negative organisms[30]. Second, states of inebriation blunt upper airway reflexes and render these individuals more susceptible to aspiration of these more virulent bacteria[31]. Third, experimental

models have demonstrated that chronic alcohol exposure impairs normal host defense mechanisms of the airway such as mucociliary clearance[32]. Finally, pathologic alcohol consumption impairs function of the primary innate immune cell of the lower airways-the alveolar macrophage-in both experimental models and human subjects[33-37]. Taken together, these data highlight the significant alterations in host immunity that predispose alcoholics to the development of lower respiratory tract infections.

ALCOHOL AND SEPSIS

Sepsis is a systemic inflammatory syndrome that occurs as a result of a severe infection. It is a leading cause of death in the hospital and, as a result, is a frequently encountered diagnosis in the ICU. Studies have indicated the incidence is rising and amounts to more than a million cases annually[38]. Importantly, the mortality from sepsis is substantial and increases across the spectrum from SIRS to septic shock, which has a mortality rate close to 50%[39]. The role of alcoholism in increasing the risk and severity of sepsis has been shown in both experimental models and human studies. In 2013, Yoseph *et al*[40] demonstrated that mice that were alcohol-fed for 12 wk have almost double the mortality as water-fed mice when they were subjected to the same septic insult. The authors concluded that alcohol altered intestinal integrity and host immune response, which explained the significant difference in mortality. The prior year, Barros *et al*[41] showed similar findings in rats that were alcohol-fed for 4 wk. Interestingly, when the alcohol-fed rats were separated into two groups based on amount of alcohol consumed, they found that mortality was six fold higher on animals that received higher doses of alcohol compared to those receiving lower amounts of alcohol. In fact, those animals that consumed less alcohol had mortality rates similar to those that did not receive any alcohol at all. These findings are consistent with the idea that in moderation alcohol is not harmful, but excessive consumption is detrimental to health. These authors also demonstrated that cytokine profiles were significantly different in alcohol-fed compared to control-fed rats, indicating that chronic alcohol consumption led to a greater severity of infection. Several other experimental sepsis studies are consistent with the idea that sepsis has worse outcomes in the setting of alcohol abuse[42-44].

Human studies have largely been consistent with the well-established findings in experimental models that chronic alcohol use both predisposes to and worsens outcomes of sepsis. Specifically, when O' Brien *et al*[45] examined over 11000 patients admitted to the ICU of two urban hospitals over a six-year time frame, they found that alcohol dependence was independently associated with sepsis, septic shock, and mortality. Previously, Moss *et al*[46] showed in a prospective epidemiological study of 220 critically ill patients with septic shock that alcohol abuse was a significant risk factor for developing both pulmonary and non-pulmonary organ dysfunction. Taken together, these findings-along with an abundance of supporting experimental studies-highlight that the presence of alcohol use disorders, independent of other patient and illness characteristics, leave individuals vulnerable to infection, which occur with greater severity and more complications, compared to those who do not abuse alcohol.

ALCOHOL AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a form of inflammatory lung injury and hypoxemic respiratory failure with specific clinical and pathological features. It affects about 200000 individuals in the United States annually and carries a mortality risk that ranges anywhere from 20% to 50%[47]. It is a common diagnosis in the ICU and occurs in about 15% to 20% of all patients that require mechanical ventilation. Important risk factors for the development of ARDS include sepsis, traumatic injury, pneumonia, and aspiration. As discussed earlier in this review, each of these risks is significantly increased in the alcoholic patient.

A landmark study in 1996 identified alcohol abuse as an independent risk factor the development of ARDS[48]. In this prospective study, 351 individuals from medical and surgical intensive care were enrolled if they had a previously identified risk factor for ARDS. The incidence of ARDS for the entire population was 29%, but those with a history of alcohol use had almost twice the incidence compared to non-alcoholics (43% *vs* 22%). The risk was even higher among those specific patients with sepsis as their risk factor. In this group, 36% developed ARDS, but alcoholics had an incidence of 52% compared to 20% among non-alcoholics, more than doubling the risk. More importantly, mortality was also significantly higher among alcoholics who developed ARDS. In the aforementioned follow-up study by Moss *et al*[46] performed in patients with septic shock, the risk for developing ARDS was an astounding 70% for those who had a history of alcohol abuse compared with 31% for those who did not have this history.

These initial observations in ARDS patients inspired a great deal of investigation on the mechanisms by which alcohol abuse increases susceptibility to lung injury and ARDS. Animal models have focused on the alveolar epithelium, as leakiness of this barrier system and consequent pulmonary edema is the characteristic finding in ARDS. It is worth mentioning that alcohol abuse plays a complex and compounding role in lung injury, as pneumonia, sepsis, aspiration, and traumatic injury are leading risk factors for the development of ARDS, but alcohol abuse by itself does not cause injury unless it is coupled with an additional insult. However, experimental studies have demonstrated that alcohol abuse primes

the alveolar epithelium for injury by promoting oxidative stress[49], increasing epithelial permeability and protein leak[50], and impairing fluid clearance through alterations in tight junction proteins within the epithelial barrier[51]. These findings at least partially explain why alcoholics, independent of their risk for developing pneumonia and sepsis, are more likely to develop acute lung injury. While we still do not have any approved therapies aimed explicitly at reversing alcohol-induced pulmonary dysfunction, experimental investigations and early human studies show promise that specific nutritional supplements and antioxidants may one day have a role in the treatment of this phenotype[33,52-54].

ALCOHOL AND GASTROINTESTINAL ILLNESS

Chronic alcohol consumption has deleterious effects throughout the entire gastrointestinal system, including the liver, pancreas, esophagus, gastric mucosa, and malabsorption syndromes involving the small intestine. Cirrhosis of the liver is the characteristic organ dysfunction induced by longstanding unhealthy use of alcohol. According the American Liver Foundation, in the United States alcoholism is the number one cause of cirrhosis and chronic liver disease, which combine to represent the twelfth most common cause of death in the country[55]. In addition to morbidity and mortality associated with cirrhosis itself, it is an important comorbidity that portends a worse prognosis in critical illness as well. For instance, Watari *et al*[56] evaluated mortality and prognostic factors in individuals admitted for community-acquired pneumonia and found that liver cirrhosis was one of three factors that was associated with 30 d mortality. Importantly, cirrhosis was the only factor that was a pre-existing condition as the other two predictors-hypotension and hypoxemia-were directly related to the severity of actual infection.

In addition to liver disease, other gastrointestinal illnesses are also affected by alcoholism. For instance, acute pancreatitis is the most common gastrointestinal cause of hospitalization in the United States, with alcohol-induced disease accounting for 30% of cases[57,58]. This finding represents a significant disease burden and many of these cases-and especially severe forms-require ICU admission. Gastrointestinal hemorrhage is also a frequent cause of ICU admission and has a significant disease burden with an annual incidence of about 100 cases per 100000 in the United States[59]. In this study, peptic ulcer disease, mucosal erosions, and esophageal varices made up over 80% of cases, all of which are impacted by alcohol abuse. Alcoholism has been implicated in peptic ulcer disease[60,61], and alcohol-induced gastropathy and gastro-esophageal varices are known complications of alcoholic cirrhosis. While an alcohol abuse history is more predictive of a variceal source of gastrointestinal hemorrhage[62], studies have clearly shown that alcoholics are significantly more likely to have complications such as rebleeding from non-variceal sources of blood loss as well[63,64]. Taken together, these observations illustrate the profound impact that alcohol use disorders have in gastrointestinal disease and critical illness.

ALCOHOL AND TRAUMA

Trauma is one of the leading causes of mortality worldwide, and in the United States is the leading cause of death in those under the age of 35[65]. The Centers for Disease Control and Prevention reports that approximately 50 million individuals receive medical care for trauma annually, and traumatic injury comprises upwards of 30% of all ICU admissions[66]. The role of alcohol use has long been recognized as a contributor to traumatic injury for both unintentional (*i.e.,* fire, fall, motor vehicle accident, drowning) and intentional (*i.e.,* suicide, homicide, assault) injuries and death. It is estimated that 50% of all alcohol-related deaths are due to injury, and alcohol is the third leading cause of preventable death in the United States[67].

Studies examining the effects of alcohol intoxication at the time injury have produced conflicting results. Blondell *et al*[68] evaluated over 1300 patients hospitalized after traumatic injury and found that almost a quarter of them had positive blood alcohol levels, while a similar study by Cornwell *et al*[69] found that more than 50% screened positive for blood alcohol levels. Interestingly, Blondell *et al*[68] found that those that were acutely intoxicated had shorter lengths of stay and lower mortality rates. Other studies have shown worse outcome for acute intoxication[70,71], while some have shown no difference when compared to patients that are not intoxicated[69,72]. There may be several reasons for this conflicting data. First, these studies only examine the effect of acute intoxication on patients with trauma, which may not represent those that have chronic alcohol use disorders. Second, blood alcohol concentrations at the time of presentation may not tell an accurate story of the true alcohol exposure depending on the time that elapsed between exposure and presentation. Third, studies may use different cutoffs for blood alcohol concentration in order to be categorized as "intoxicated". Similarly, in this instance the blood alcohol concentration may not be representative of actual intoxication at the time of injury, and continues to fail in identifying the extent of chronic exposure. One study by Jurkovich *et al*[73] aimed to reconcile these differences by comparing the effect of acute intoxication against those that had an actual history of chronic alcohol abuse. Similar to Blondell's study, they found that acutely intoxicated patients had shorter lengths of stay and better outcomes, but those with behavioral and biochemical evidence of chronic alcohol abuse had a two-fold increase in complication rate. The complications seen in this study were consistent with known risk factors for alcoholics, including pneumonia and other infections. Later studies evaluating trauma and surgical patients are also consistent with findings that individuals with a chronic alcohol abuse experience worse outcomes[74-76].

While the effect of acute intoxication on trauma

outcomes in general may show conflicting results, the effect on burn injury is much more convincing. Specifically, the results of large review on the topic by Howland and Hingson[77] demonstrated that 50% of all people who died in a fire were legally intoxicated. A later study by McGill *et al*[78] compared alcohol users, drug users, and control subjects. They found that both alcohol users and drug users suffered significantly more severe burn injuries compared to control subjects. Mortality among alcohol users was twice that of drug users and six times that of control subjects. This study was interesting in that alcohol users, despite a similar injury pattern, had worse outcomes when compared to other substance abusers. In this study, it may not be completely unbiased to compare outcomes between the alcohol group and the control group since the extent of injury was more severe among the alcoholics. However, a more recent case-control study by Silver *et al*[79] matched burn-injured patients with a positive blood alcohol concentration to those without alcohol exposure. Due to the matching design, these researchers were able to match the control group by age, gender, and extent of injury (*i.e.,* total body surface area involved, inhalation injury, *etc.*). Despite a similar injuries and mechanism, those burn victims with positive blood alcohol concentration had significantly worse short-term and long-term outcomes with higher severity of illness scores, greater fluid requirements, worse acidemia, more than three-fold longer duration of mechanical ventilation, and more than double the ICU length of stay compared to matched controls. Taken together, these studies demonstrate the significant detrimental effects of alcohol exposure on burn injury outcomes.

OTHER CONSIDERATIONS

A history of alcohol abuse also has implications for critically ill patients undergoing surgery[75,80-83]. The accumulated data from these studies suggest that patients with alcohol use disorders who undergo surgery have greater risks for complications, including delayed wound healing, pneumonia, and infection. They also have longer ICU lengths of stay and increased mortality. These observations are analogous to the conclusions derived from studies on non-surgical alcoholic patients and suggest that surgeons may need to be judicious about considering major elective surgery in these susceptible patients.

While the focus of this review has been on known complications of alcoholism during critical illness, there is a potential for alcohol use disorders to play a role in previously unstudied associations. For instance, critical illness polyneuropathy (CIP) and myopathy (CIM) are significant complications of critical illness. Sepsis, systemic inflammatory response syndrome, multiple organ failure, and prolonged critical illness are crucial risks for developing CIP and CIM[84,85], and intriguingly these same factors are known threats that alcoholics face. Further, alcoholics are clinically prone to both myopathies and neuropathies[86,87]. While the risk for CIP and CIM with alcohol abuse has not been formally established, this may have specific implications for management. Experimental studies show that oxidative stress plays a role in alcoholic myopathy, and reversing this oxidant stress is able to attenuate the myopathy[88-90].

CONCLUSION

Alcohol use and abuse are commonplace in society and present a major burden for our healthcare system. Alcohol use disorders not only predispose individuals to develop critical illness, but also leave these vulnerable patients with longer ICU stays, more complications, and ultimately greater mortality. Despite the pervasiveness of alcohol use disorders in hospitalized patients, and especially among those admitted to the ICU, recognition of these disorders remains poor and no guidelines exist on the best way to screen for alcohol dependence and risk for withdrawal syndromes. While there may be several explanations for why alcohol use disorders are not consistently identified in the ICU setting, critical care providers should employ any and all methods to better evaluate their patients for these conditions and their potential implications. While there are currently limited therapeutic options aimed directly at combating the alcohol-induced organ dysfunction experienced by critically ill patients, earlier identification will allow for more timely intervention and an opportunity to assist these individuals to confront their addiction. Hopefully, this approach will lead to improved outcomes as we await newer treatments to benefit this susceptible patient population.

REFERENCES

1 **Lieber CS**. Medical disorders of alcoholism. *N Engl J Med* 1995; **333**: 1058-1065 [PMID: 7675050 DOI: 10.1056/NEJM199510193331607]

2 **Substance Abuse and Mental Health Services Administration**. Results from the 2008 National Survey on Drug Use and Health: National Findings. Rockville, MD: HHS Publication, 2009

3 **Hasin DS**, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007; **64**: 830-842 [PMID: 17606817 DOI: 10.1001/archpsyc.64.7.830]

4 **Bouchery EE**, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the U.S., 2006. *Am J Prev Med* 2011; **41**: 516-524 [PMID: 22011424 DOI: 10.1016/j.amepre.2011.06.045]

5 **Doering-Silveira J**, Fidalgo TM, Nascimento CL, Alves JB, Seito CL, Saita MC, Belluzzi LO, Silva LC, Silveira D, Rosa-Oliveira L. Assessing alcohol dependence in hospitalized patients. *Int J Environ Res Public Health* 2014; **11**: 5783-5791 [PMID: 24879488 DOI: 10.3390/ijerph110605783]

6 **Gerke P**, Hapke U, Rumpf HJ, John U. Alcohol-related diseases in general hospital patients. *Alcohol Alcohol* 1997; **32**: 179-184 [PMID: 9105512]

7 **Smothers BA**, Yahr HT, Ruhl CE. Detection of alcohol use disorders in general hospital admissions in the United States. *Arch Intern Med* 2004; **164**: 749-756 [PMID: 15078644 DOI: 10.1001/archinte.164.7.749]

8 **Department of Health and Human Services**, Department of

Agriculture. Dietary Guidelines Advisory Committee. Dietary guidelines for Americans. 7th ed. Washington, DC: GPO, 2010
9 **American Psychiatric Association**. American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington DC, 2013
10 **American Psychiatric Association**. Diagnostic criteria from DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000
11 **Uusaro A**, Parviainen I, Tenhunen JJ, Ruokonen E. The proportion of intensive care unit admissions related to alcohol use: a prospective cohort study. *Acta Anaesthesiol Scand* 2005; **49**: 1236-1240 [PMID: 16146458 DOI: 10.1111/j.1399-6576.2005.00839.x]
12 **de Wit M**, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. Alcohol-use disorders in the critically ill patient. *Chest* 2010; **138**: 994-1003 [PMID: 20923804 DOI: 10.1378/chest.09-1425]
13 **Spies CD**, Dubisz N, Neumann T, Blum S, Müller C, Rommelspacher H, Brummer G, Specht M, Sanft C, Hannemann L, Striebel HW, Schaffartzik W. Therapy of alcohol withdrawal syndrome in intensive care unit patients following trauma: results of a prospective, randomized trial. *Crit Care Med* 1996; **24**: 414-422 [PMID: 8625628]
14 **Chen CH**, Chen WJ, Cheng AT. Prevalence and identification of alcohol use disorders among nonpsychiatric inpatients in one general hospital. *Gen Hosp Psychiatry* 2004; **26**: 219-225 [PMID: 15121350 DOI: 10.1016/j.genhosppsych.2004.01.001]
15 **McPeake J**, Bateson M, O'Neill A, Kinsella J. Assessment and management of alcohol-related admissions to UK intensive care units. *Nurs Crit Care* 2013; **18**: 187-192 [PMID: 23782112 DOI: 10.1111/nicc.12006]
16 **Francis J**. Delirium in older patients. *J Am Geriatr Soc* 1992; **40**: 829-838 [PMID: 1634729]
17 **Francis J**, Kapoor WN. Prognosis after hospital discharge of older medical patients with delirium. *J Am Geriatr Soc* 1992; **40**: 601-606 [PMID: 1587979]
18 **McNicoll L**, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc* 2003; **51**: 591-598 [PMID: 12752832]
19 **Ely EW**, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard R, Inouye SK. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med* 2001; **27**: 1892-1900 [PMID: 11797025 DOI: 10.1007/s00134-001-1132-2]
20 **Mehta S**, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, Herridge M, Steinberg M, Granton J, Ferguson N, Tanios M, Dodek P, Fowler R, Burns K, Jacka M, Olafson K, Mallick R, Reynolds S, Keenan S, Burry L. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med* 2015; **43**: 557-566 [PMID: 25493968 DOI: 10.1097/CCM.0000000000000727]
21 **Huai J**, Ye X. A meta-analysis of critically ill patients reveals several potential risk factors for delirium. *Gen Hosp Psychiatry* 2014; **36**: 488-496 [PMID: 24950918 DOI: 10.1016/j.genhosppsych.2014.05.002]
22 **Foy A**, Kay J, Taylor A. The course of alcohol withdrawal in a general hospital. *QJM* 1997; **90**: 253-261 [PMID: 9307759]
23 **Awissi DK**, Lebrun G, Coursin DB, Riker RR, Skrobik Y. Alcohol withdrawal and delirium tremens in the critically ill: a systematic review and commentary. *Intensive Care Med* 2013; **39**: 16-30 [PMID: 23184039 DOI: 10.1007/s00134-012-2758-y]
24 **Erwin WE**, Williams DB, Speir WA. Delirium tremens. *South Med J* 1998; **91**: 425-432 [PMID: 9598848]
25 **Osler W**. The principles and practice of medicine: designed for the use of practitioners and students of medicine. 3th ed. New York: Appleton and Company, 1899
26 **de Roux A**, Cavalcanti M, Marcos MA, Garcia E, Ewig S, Mensa J, Torres A. Impact of alcohol abuse in the etiology and severity of community-acquired pneumonia. *Chest* 2006; **129**: 1219-1225 [PMID: 16685012 DOI: 10.1378/chest.129.5.1219]
27 **Chalmers JD**, Singanayagam A, Murray MP, Scally C, Fawzi A, Hill AT. Risk factors for complicated parapneumonic effusion and empyema on presentation to hospital with community-acquired pneumonia. *Thorax* 2009; **64**: 592-597 [PMID: 19131449 DOI: 10.1136/thx.2008.105080]
28 **Marik PE**. The clinical features of severe community-acquired pneumonia presenting as septic shock. Norasept II Study Investigators. *J Crit Care* 2000; **15**: 85-90 [PMID: 11011820]
29 **Bochicchio GV**, Joshi M, Bochicchio K, Tracy K, Scalea TM. A time-dependent analysis of intensive care unit pneumonia in trauma patients. *J Trauma* 2004; **56**: 296-301; discussion 301-303 [PMID: 14960971 DOI: 10.1097/01.ta.0000109857.22312.df]
30 **Fuxench-López Z**, Ramírez-Ronda CH. Pharyngeal flora in ambulatory alcoholic patients: prevalence of gram-negative bacilli. *Arch Intern Med* 1978; **138**: 1815-1816 [PMID: 363086]
31 **Joshi PC**, Guidot DM. The alcoholic lung: epidemiology, pathophysiology, and potential therapies. *Am J Physiol Lung Cell Mol Physiol* 2007; **292**: L813-L823 [PMID: 17220370 DOI: 10.1152/ajplung.00348.2006]
32 **Sisson JH**, Pavlik JA, Wyatt TA. Alcohol stimulates ciliary motility of isolated airway axonemes through a nitric oxide, cyclase, and cyclic nucleotide-dependent kinase mechanism. *Alcohol Clin Exp Res* 2009; **33**: 610-616 [PMID: 19183138 DOI: 10.1111/j.1530-0277.2008.00875.x]
33 **Mehta AJ**, Yeligar SM, Elon L, Brown LA, Guidot DM. Alcoholism causes alveolar macrophage zinc deficiency and immune dysfunction. *Am J Respir Crit Care Med* 2013; **188**: 716-723 [PMID: 23805851 DOI: 10.1164/rccm.201301-0061OC]
34 **Brown LA**, Ping XD, Harris FL, Gauthier TW. Glutathione availability modulates alveolar macrophage function in the chronic ethanol-fed rat. *Am J Physiol Lung Cell Mol Physiol* 2007; **292**: L824-L832 [PMID: 17122355 DOI: 10.1152/ajplung.00346.2006]
35 **Burnham EL**, Phang TL, House R, Vandivier RW, Moss M, Gaydos J. Alveolar macrophage gene expression is altered in the setting of alcohol use disorders. *Alcohol Clin Exp Res* 2011; **35**: 284-294 [PMID: 21121937 DOI: 10.1111/j.1530-0277.2010.01344.x]
36 **D'Souza NB**, Nelson S, Summer WR, Deaciuc IV. Alcohol modulates alveolar macrophage tumor necrosis factor-alpha, superoxide anion, and nitric oxide secretion in the rat. *Alcohol Clin Exp Res* 1996; **20**: 156-163 [PMID: 8651446]
37 **Gauthier TW**, Ping XD, Harris FL, Wong M, Elbahesh H, Brown LA. Fetal alcohol exposure impairs alveolar macrophage function via decreased glutathione availability. *Pediatr Res* 2005; **57**: 76-81 [PMID: 15531743 DOI: 10.1203/01.PDR.0000149108.44152.D3]
38 **Walkey AJ**, Wiener RS, Lindenauer PK. Utilization patterns and outcomes associated with central venous catheter in septic shock: a population-based study. *Crit Care Med* 2013; **41**: 1450-1457 [PMID: 23507718 DOI: 10.1097/CCM.0b013e31827caa89]
39 **Rangel-Frausto MS**, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995; **273**: 117-123 [PMID: 7799491]
40 **Yoseph BP**, Breed E, Overgaard CE, Ward CJ, Liang Z, Wagener ME, Lexcen DR, Lusczek ER, Beilman GJ, Burd EM, Farris AB, Guidot DM, Koval M, Ford ML, Coopersmith CM. Chronic alcohol ingestion increases mortality and organ injury in a murine model of septic peritonitis. *PLoS One* 2013; **8**: e62792 [PMID: 23717394 DOI: 10.1371/journal.pone.0062792]
41 **Barros FR**, Castro-Faria-Neto HC, Castro CL, Aguiar Nemer AS, Rocha EM, Silva Fonseca VA. Effects of chronic ethanol consumption in experimental sepsis. *Alcohol Alcohol* 2012; **47**: 677-682 [PMID: 22805349 DOI: 10.1093/alcalc/ags081]
42 **Pruett SB**, Fan R, Cheng B, Glover M, Tan W, Deng X. Innate immunity and inflammation in sepsis: mechanisms of suppressed host resistance in mice treated with ethanol in a binge-drinking model. *Toxicol Sci* 2010; **117**: 314-324 [PMID: 20624996 DOI: 10.1093/toxsci/kfq215]
43 **Allameh A**, Razavi-Azarkhiavi K, Mohsenifar A, Jamali-Zavarei M. Effect of acute ethanol treatment on biochemical and histopathological factors in rat liver in an experimental sepsis

model. *Pathol Res Pract* 2012; **208**: 331-337 [PMID: 22455867 DOI: 10.1016/j.prp.2012.02.006]
44 **Morais PH**, Ribeiro VL, Caetano de Farias IE, Almeida Silva LE, Carneiro FP, Russomano Veiga JP, Batista de Sousa J. Alcohol acute intoxication before sepsis impairs the wound healing of intestinal anastomosis: rat model of the abdominal trauma patient. *World J Emerg Surg* 2012; **7** Suppl 1: S10 [PMID: 23566566 DOI: 10.1186/1749-7922-7-S1-S10]
45 **O'Brien JM**, Lu B, Ali NA, Martin GS, Aberegg SK, Marsh CB, Lemeshow S, Douglas IS. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. *Crit Care Med* 2007; **35**: 345-350 [PMID: 17205003 DOI: 10.1097/01.CCM.0000254340.91644.B2]
46 **Moss M**, Parsons PE, Steinberg KP, Hudson LD, Guidot DM, Burnham EL, Eaton S, Cotsonis GA. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. *Crit Care Med* 2003; **31**: 869-877 [PMID: 12626999 DOI: 10.1097/01.CCM.0000055389.64497.11]
47 **Rubenfeld GD**, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; **353**: 1685-1693 [PMID: 16236739 DOI: 10.1056/NEJMoa050333]
48 **Moss M**, Bucher B, Moore FA, Moore EE, Parsons PE. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA* 1996; **275**: 50-54 [PMID: 8531287]
49 **Guidot D**, Moss M, Holguin F, Lois M, Brown L. Ethanol ingestion impairs alveolar epithelial glutathione homeostasis and function, and predisposes to endotoxin-mediated acute lung injury. *Chest* 1999; **116**: 82S [PMID: 10424603]
50 **Guidot DM**, Modelska K, Lois M, Jain L, Moss IM, Pittet JF, Brown LA. Ethanol ingestion via glutathione depletion impairs alveolar epithelial barrier function in rats. *Am J Physiol Lung Cell Mol Physiol* 2000; **279**: L127-L135 [PMID: 10893211]
51 **Overgaard CE**, Mitchell LA, Koval M. Roles for claudins in alveolar epithelial barrier function. *Ann N Y Acad Sci* 2012; **1257**: 167-174 [PMID: 22671603 DOI: 10.1111/j.1749-6632.2012.06545.x]
52 **Joshi PC**, Mehta A, Jabber WS, Fan X, Guidot DM. Zinc deficiency mediates alcohol-induced alveolar epithelial and macrophage dysfunction in rats. *Am J Respir Cell Mol Biol* 2009; **41**: 207-216 [PMID: 19109243 DOI: 10.1165/rcmb.2008-0209OC]
53 **Mehta AJ**, Joshi PC, Fan X, Brown LA, Ritzenthaler JD, Roman J, Guidot DM. Zinc supplementation restores PU.1 and Nrf2 nuclear binding in alveolar macrophages and improves redox balance and bacterial clearance in the lungs of alcohol-fed rats. *Alcohol Clin Exp Res* 2011; **35**: 1519-1528 [PMID: 21447000 DOI: 10.1111/j.1530-0277.2011.01488.x]
54 **Brown LA**, Harris FL, Bechara R, Guidot DM. Effect of chronic ethanol ingestion on alveolar type II cell: glutathione and inflammatory mediator-induced apoptosis. *Alcohol Clin Exp Res* 2001; **25**: 1078-1085 [PMID: 11505036]
55 **Murphy SL**, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep* 2013; **61**: 1-117 [PMID: 24979972]
56 **Watari M**, Ohe M, Kunimoto E, Tsukamoto R, Komagata H. [Mortality and prognostic factors in patients with community-acquired pneumonia: an analysis of 231 cases]. *Nihon Kokyuki Gakkai Zasshi* 2000; **38**: 509-517 [PMID: 11019564]
57 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187.e1-3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]
58 **Yang AL**, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med* 2008; **168**: 649-656 [PMID: 18362258 DOI: 10.1001/archinte.168.6.649]
59 **Longstreth GF**. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol* 1995; **90**: 206-210 [PMID: 7847286]
60 **Goodwin RD**, Keyes KM, Stein MB, Talley NJ. Peptic ulcer and mental disorders among adults in the community: the role of nicotine and alcohol use disorders. *Psychosom Med* 2009; **71**: 463-468 [PMID: 19443694 DOI: 10.1097/PSY.0b013e3181988137]
61 **Ko JK**, Cho CH. Alcohol drinking and cigarette smoking: a "partner" for gastric ulceration. *Zhonghua Yixue Zazhi* (Taipei) 2000; **63**: 845-854 [PMID: 11195134]
62 **Alharbi A**, Almadi M, Barkun A, Martel M. Predictors of a variceal source among patients presenting with upper gastrointestinal bleeding. *Can J Gastroenterol* 2012; **26**: 187-192 [PMID: 22506257]
63 **Bang CS**, Lee YS, Lee YH, Sung H, Park HJ, Kim HS, Kim JB, Baik GH, Kim YS, Yoon JH, Kim DJ, Suk KT. Characteristics of nonvariceal upper gastrointestinal hemorrhage in patients with chronic kidney disease. *World J Gastroenterol* 2013; **19**: 7719-7725 [PMID: 24282360 DOI: 10.3748/wjg.v19.i43.7719]
64 **Wang YU**, Yuan C, Liu X. Characteristics of gastrointestinal hemorrhage associated with pancreatic cancer: A retrospective review of 246 cases. *Mol Clin Oncol* 2015; **3**: 902-908 [PMID: 26171204 DOI: 10.3892/mco.2015.563]
65 **Feliciano DV**, Mattox KL, Moore EE. Trauma, 6th ed. New York: McGraw-Hill Medical, 2008
66 **Mackenzie EJ**, Rivara FP, Jurkovich GJ, Nathens AB, Frey KP, Egleston BL, Salkever DS, Weir S, Scharfstein DO. The National Study on Costs and Outcomes of Trauma. *J Trauma* 2007; **63**: S54-S67; discussion S81-S86 [PMID: 18091213 DOI: 10.1097/TA.0b013e31815acb09]
67 **Schermer CR**. Alcohol and injury prevention. *J Trauma* 2006; **60**: 447-451 [PMID: 16508516 DOI: 10.1097/01.ta.0000196956.49282.91]
68 **Blondell RD**, Looney SW, Hottman LM, Boaz PW. Characteristics of intoxicated trauma patients. *J Addict Dis* 2002; **21**: 1-12 [PMID: 12296497 DOI: 10.1300/J069v21n04_01]
69 **Cornwell EE**, Belzberg H, Velmahos G, Chan LS, Demetriades D, Stewart BM, Oder DB, Kahaku D, Chan D, Asensio JA, Berne TV. The prevalence and effect of alcohol and drug abuse on cohort-matched critically injured patients. *Am Surg* 1998; **64**: 461-465 [PMID: 9585786]
70 **Fabbri A**, Marchesini G, Morselli-Labate AM, Rossi F, Cicognani A, Dente M, Iervese T, Ruggeri S, Mengozzi U, Vandelli A. Blood alcohol concentration and management of road trauma patients in the emergency department. *J Trauma* 2001; **50**: 521-528 [PMID: 11265033]
71 **Cunningham RM**, Maio RF, Hill EM, Zink BJ. The effects of alcohol on head injury in the motor vehicle crash victim. *Alcohol Alcohol* 2002; **37**: 236-240 [PMID: 12003910]
72 **Madan AK**, Yu K, Beech DJ. Alcohol and drug use in victims of life-threatening trauma. *J Trauma* 1999; **47**: 568-571 [PMID: 10498317]
73 **Jurkovich GJ**, Rivara FP, Gurney JG, Fligner C, Ries R, Mueller BA, Copass M. The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. *JAMA* 1993; **270**: 51-56 [PMID: 8510296]
74 **Spies CD**, Kissner M, Neumann T, Blum S, Voigt C, Funk T, Runkel N, Pragst F. Elevated carbohydrate-deficient transferrin predicts prolonged intensive care unit stay in traumatized men. *Alcohol Alcohol* 1998; **33**: 661-669 [PMID: 9872357]
75 **Spies CD**, Nordmann A, Brummer G, Marks C, Conrad C, Berger G, Runkel N, Neumann T, Müller C, Rommelspacher H, Specht M, Hannemann L, Striebel HW, Schaffartzik W. Intensive care unit stay is prolonged in chronic alcoholic men following tumor resection of the upper digestive tract. *Acta Anaesthesiol Scand* 1996; **40**: 649-656 [PMID: 8836256]
76 **Spies CD**, Neuner B, Neumann T, Blum S, Müller C, Rommelspacher H, Rieger A, Sanft C, Specht M, Hannemann L, Striebel HW, Schaffartzik W. Intercurrent complications in chronic alcoholic men admitted to the intensive care unit following trauma. *Intensive Care Med* 1996; **22**: 286-293 [PMID: 8708164]
77 **Howland J**, Hingson R. Alcohol as a risk factor for injuries or

death due to fires and burns: review of the literature. *Public Health Rep* 1987; **102**: 475-483 [PMID: 3116577]
78 **McGill V**, Kowal-Vern A, Fisher SG, Kahn S, Gamelli RL. The impact of substance use on mortality and morbidity from thermal injury. *J Trauma* 1995; **38**: 931-934 [PMID: 7602638]
79 **Silver GM**, Albright JM, Schermer CR, Halerz M, Conrad P, Ackerman PD, Lau L, Emanuele MA, Kovacs EJ, Gamelli RL. Adverse clinical outcomes associated with elevated blood alcohol levels at the time of burn injury. *J Burn Care Res* 2008; **29**: 784-789 [PMID: 18695611 DOI: 10.1097/BCR.0b013e31818481bc]
80 **Delgado-Rodríguez M**, Gómez-Ortega A, Mariscal-Ortiz M, Palma-Pérez S, Sillero-Arenas M. Alcohol drinking as a predictor of intensive care and hospital mortality in general surgery: a prospective study. *Addiction* 2003; **98**: 611-616 [PMID: 12751978]
81 **Kork F**, Neumann T, Spies C. Perioperative management of patients with alcohol, tobacco and drug dependency. *Curr Opin Anaesthesiol* 2010; **23**: 384-390 [PMID: 20404723 DOI: 10.1097/ACO.0b013e3283391f79]
82 **Lau A**, von Dossow V, Sander M, MacGuill M, Lanzke N, Spies C. Alcohol use disorder and perioperative immune dysfunction. *Anesth Analg* 2009; **108**: 916-920 [PMID: 19224804 DOI: 10.1213/ane.0b013e318193fd89]
83 **Spies C**, Tønnesen H, Andreasson S, Helander A, Conigrave K. Perioperative morbidity and mortality in chronic alcoholic patients. *Alcohol Clin Exp Res* 2001; **25**: 164S-170S [PMID: 11391067]
84 **Hermans G**, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. *Crit Care* 2008; **12**: 238 [PMID: 19040777 DOI: 10.1186/cc7100]
85 **Witt NJ**, Zochodne DW, Bolton CF, Grand'Maison F, Wells G, Young GB, Sibbald WJ. Peripheral nerve function in sepsis and multiple organ failure. *Chest* 1991; **99**: 176-184 [PMID: 1845860]
86 **Chopra K**, Tiwari V. Alcoholic neuropathy: possible mechanisms and future treatment possibilities. *Br J Clin Pharmacol* 2012; **73**: 348-362 [PMID: 21988193 DOI: 10.1111/j.1365-2125.2011.04111.x]
87 **Lang CH**, Kimball SR, Frost RA, Vary TC. Alcohol myopathy: impairment of protein synthesis and translation initiation. *Int J Biochem Cell Biol* 2001; **33**: 457-473 [PMID: 11331201]
88 **Otis JS**, Guidot DM. Procysteine stimulates expression of key anabolic factors and reduces plantaris atrophy in alcohol-fed rats. *Alcohol Clin Exp Res* 2009; **33**: 1450-1459 [PMID: 19426167 DOI: 10.1111/j.1530-0277.2009.00975.x]
89 **Clary CR**, Guidot DM, Bratina MA, Otis JS. Chronic alcohol ingestion exacerbates skeletal muscle myopathy in HIV-1 transgenic rats. *AIDS Res Ther* 2011; **8**: 30 [PMID: 21846370 DOI: 10.1186/1742-6405-8-30]
90 **Otis JS**, Brown LA, Guidot DM. Oxidant-induced atrogin-1 and transforming growth factor-beta1 precede alcohol-related myopathy in rats. *Muscle Nerve* 2007; **36**: 842-848 [PMID: 17721978 DOI: 10.1002/mus.20883]

P- Reviewer: Adrian I **S- Editor**: Qiu S **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.36

World J Crit Care Med 2016 February 4; 5(1): 36-46
ISSN 2220-3141 (online)

REVIEW

Neuroprotective measures in children with traumatic brain injury

Shruti Agrawal, Ricardo Garcia Branco

Shruti Agrawal, Ricardo Garcia Branco, Department of Paediatric Intensive Care, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, United Kingdom

Author contributions: Agrawal S did the research and drafted the article; Branco RG made critical revisions related to important intellectual content of the manuscript.

Conflict-of-interest statement: Agrawal S and Branco RG have no conflicts of interest to declare for this article.

Correspondence to: Shruti Agrawal, MD, FRCPCH, FFICM, Department of Paediatric Intensive Care, Cambridge University Hospitals NHS Foundation Trust, Box 7, Addenbrookes Hospital, Hills Road, Cambridge CB2 0QQ, United Kingdom. shruti.agrawal@addenbrookes.nhs.uk
Telephone: +44-1223-348066
Fax: +44-1223-586794

Received: September 29, 2015
Peer-review started: October 2, 2015
First decision: October 27, 2015
Revised: December 1, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016
Published online: February 4, 2016

Abstract

Traumatic brain injury (TBI) is a major cause of death and disability in children. Severe TBI is a leading cause of death and often leads to life changing disabilities in survivors. The modern management of severe TBI in children on intensive care unit focuses on preventing secondary brain injury to improve outcome. Standard neuroprotective measures are based on management of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) to optimize the cerebral blood flow and oxygenation, with the intention to avoid and minimise secondary brain injury. In this article, we review the current trends in management of severe TBI in children, detailing the general and specific measures followed to achieve the desired ICP and CPP goals. We discuss the often limited evidence for these therapeutic interventions in children, extrapolation of data from adults, and current recommendation from paediatric guidelines. We also review the recent advances in understanding the intracranial physiology and neuroprotective therapies, the current research focus on advanced and multi-modal neuromonitoring, and potential new therapeutic and prognostic targets.

Key words: Paediatrics; Intracranial pressure; Traumatic brain injury; Neuroprotection; Paediatric critical care; Advanced neuromonitoring

Core tip: Paediatric traumatic brain injury (TBI) causes significant morbidity and mortality. The modern management of severe TBI in children focuses on preventing secondary brain injury to improve outcome. In this article, we review the current management of severe TBI in children. We also review the recent advances in understanding intracranial physiology and neuroprotective therapies, advanced and multi-modal neuromonitoring, and potential new therapeutic and prognostic targets.

Agrawal S, Branco RG. Neuroprotective measures in children with traumatic brain injury. *World J Crit Care Med* 2016; 5(1): 36-46 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/36.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.36

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in children and young adults worldwide. It is considered a "silent epidemic" because the general public is mostly unaware of the scale of the problem[1]. In the United States, it is estimated that around 1.7 million people sustain TBI each year, and in Europe 235 per 100000 people are admitted to hospital following a TBI[2,3]. Data from many parts of the world consistently show peak incidence rates in children, young adults and elderly people.

TBI occurs when head suffers the influence of an external mechanical force. This force can displace brain inside the skull and induce injury against the meningeal membrane or the cranium. Acceleration and deceleration forces can also disrupt nervous tissue and blood vessels of the brain. All grades of injury can occur, ranging from mild to severe TBI with cerebral oedema or large collections of blood. Severe TBI, defined as a post resuscitation Glasgow coma scale (GCS) of less than 9[4], is associated with highest rates of mortality and significant morbidity in survivors often causing life changing disability and cognitive function loss[5].

The mechanism of injury in TBI comprises of primary and secondary injuries. The primary injury is the direct consequence of the initial physical insult. It comprises irreversible cell damage that is the main determinant of clinical outcome. In the secondary injury, inflammatory and neurotoxic responses triggered by the primary injury induce oedema, hypoperfusion, hypoxia and ischaemia[6-8]. These changes often lead to raised intracranial pressure (ICP), temperature dysregulation, loss of autoregulation and seizures[9]. Much of these secondary injuries may be amenable to intervention, and left untreated can significantly increase morbidity and mortality associated with TBI[6].

Raised ICP plays a key role in secondary brain injury[9]. Skull is a rigid fixed volume compartment; the three elements within it namely, the brain parenchyma, blood and cerebro-spinal fluid (CSF) are relatively incompressible and changes in the volume of one leads to compression of the other[10]. Beyond the limits of compensation, the pressure rises sharply, this can severely impact the cerebral blood flow (CBF). The secondary insults can also arise from systemic factors, hypoxia and hypotension post head injury being the key determinants for outcome[7,11].

Early stabilisation post TBI includes rapid assessment for life threatening injuries followed by secondary survey according to ATLS/APLS guidelines[12,13]. After the initial resuscitation to ensure adequate airway, ventilation and haemodynamic stability, early neuro-imaging is required to look for intra-cranial pathologies requiring surgical intervention and neuroprotection[14]. There is evidence to support multi-disciplinary input and protocolized management for improved outcomes from head injury[15]. All children with moderate to severe traumatic brain injury should ideally be managed in centres with expertise and experience in managing such patients. The contemporary post-injury resuscitation and management focuses on prevention and mitigation of secondary insults[7,14]. This review will focus on the neuroprotective measures to decrease the damage caused by secondary brain injury in children with TBI requiring intensive care treatment.

GENERAL INTENSIVE CARE MEASURES

Airway control and ventilation

All children with severe TBI and those with deteriorating GCS need definitive airway management with endotracheal intubation. As paediatric definitive airway needs specialist skills and experience, pre-hospital intubation at the scene for children with TBI is controversial[16]. However, early airway control is recommended to avoid hypoxemia, hypercarbia and aspiration[17]. The adequacy of oxygenation and ventilation should be measured continuously with pulse oximetry and end-tidal carbon dioxide (CO_2) monitoring respectively and serial blood gas measurements. In children with TBI requiring ventilation, arterial PaO_2 should be maintained above 11 kPa (saturations > 90%) and $PaCO_2$ between 4.5-5 kPa. Although there are no randomised controlled trials (RCT) to determine the exact values for PaO_2 in TBI, the damaging effects of hypoxia[17,18] and to a lesser extent hyperoxia[19] are well known. Similarly, the effect of CO_2 on cerebrovascular reactivity has been widely studied[19-21]. Hypercapnea causes vasodilatation leading to cerebral hyperaemia and hypocapnea causes ischemia by cerebral vasoconstriction[9,21,22].

Circulatory support

Hypotension (defined as systolic blood pressure below the fifth percentile for age) or shock any time after injury can have major implications for clinical outcome and should be actively prevented and aggressively treated with fluid boluses and vasoactive agents[16]. Isotonic saline is recommended for fluid resuscitation and maintenance. In the presence of hypotension, patient also needs careful evaluation for extracranial injuries as the potential source of blood loss[23,24]. It is important to consider adrenocorticotropic hormone (ACTH) deficiency in patients with refractory hypotension; TBI induced pituitary dysfunction has been reported in nearly one quarter of children with TBI in the acute phase[25,26]. As the primary injury often impairs cerebral autoregulation, the cerebral perfusion may become directly dependent on the mean arterial pressure. Management of blood pressure in the intensive care is one of the cornerstones of the management of severe TBI[14]. While hypotension can potentially cause brain ischemia, hypertension can exacerbate vasogenic oedema in the cerebral parenchyma[27] and requires careful titration of blood pressure based on various parameters studied (discussed in details under specific interventions).

Sedation, analgesia and neuromuscular blockade

Although there are no RCTs studying the effect of sedation on outcome, it's well known that any noxious stimulus

increases ICP[28] and cerebral metabolic demand for oxygen[29]. Appropriate sedation and analgesia reduces anxiety and pain, facilitates ventilation and general intensive care management, and helps reduce the cerebral oxygen demand, thereby reducing the risk of secondary brain injury[30]. In children, a combination of benzodiazepines and opioids is most often used. This combination can cause hypotension, so careful titration to the desired effect with continuous monitoring and management of blood pressure is essential to minimize risks of cerebral ischemia. Propofol, often used in adults, has restricted licence status in children, therefore, is only used in exceptional circumstances.

Neuromuscular paralysis can help reduce airway and intrathoracic pressure which improves the cerebral venous return. It can prevent shivering and posturing, and the lack of skeletal muscle movement also helps to reduce cerebral metabolic demand[30]. The main disadvantage of neuromuscular blockade is masking of clinical seizures which should then ideally be monitored by continuous electroencephalograph (EEG). Its continuous use can also induce myopathy, increase length of ventilation, and cause nosocomial pneumonia and cardiovascular side effects[31]. However, judicious neuromuscular blockage use in children with severe TBI can minimize complications[32]. Therefore, neuromuscular blockade is recommended as part of the first tier management of children with severe TBI[14].

Fluids and nutrition

There is no single best fluid for children with traumatic brain injury, but isotonic crystalloids are widely used and have good scientific basis. Normal saline or lactated ringer's solution should be the standard resuscitation fluid until further studies show a clear benefit from other therapies. Use of colloids is not routinely recommended and evidence suggests that use of albumin may have deleterious effects[33]. Fluid restriction is no longer recommended.

Nutritional support is required for tissue repair, wound healing and optimal organ function. Due to lack of evidence, there is no specific recommendation for the nutrition regimen. Adult data supports early introduction of feeds after haemodynamic stability aiming for full feeds, either enteral or parenteral, by the end of first week[34,35]. Hyperglycaemia frequently occurs associated with the stress response to injury; therefore glucose is not routinely added to maintenance fluids in early phase of recovery regardless of the child's age. Hyperglycaemia has been linked to poor neurological outcome in TBI[36-38] but the optimal glucose target has not been defined. Use of insulin to achieve tight glycaemic control may result in a net reduction in CSF microdialysis glucose and an increase in microdialysis glutamate and lactate pyruvate ratio (LPR) without conveying a functional outcome advantage[39]. Tight glycaemic control has also been associated with reduced cerebral extracellular glucose availability and increased prevalence of brain energy crisis, which in turn correlates with increased mortality[40]. Currently we recommend prevention of severe hyperglycaemia, keeping blood glucose levels below 180 mg/dL (10 mmol/L).

General care

Children should be nursed in neutral head position and head-end elevation by 15°-30° to improve cerebral venous drainage[41,42]. Good nursing care, with regular turning, eye care and physiotherapy are important. Stress ulcer prophylaxis and laxatives are used as per the child's requirements. Although evidence shows higher incidence of deep vein thrombosis (DVT) with increasing severity of trauma and increasing age in children[43], there are no universal recommendations for regular thromboprophylaxis in this age group. One study supports thromboprophylaxis to prevent DVT in paediatric trauma patients[44]. In our setting, compression stockings are routinely used in fully sedated and paralysed children with severe TBI, but the chemical prophylaxis is restricted to older children and is discussed on case by case basis.

SPECIFIC INTERVENTIONS

Intracranial pressure monitoring

The ICP can rise after TBI from either mass effect (haematoma) or cerebral oedema secondary to the injury. There is a direct association between raised ICP and poor clinical outcomes, and sustained raised ICP is an independent predictor of poor outcome following TBI[45-47]. While majority of evidence supports aggressive management of raised ICP[47-49], recent adult RCT failed to identify any benefit associated with ICP monitoring[50]. The results of this study[50] however need to be interpreted in the context of population studied and may not be generalizable to all TBI victims[51]. The lack of controlled trials for ICP monitoring has limited the recommendation (level Ⅲ) in the most up-to-date guidelines[14,52] although ICP monitoring remains the integral part in the management of patients with severe TBI in most centres.

There are various different methods for ICP monitoring using either fluid filled catheters or pressure microtransducers. Interventricular catheters are considered to be the gold standard for measuring ICP and also allow CSF drainage if ICP is high. However, there are practical limitations to their use including infection and technical difficulty in insertion in children with small ventricles[53,54]. Pressure microtransducers can reliably measure pressure from brain parenchyma (intraparenchymal) as well as epidural or subarachnoid spaces. Intraparenchymal probes are often preferred because they are easy to insert and have very low infection risk. However, they may not reflect the true ICP if there are pressure gradients within the cranium, and although the zero drift is minimal, they cannot be recalibrated once inserted[53].

The threshold for treating ICP in children has been extrapolated from adult guidelines[52]. There is some suggestion that the treatment thresholds for younger children and infants need to be different as the normal

values of mean ABP and hence Cerebral perfusion pressure (CPP) are lower in children[55]. Keeping the ICP < 20 mmHg is the standard part of management of severe TBI on PICU[14].

Our current local protocol uses an age related threshold for ICP in children (Figure 1). If the ICP stays above the target, we first optimise sedation and the ventilation targets. If it still stays up, we use hyperosmolar therapy and consider repeat neuroimaging. If the scan doesn't show any surgically correctible lesion (haematoma evacuation, ventricular drain), we move to tier 2 treatment (hypothermia, anticonvulsants). Decompressive craniectomy and thiopentone coma are used only in exceptional circumstances after multi-disciplinary input.

CPP

CPP is defined as the difference between mean arterial pressure (MAP) and ICP, and is considered the driving pressure for cerebral blood flow and perfusion. In the normal brain, cerebral autoregulation maintains CPP within a specific range to couple oxygen delivery with cerebral metabolic rate. However, TBI impairs the cerebral autoregulatory capacity making brain vulnerable to both systemic hypotension and raised ICP. In adults, keeping CPP above a recommended threshold (60 or 70 mmHg) is associated with improved clinical outcomes[52,55]; some paediatric evidence also supports targeting higher CPP in children[56,57]. However, there are age related differences in MAP, CBF, and cerebral metabolic rate and there are no studies to demonstrate active management of CPP above a target threshold reducing mortality or morbidity[14]. Therefore, defining an ideal CPP for children is challenging and the current guidelines support maintaining a minimum CPP of 40 mmHg and a threshold of 40-50 mmHg[14]. Targeting very high CPP with use of vasopressors and fluids is associated with serious systemic toxicity and does not give better outcomes[52]. Also, in the absence of autoregulation, very high CPP can increase cerebral blood volume leading to an increasing ICP and also increase vasogenic oedema by increasing the hydrostatic pressure across the capillary bed[27].

Our management targets are described in Figure 1, we achieve target CPP by maintaining systemic blood pressure towards the upper limit of normal blood pressure for age with the use of fluids to achieve normovolemia and inotropic support (most commonly noradrenaline infusion). However, if the ICP is very high, we do not increase MBP beyond the age related MBP limits and instead, focus on improving CPP by reduction in ICP.

Hyperosmolar therapy

Hyperosmolar therapy has been the hallmark of ICP management for decades. Hyperosmolar agents create osmotic gradient across the cerebral vascular bed, thereby decreasing oedema. They work best for acute rises in ICP. Various osmotic agents have been studied in the treatment of TBI, but mannitol and hypertonic saline are the most widely used.

Mannitol has been used to reduce raised ICP for close to a century. It reduces ICP by reducing blood viscosity (rapid response) and by an osmotic effect (delayed response)[58]. These effects are more pronounced when the blood brain barrier is intact and autoregulation is preserved. In TBI, these mechanisms may be disrupted, so the response can be variable[59]. Mannitol can also reduce intravascular volume by causing osmotic diuresis (which could have a negative impact on CPP) and has the potential to induce reverse osmotic gradient by accumulating in the brain parenchyma (which could cause an increase in ICP) especially with prolonged use[60].

Hypertonic saline has been studied extensively in the last few decades as treatment for raised ICP. It shares the same rheologic and osmolar properties with mannitol that lower the ICP. It can also act as a volume expander, enhance cardiac output, improve CBF and inhibit inflammation[61-63]. Current guidelines support the use of hypertonic saline, but make no specific recommendation on the concentration[14]. Different studies and institutions use various concentrations from 1.7% to 29.2%[64,65]; in our institute, we use 5% saline (Figure 1). Delivery through a central access is recommended (but not essential) due to high osmolality. We use 2-4 mL/kg boluses of 5% saline (Figure 1).

Serum osmolarity plays an important role in determining fluid shifts in injured brain. Low serum osmolarity can increase vasogenic brain oedema, so hyperosmolar agents are used to normalise or increase serum osmolarity. Different upper limits of osmolarity are recommended for treatment with mannitol (320 mOsm) and hypertonic saline (360 mOsm), respectively. If using hypertonic saline, serum sodium levels need to be monitored as well and kept < 160 mmol/L. Due to lack of evidence for mannitol use in children with TBI, hypertonic saline has been recommended as the preferred osmotic agent in management of paediatric TBI[65,66].

Children with TBI are also susceptible to develop disorders of salt and water, like central diabetes insipidus, cerebral salt wasting and syndrome of inappropriate anti-diuretic hormone. A detailed description of these is beyond the scope of this article, but a careful understanding and monitoring of serum and urine electrolytes and osmolarity is required[67].

Temperature control

Hyperthermia can cause significant secondary brain injury by increasing cerebral metabolic demand, promoting inflammation and decreasing the seizure threshold, so needs to be avoided aggressively to protect brain[68]. Temperature control to avoid hyperthermia has become an integral part of neuroprotection in children with TBI[14]. Inducing hypothermia to reduce cerebral metabolic demand, inflammation and seizures, is more contentious.

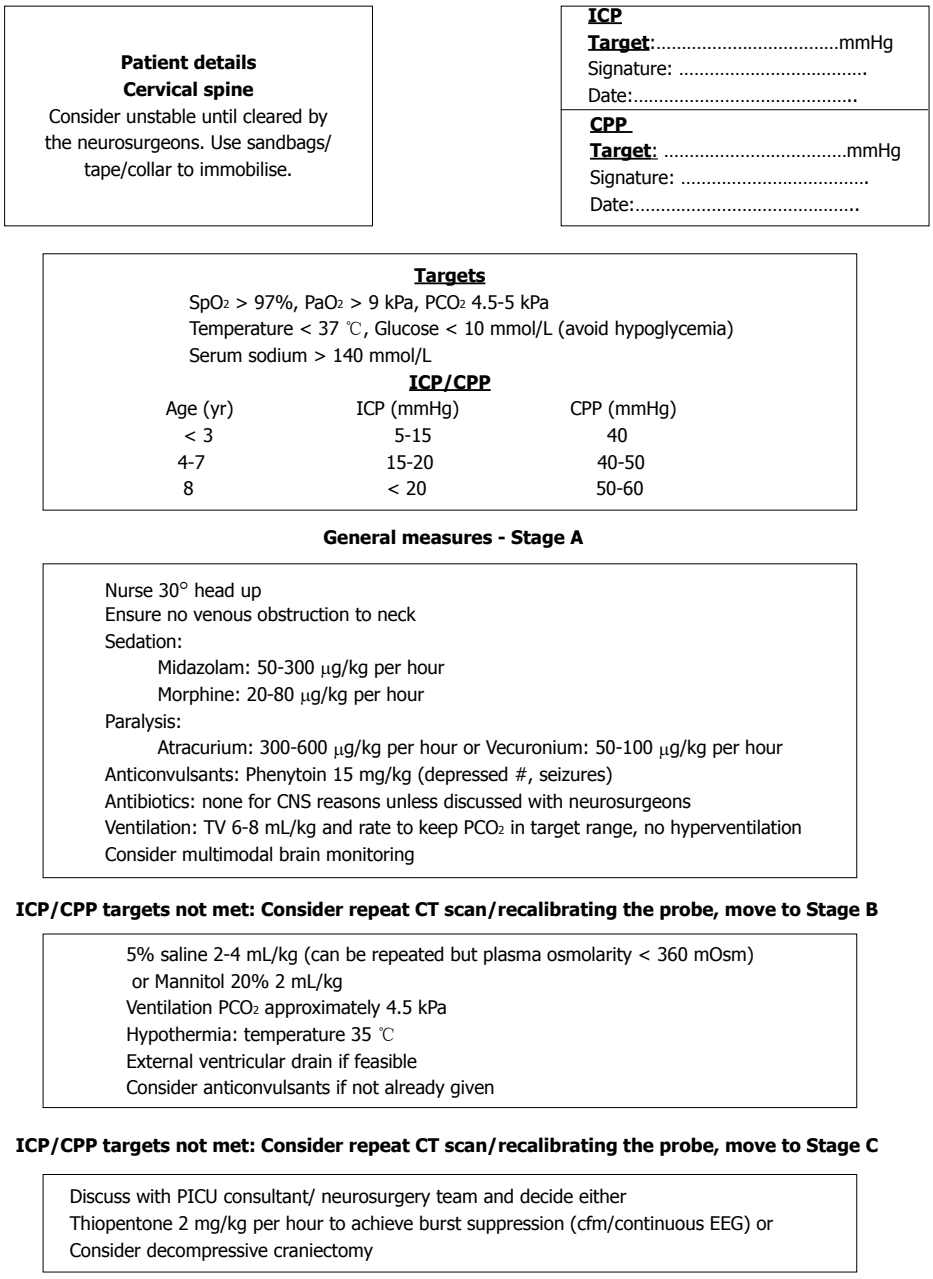


Figure 1 Protocol for managing severe traumatic brain injury in children. ICP: Intracranial pressure; CPP: Cerebral perfusion; CT: Computed tomography; PICU: Pediatric intensive care unit; EEG: Electroencephalograph.

The theoretical benefits of induced hypothermia have not been confirmed in multi-centric trials despite a consistent decrease in ICP in the hypothermic patients. Rebound rise in ICP during rewarming and the delay to achieve target temperature have been suggested as the limiting factors that lead to no difference in neurological outcome of children receiving hypothermia[69,70]. Despite the lack of evidence, induced moderate hypothermia (32 ℃-33 ℃) is used as a second tier strategy to control ICP if the first tier strategies (sedation, analgesia, paralysis, osmolar therapy) have failed. The specific recommendation is to induce hypothermia early (within 8 h) for 48 h followed by very gradual rewarming (≤ 0.5 ℃/h)[14].

We use cooling blankets to keep patients normothermic (36 ℃-37 ℃) and only use hypothermia (35 ℃) for uncontrolled ICP after optimising other therapies and ruling out surgically correctible pathologies (Figure 1).

Hyperventilation

CO_2 is a potent determinant of cerebral vessel diameter. Lowering CO_2 reduces ICP by causing vasoconstriction, but it also causes cerebral ischemia with a reduction in cerebral blood flow[21,22,71]. For this reason, hyperventilation cannot be recommended for treatment of ICP unless the patient has advanced neuromonitoring in place[14]. Despite the lack of evidence to support this strategy, evidence suggests it remains the most commonly used strategy to lower ICP[22,72]. We do not hyperventilate children with severe TBI and actively manage $PaCO_2$ levels between 4.5-5 kPa (Figure 1).

Barbiturate coma

Barbiturates lower ICP through suppression of cerebral metabolic demand and alteration of vascular tone[73,74]. It improves coupling of regional blood flow to metabolic demands resulting in improved brain oxygenation at lower cerebral blood flow and decreased ICP. Although barbiturates are effective in lowering ICP, some studies suggest it does not improve clinical outcome in adults[75] and the literature in children is very scarce. Barbiturates have very significant systemic side effects, most notably severe haemodynamic compromise and increased intrapulmonary shunt. These side effects significantly limit the use of barbiturates in PICU and may be responsible for a number of complications observed in patients receiving this therapy. Also, the agent half-life is very long, making neurological assessment difficult. Barbiturates currently cannot be recommended for routine use in care of patients with raised ICP[76], but may be used as a rescue therapy in raised ICP unresponsive to first line treatment. Continuous EEG monitoring is recommended in children with TBI using barbiturates, and the agent should be titrated to achieve burst suppression[14].

Anti-seizures medication

Seizures are common post head injury and are often missed as patients are sedated and paralysed, but not always receive continuous EEG monitoring[77]. Although there is limited evidence to support the use of prophylactic anti-convulsants in severe TBI patients, the current guidelines still make a level Ⅲ recommendation for their use to reduce early post traumatic seizures[14].

Surgical treatment

Surgical management is a crucial part of management in TBI. If there is space-occupying haematoma post head-injury, its evacuation is the most effective mechanism of reducing ICP and avoiding secondary brain insult. Neuro-imaging is the cornerstone for diagnosing these and should be repeated for any persistent ICP rise. Space occupying lesions are often time-sensitive injuries and surgical evacuation should be performed as soon as possible, without delays.

Other surgical options for controlling ICP are CSF diversion (ventricular/lumbar drain) and decompressive craniectomy. CSF diversion can reduce CSF volume and ICP, and is recommended for eligible patients[14]. External ventricular drain (EVD) is a common method for CSF diversion and can also be used for monitoring ICP. Insertion of an EVD can be technically challenging in injured brain and may not offer any benefit if there is significant cerebral oedema causing collapsed ventricles[78]. Lumbar drain is only advised in conjunction with the EVD when there is no mass effect and cisterns are open[79].

Decompressive craniectomy can reduce ICP by allowing oedematous brain to expand by raising a bone flap and opening the dura. Although the technique lowers ICP, its benefits for outcome are not proven[80]. The current guidelines only make a level Ⅲ recommendation for its use in refractory intracranial hypertension which is resistant to other treatment strategies[14]. A recent randomized controlled trial in adults suggested that decompressive craniectomy increase the number of unfavourable outcomes despite lowering ICP and shortening length of ICU stay[80].

ADVANCED NEUROMONITORING

The pathophysiology of secondary brain injury is complex. It involves interactions between cerebral metabolic demand and supply with a complex relationship of cerebral blood flow, oxygenation, autoregulatory mechanisms and physiological derangements within an injured brain. Monitoring and maintaining ICP and CPP may be too simplistic to prevent secondary insults and there is growing evidence to support that factors other than ICP and CPP independently relate to the outcome. Some of these factors can be monitored with additional therapeutic targets with a potential to improve patient outcome. Although limited in paediatric TBI, some of these modalities are being increasingly studied and hold promise. The most common targets are CBF, cerebral autoregulation, cerebral oxygenation and metabolism. Also continuous monitoring of various physiological parameters in modern intensive care environment, such as oxygen saturations, respiratory rate, heart rate, ECG, CO_2, temperature, blood pressure and intracranial pressure allow for the development of multi-modal monitoring in neurocritical care. Multi-modal monitoring can interpret the relationship of these different parameters with each other and give unique information over and above the individual numbers that could be used to optimise clinical management[81].

CBF and autoregulation

CBF is the single most important parameter in defining the outcome after TBI. The normal brain is able to maintain near constant CBF over a range of systemic blood pressure fluctuations from about 50 to 150 mmHg by cerebrovascular pressure reactivity and autoregulation mechanisms[82]. Impaired cerebral autoregulation is common post TBI and influences the patient outcome[83-86].

Pressure reactivity index

Pressure reactivity index (PRx), which is a correlation coefficient between ABP and ICP, relating the ABP changes with slow fluctuations in ICP, has been studied extensively[87,88]. In intact autoregulation state, fluctuations in ABP are compensated by reactive changes in vasomotor tone. For example, a drop in ABP induces vasodilatation which increases cerebral blood volume and ICP, giving a negative correlation between ABP and ICP, and a negative PRx. Impaired autoregulation on the other hand, would lead to passive transmission of ABP fluctuations to ICP and hence a positive PRx[87]. By continuously studying cerebrovascular reactivity through PRx and plotting it against CPP, the CPP at which the vasculature is most

reactive can be calculated and the optimum CPP (CPPopt) can be estimated[89,90]. This is particularly important in young children in whom CPP data is scarce and CPPopt gives an ideal therapeutic target. It is important to remember that autoregulation is dynamic and changes both between individuals and at different times within an individual patient depending on type of injury and time since injury[91,92]. Therefore, PRx and CPPopt also provide dynamic values in real time that can be used to individualise therapeutic targets for a given patient and changing targets over time depending on the state of cerebral autoregulation[93,94]. The time CPP stays above or below CPPopt has been shown to be associated with outcome[89]; whether an active management of PRx and CPPopt would affect the outcome remains to be proven in randomised controlled trial.

Transcranial Doppler ultrasonography

Transcranial Doppler ultrasonography (TCD) is a non-invasive method that measures the flow velocity in middle cerebral artery[95]. It gives non quantitative estimate of CBF and state of cerebral autoregulation based on the assumption that the diameter of the vessels insonated is relatively constantly maintained despite changes in BP and $PaCO_2$, so the changes in flow velocity would estimate the changes in CBF. It is easy to use and can be repeated bedside, however, it is difficult to get a continuous assessment and it is liable to inter-observer variability. Various indices have been developed to interpret state of CBF and autoregulation, CPP and ICP and CO_2 reactivity by using TCD. One such index called pulsatility index (PI) is based on analysing the waveform of diastolic and systolic flows in the middle cerebral artery. PI has been used to assess brain compliance and CPP, and has been shown to have an association with ICP[96,97]. Cerebrovascular resistance is estimated by a ratio of MAP to changes in flow velocity measured by TCD which is then used to calculate autoregulation index which reflects the state of autoregulation[86,98]. Alternatively, manipulation of systemic blood pressure can also be used to study the effect of ABP changes in the TCD parameters to assess autoregulation[85,86]. TCD is being increasingly used in children[85,86]; further studies are required to validate the preliminary results.

Brain tissue oxygenation

Adequate oxygen delivery to brain tissue is important to prevent secondary brain injury. The relationship between oxygen demand (cerebral metabolic rate, $CMRO_2$) and supply (CBF) is complex post head injury due to unknown changes in metabolic demands at the cellular level, hence optimal management of ICP and CPP (surrogates for CBF) does not always prevent brain hypoxia[99].

Direct brain tissue oxygenation monitoring

Direct brain tissue oxygenation monitoring ($PbtO_2$) has been used for over two decades and there is significant evidence to support its use in paediatric TBI[56,100]. The latest guidelines make a level Ⅲ recommendation to keep $PbtO_2$ above 10 mmHg in paediatric TBI[14]. The commonest method used to monitor $PbtO_2$ is by insertion of a polarographic electrode in the brain parenchyma with the ICP bolt and the value measured is the oxygen accumulated in the brain parenchyma at the tip of the transducer, which is influenced by oxygen supply, demand and utilization. The probe placement is crucial. In focal injury, it should be placed in the pericontusional area while in diffuse injuries; it is usually placed in the non-dominant hemisphere. Although the normal values of $PbtO_2$ are not clearly understood, animal studies suggest 20-30 mmHg as the normal values for normal uninjured brain[101]. A threshold of 10 mmHg has been accepted as the ischemic threshold and $PbtO_2$ levels below 10 mmHg have been associated with poor outcome. $PbtO_2$ values can be improved by increasing inspired oxygen/ventilation, haemoglobin levels and MBP[57,102].

Continuous jugular venous saturation monitoring

Continuous jugular venous saturation monitoring ($SjvO_2$) is another method used to understand the relationship between CBF and brain metabolism and gives the difference between cerebral oxygen supply and demand. A retrograde catheter inserted in the jugular venous bulb measures continuous $SjvO_2$. There is no consensus for normal levels of $SjvO_2$ in children but in adults 50%-75% is considered normal. Values outside this range are considered abnormal and have been shown to be associated with poor outcome[52,103]. Due to technical difficulties, paediatric experience with the use of $SjvO_2$ is limited. It is also not a good indicator of regional changes in the injured brain.

Thermal diffusion probes

Regional cerebral blood flow can be measured directly by thermal diffusion probes (TDP) inserted in brain parenchyma. The technique has been validated with good agreement between TDP and xenon-CT for regional CBF measurements. In combination with PbtO2, TDP can be potentially useful in optimizing management of CPP[104].

Brain metabolism and chemistry

It is possible to study the concentration of chemicals found in the brain parenchyma by using microdialysis and is now frequently used in monitoring and managing adult TBI. It is possible to measure markers of brain metabolism (glucose, lactate and pyruvate), neurotransmitters (glutamate) and tissue damage (glycerol) at select intervals on small amounts of interstitial fluid collected by the microdialysis catheter inserted into the brain parenchyma alongside the ICP monitor and $PbtO_2$ probe and there are established normal values for adults for some of these chemicals[105]. LPR is of particular interest as it signifies the balance between aerobic and anaerobic metabolism; LPR can also be elevated in states of hyperglycolysis or mitochondrial

dysfunction[105,106]. Sustained elevations of LPR have been identified in pericontusional tissue[107] and have been shown to be associated with poor outcome[108]. Similarly, brain glucose levels can be used to guide optimal threshold for blood glucose levels[40]. At present, microdialysis is predominantly used for research purposes, but holds promise for future. Similar to $PbtO_2$ probe, the position of the catheter is crucial and influences the results.

CONCLUSION

Paediatric TBI is a complex disease and requires multi-disciplinary input. Advancements in the field of paediatric neurocritical care and improved understanding of TBI pathophysiology are being translated to bedside therapies but clinical benefit from most of these therapies is yet to be proved in clinical trials. Despite this, implementations of guideline-based management protocols have impacted significantly on the outcome of TBI in recent years. New monitoring techniques have improved our ability to recognise adverse events and mechanisms of secondary brain injury. The role of these new techniques of individualized management need to be further evaluated.

REFERENCES

1 **Langlois JA**, Marr A, Mitchko J, Johnson RL. Tracking the silent epidemic and educating the public: CDC's traumatic brain injury-associated activities under the TBI Act of 1996 and the Children's Health Act of 2000. *J Head Trauma Rehabil* 2005; **20**: 196-204 [PMID: 15908820 DOI: 10.1097/00001199-200505000-00002]

2 **Faul M**, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010. Available from: URL: http://www.cdc.gov/TraumaticBrainInjury

3 **Tagliaferri F**, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. *Acta Neurochir* (Wien) 2006; **148**: 255-268; discussion 268 [PMID: 16311842 DOI: 10.1007/s00701-005-0651-y]

4 **Teasdale G**, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; **2**: 81-84 [PMID: 4136544 DOI: 10.1016/s0140-6736(74)91639-0]

5 **Shaklai S**, Peretz R, Spasser R, Simantov M, Groswasser Z. Long-term functional outcome after moderate-to-severe paediatric traumatic brain injury. *Brain Inj* 2014; **28**: 915-921 [PMID: 24826955 DOI: 10.310902699052.2013.862739]

6 **Pigula FA**, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg* 1993; **28**: 310-314 [PMID: 8468638 DOI: 10.1016/0022-3468(93)90223-8]

7 **Chesnut RM**, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma* 1993; **34**: 216-222 [PMID: 8459458 DOI: 10.1097/00005373-199302000-00006]

8 **Stocchetti N**, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma* 1996; **40**: 764-767 [PMID: 8614077 DOI: 10.1097/00005373-199605000-00014]

9 **Muizelaar JP**, Marmarou A, DeSalles AA, Ward JD, Zimmerman RS, Li Z, Choi SC, Young HF. Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GCS score, outcome, ICP, and PVI. *J Neurosurg* 1989; **71**: 63-71 [PMID: 2738643 DOI: 10.3171/jns.1989.71.1.0063]

10 **Andrews PJ**, Citerio G. Intracranial pressure. Part one: historical overview and basic concepts. *Intensive Care Med* 2004; **30**: 1730-1733 [PMID: 15243684 DOI: 10.1007/s00134-004-2376-4]

11 **Unterberg AW**, Stover J, Kress B, Kiening KL. Edema and brain trauma. *Neuroscience* 2004; **129**: 1021-1029 [PMID: 15561417 DOI: 10.1016/j.neuroscience.2004.06.046]

12 Advanced Paediatric Life Support: The practical approach. In: Samuels M, Wieteska S, editors. UK: Wiley-Blackwell, 2011: 139-200

13 Advanced Trauma Life Support: ATLS student course manual. 9th ed. American College of Surgeons Committee on Trauma. UK: Wiley-Blackwell, 2012: 246-270

14 **Kochanek PM**, Carney N, Adelson PD, Ashwal S, Bell MJ, Bratton S, Carson S, Chesnut RM, Ghajar J, Goldstein B, Grant GA, Kissoon N, Peterson K, Selden NR, Tasker RC, Tong KA, Vavilala MS, Wainwright MS, Warden CR. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. *Pediatr Crit Care Med* 2012; **13** Suppl 1: S1-S82 [PMID: 22217782 DOI: 10.1097/PCC.0b013e31823f435c]

15 **Pineda JA**, Leonard JR, Mazotas IG, Noetzel M, Limbrick DD, Keller MS, Gill J, Doctor A. Effect of implementation of a paediatric neurocritical care programme on outcomes after severe traumatic brain injury: a retrospective cohort study. *Lancet Neurol* 2013; **12**: 45-52 [PMID: 23200264 DOI: 10.1016/S1474-4422(12)70269-7]

16 **Adelson PD**, Bratton SL, Carney NA, Chesnut RM, du Coudray HE, Goldstein B, Kochanek PM, Miller HC, Partington MP, Selden NR, Warden CR, Wright DW. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 19. The role of anti-seizure prophylaxis following severe pediatric traumatic brain injury. *Pediatr Crit Care Med* 2003; **4**: S72-S75 [PMID: 12847355 DOI: 10.1097/01.ccm.0000066600.71233.01]

17 **Stiefel MF**, Udoetuk JD, Spiotta AM, Gracias VH, Goldberg A, Maloney-Wilensky E, Bloom S, Le Roux PD. Conventional neurocritical care and cerebral oxygenation after traumatic brain injury. *J Neurosurg* 2006; **105**: 568-575 [PMID: 17044560 DOI: 10.3171/jns.2006.105.4.568]

18 **Davis DP**, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, Steele J, Coimbra R. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. *J Neurotrauma* 2009; **26**: 2217-2223 [PMID: 19811093 DOI: 10.1089/neu.2009.0940]

19 **Lee JH**, Kelly DF, Oertel M, McArthur DL, Glenn TC, Vespa P, Boscardin WJ, Martin NA. Carbon dioxide reactivity, pressure autoregulation, and metabolic suppression reactivity after head injury: a transcranial Doppler study. *J Neurosurg* 2001; **95**: 222-232 [PMID: 11780891 DOI: 10.3171/jns.2001.95.2.0222]

20 **McLaughlin MR**, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. *J Neurosurg* 1996; **85**: 871-876 [PMID: 8893726 DOI: 10.3171/jns.1996.85.5.0871]

21 **Stringer WA**, Hasso AN, Thompson JR, Hinshaw DB, Jordan KG. Hyperventilation-induced cerebral ischemia in patients with acute brain lesions: demonstration by xenon-enhanced CT. *AJNR Am J Neuroradiol* 1993; **14**: 475-484 [PMID: 8456732]

22 **Curry R**, Hollingworth W, Ellenbogen RG, Vavilala MS. Incidence of hypo- and hypercarbia in severe traumatic brain injury before and after 2003 pediatric guidelines. *Pediatr Crit Care Med* 2008; **9**: 141-146 [PMID: 18477926 DOI: 10.1097/PCC.0B013e318166870e]

23 **Weinberg JA**. Head trauma. *Indian J Pediatr* 1988; **55**: 739-748 [PMID: 3073127 DOI: 10.1007/bf02734295]

24 **Cantor RM**, Leaming JM. Evaluation and management of pediatric major trauma. *Emerg Med Clin North Am* 1998; **16**: 229-256 [PMID: 9496323 DOI: 10.1016/S0733-8627(05)70357-6]

25 **Hannon MJ**, Crowley RK, Behan LA, O'Sullivan EP, O'Brien MM, Sherlock M, Rawluk D, O'Dwyer R, Tormey W, Thompson CJ. Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. *J Clin Endocrinol Metab* 2013; **98**: 3229-3237 [PMID: 23690314

DOI: 10.1210/jc.2013-1555]
26 **Ulutabanca H**, Hatipoglu N, Tanriverdi F, Gökoglu A, Keskin M, Selcuklu A, Kurtoglu S, Kelestimur F. Prospective investigation of anterior pituitary function in the acute phase and 12 months after pediatric traumatic brain injury. *Childs Nerv Syst* 2014; **30**: 1021-1028 [PMID: 24322605 DOI: 10.1007/s00381-013-2334-y]
27 **Grände PO**, Asgeirsson B, Nordström C. Aspects on the cerebral perfusion pressure during therapy of a traumatic head injury. *Acta Anaesthesiol Scand Suppl* 1997; **110**: 36-40 [PMID: 9248525 DOI: 10.1111/j.1399-6576.1997.tb05493.x]
28 **Raju TN**, Vidyasagar D, Torres C, Grundy D, Bennett EJ. Intracranial pressure during intubation and anesthesia in infants. *J Pediatr* 1980; **96**: 860-862 [PMID: 7365587 DOI: 10.1016/s0022-3476(80)80558-0]
29 **Nilsson B**, Rehncrona S, Siesjö BK. Coupling of cerebral metabolism and blood flow in epileptic seizures, hypoxia and hypoglycaemia. *Ciba Found Symp* 1978; **56**: 199-218 [PMID: 27337 DOI: 10.1002/9780470720370.ch11]
30 **Vernon DD**, Witte MK. Effect of neuromuscular blockade on oxygen consumption and energy expenditure in sedated, mechanically ventilated children. *Crit Care Med* 2000; **28**: 1569-1571 [PMID: 10834713 DOI: 10.1097/00003246-200005000-00051]
31 **Greenberg SB**, Vender J. The use of neuromuscular blocking agents in the ICU: where are we now? *Crit Care Med* 2013; **41**: 1332-1344 [PMID: 23591211 DOI: 10.1097/CCM.0b013e31828ce07c]
32 **Chin KH**, Bell MJ, Wisniewski SR, Balasubramani GK, Kochanek PM, Beers SR, Brown SD, Adelson PD. Effect of administration of neuromuscular blocking agents in children with severe traumatic brain injury on acute complication rates and outcomes: a secondary analysis from a randomized, controlled trial of therapeutic hypothermia. *Pediatr Crit Care Med* 2015; **16**: 352-358 [PMID: 25599147 DOI: 10.1097/PCC.0000000000000344]
33 **Myburgh J**, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; **357**: 874-884 [PMID: 17761591 DOI: 10.1056/nejmoa067514]
34 **Perel P**, Yanagawa T, Bunn F, Roberts I, Wentz R, Pierro A. Nutritional support for head-injured patients. *Cochrane Database Syst Rev* 2006; **4**: CD001530 [PMID: 17054137 DOI: 10.1002/14651858.cd001530.pub2]
35 **Borzotta AP**, Pennings J, Papasadero B, Paxton J, Mardesic S, Borzotta R, Parrott A, Bledsoe F. Enteral versus parenteral nutrition after severe closed head injury. *J Trauma* 1994; **37**: 459-468 [PMID: 8083910 DOI: 10.1097/00005373-199409000-00022]
36 **Cochran A**, Scaife ER, Hansen KW, Downey EC. Hyperglycemia and outcomes from pediatric traumatic brain injury. *J Trauma* 2003; **55**: 1035-1038 [PMID: 14676647 DOI: 10.1097/01.ta.0000031175.96507.48]
37 **Michaud LJ**, Rivara FP, Longstreth WT, Grady MS. Elevated initial blood glucose levels and poor outcome following severe brain injuries in children. *J Trauma* 1991; **31**: 1356-1362 [PMID: 1942143 DOI: 10.1097/00005373-199110000-00007]
38 **Elkon B**, Cambrin JR, Hirshberg E, Bratton SL. Hyperglycemia: an independent risk factor for poor outcome in children with traumatic brain injury*. *Pediatr Crit Care Med* 2014; **15**: 623-631 [PMID: 24849146 DOI: 10.1097/PCC.0000000000000170]
39 **Vespa P**, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, Glenn T, Martin N, Hovda D. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. *Crit Care Med* 2006; **34**: 850-856 [PMID: 16505665 DOI: 10.1097/01.ccm.0000201875.12245.6f]
40 **Oddo M**, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. *Crit Care Med* 2008; **36**: 3233-3238 [PMID: 18936695 DOI: 10.1097/CCM.0b013e31818f4026]
41 **Agbeko RS**, Pearson S, Peters MJ, McNames J, Goldstein B. Intracranial pressure and cerebral perfusion pressure responses to head elevation changes in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2012; **13**: e39-e47 [PMID: 21242856 DOI: 10.1097/PCC.0b013e31820ac2ad]
42 **Ng I**, Lim J, Wong HB. Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. *Neurosurgery* 2004; **54**: 593-597; discussion 598 [PMID: 15028132 DOI: 10.1227/01.NEU.0000108639.16783.39]
43 **Harris DA**, Lam S. Venous thromboembolism in the setting of pediatric traumatic brain injury. *J Neurosurg Pediatr* 2014; **13**: 448-455 [PMID: 24559280 DOI: 10.3171/2014.1.PEDS13479]
44 **Hanson SJ**, Punzalan RC, Arca MJ, Simpson P, Christensen MA, Hanson SK, Yan K, Braun K, Havens PL. Effectiveness of clinical guidelines for deep vein thrombosis prophylaxis in reducing the incidence of venous thromboembolism in critically ill children after trauma. *J Trauma Acute Care Surg* 2012; **72**: 1292-1297 [PMID: 22673257 DOI: 10.1097/TA.0b013e31824964d1]
45 **Michaud LJ**, Rivara FP, Grady MS, Reay DT. Predictors of survival and severity of disability after severe brain injury in children. *Neurosurgery* 1992; **31**: 254-264 [PMID: 1513431 DOI: 10.1097/00006123-199208000-00010]
46 **White JR**, Farukhi Z, Bull C, Christensen J, Gordon T, Paidas C, Nichols DG. Predictors of outcome in severely head-injured children. *Crit Care Med* 2001; **29**: 534-540 [PMID: 11373416 DOI: 10.1097/00003246-200103000-00011]
47 **Jagannathan J**, Okonkwo DO, Yeoh HK, Dumont AS, Saulle D, Haizlip J, Barth JT, Jane JA, Jane JA. Long-term outcomes and prognostic factors in pediatric patients with severe traumatic brain injury and elevated intracranial pressure. *J Neurosurg Pediatr* 2008; **2**: 240-249 [PMID: 18831656 DOI: 10.3171/PED.2008.2.10.240]
48 **Alberico AM**, Ward JD, Choi SC, Marmarou A, Young HF. Outcome after severe head injury. Relationship to mass lesions, diffuse injury, and ICP course in pediatric and adult patients. *J Neurosurg* 1987; **67**: 648-656 [PMID: 3668633 DOI: 10.3171/jns.1987.67.5.0648]
49 **Tilford JM**, Aitken ME, Anand KJ, Green JW, Goodman AC, Parker JG, Killingsworth JB, Fiser DH, Adelson PD. Hospitalizations for critically ill children with traumatic brain injuries: a longitudinal analysis. *Crit Care Med* 2005; **33**: 2074-2081 [PMID: 16148483 DOI: 10.1097/01.ccm.0000171839.65687.f5]
50 **Chesnut RM**, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, Petroni G, Lujan S, Pridgeon J, Barber J, Machamer J, Chaddock K, Celix JM, Cherner M, Hendrix T. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012; **367**: 2471-2481 [PMID: 23234472 DOI: 10.1056/nejmoa1207363]
51 **Chesnut RM**, Bleck TP, Citerio G, Classen J, Cooper DJ, Coplin WM, Diringer MN, Grände PO, Hemphill JC, Hutchinson PJ, Le Roux P, Mayer SA, Menon DK, Myburgh JA, Okonkwo DO, Robertson CS, Sahuquillo J, Stocchetti N, Sung G, Temkin N, Vespa PM, Videtta W, Yonas H. A Consensus-Based Interpretation of the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure Trial. *J Neurotrauma* 2015; **32**: 1722-1724 [PMID: 26061135 DOI: 10.1089/neu.2015.3976]
52 **Bratton SL**, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury. XV. Steroids. *J Neurotrauma* 2007; **24** Suppl 1: S91-S95 [PMID: 17511554 DOI: 10.1089/neu.2007.9999]
53 **Steiner LA**, Andrews PJ. Monitoring the injured brain: ICP and CBF. *Br J Anaesth* 2006; **97**: 26-38 [PMID: 16698860 DOI: 10.1093/bja/ael110]
54 **Aucoin PJ**, Kotilainen HR, Gantz NM, Davidson R, Kellogg P, Stone B. Intracranial pressure monitors. Epidemiologic study of risk factors and infections. *Am J Med* 1986; **80**: 369-376 [PMID: 3953614 DOI: 10.1097/00132586-198612000-00044]
55 **Chambers IR**, Treadwell L, Mendelow AD. Determination of threshold levels of cerebral perfusion pressure and intracranial

pressure in severe head injury by using receiver-operating characteristic curves: an observational study in 291 patients. *J Neurosurg* 2001; **94**: 412-416 [PMID: 11235944 DOI: 10.3171/jns.2001.94.3.0412]

56 **Figaji AA**, Zwane E, Thompson C, Fieggen AG, Argent AC, Le Roux PD, Peter JC. Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury. Part 1: Relationship with outcome. *Childs Nerv Syst* 2009; **25**: 1325-1333 [PMID: 19214532 DOI: 10.1007/s00381-009-0822-x]

57 **Narotam PK**, Burjonrappa SC, Raynor SC, Rao M, Taylon C. Cerebral oxygenation in major pediatric trauma: its relevance to trauma severity and outcome. *J Pediatr Surg* 2006; **41**: 505-513 [PMID: 16516625 DOI: 10.1016/j.jpedsurg.2005.11.069]

58 **Mendelow AD**, Teasdale GM, Russell T, Flood J, Patterson J, Murray GD. Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. *J Neurosurg* 1985; **63**: 43-48 [PMID: 3925092 DOI: 10.3171/jns.1985.63.1.0043]

59 **James HE**. Methodology for the control of intracranial pressure with hypertonic mannitol. *Acta Neurochir* (Wien) 1980; **51**: 161-172 [PMID: 6768226]

60 **Bullock R**. Mannitol and other diuretics in severe neurotrauma. *New Horiz* 1995; **3**: 448-452 [PMID: 7496753 DOI: 10.1007/bf01406742]

61 **Fisher B**, Thomas D, Peterson B. Hypertonic saline lowers raised intracranial pressure in children after head trauma. *J Neurosurg Anesthesiol* 1992; **4**: 4-10 [PMID: 15815431 DOI: 10.1097/00008506-199201000-00002]

62 **Peterson B**, Khanna S, Fisher B, Marshall L. Prolonged hypernatremia controls elevated intracranial pressure in head-injured pediatric patients. *Crit Care Med* 2000; **28**: 1136-1143 [PMID: 10809295 DOI: 10.1097/00003246-200004000-00037]

63 **Zornow MH**. Hypertonic saline as a safe and efficacious treatment of intracranial hypertension. *J Neurosurg Anesthesiol* 1996; **8**: 175-177 [PMID: 8829566 DOI: 10.1097/00008506-199604000-00021]

64 **Suarez JI**, Qureshi AI, Bhardwaj A, Williams MA, Schnitzer MS, Mirski M, Hanley DF, Ulatowski JA. Treatment of refractory intracranial hypertension with 23.4% saline. *Crit Care Med* 1998; **26**: 1118-1122 [PMID: 9635664 DOI: 10.1097/00003246-199806000-00038]

65 **Vialet R**, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, Martin C. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med* 2003; **31**: 1683-1687 [PMID: 12794404 DOI: 10.1097/01.ccm.0000063268.91710.df]

66 **Mangat HS**, Chiu YL, Gerber LM, Alimi M, Ghajar J, Härtl R. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury. *J Neurosurg* 2015; **122**: 202-210 [PMID: 25380107 DOI: 10.3171/2014.10.JNS132545]

67 **Rivkees SA**. Differentiating appropriate antidiuretic hormone secretion, inappropriate antidiuretic hormone secretion and cerebral salt wasting: the common, uncommon, and misnamed. *Curr Opin Pediatr* 2008; **20**: 448-452 [PMID: 18622203 DOI: 10.1097/MOP.0b013e328305e403]

68 **Heindl UT**, Laub MC. Outcome of persistent vegetative state following hypoxic or traumatic brain injury in children and adolescents. *Neuropediatrics* 1996; **27**: 94-100 [PMID: 8737825 DOI: 10.1055/s-2007-973756]

69 **Hutchison JS**, Ward RE, Lacroix J, Hébert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW. Hypothermia therapy after traumatic brain injury in children. *N Engl J Med* 2008; **358**: 2447-2456 [PMID: 18525042 DOI: 10.1056/NEJMoa0706930]

70 **Adelson PD**, Wisniewski SR, Beca J, Brown SD, Bell M, Muizelaar JP, Okada P, Beers SR, Balasubramani GK, Hirtz D. Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial. *Lancet Neurol* 2013; **12**: 546-553 [PMID: 23664370 DOI: 10.1016/S1474-4422(13)70077-2]

71 **Muizelaar JP**, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg* 1991; **75**: 731-739 [PMID: 1919695 DOI: 10.3171/jns.1991.75.5.0731]

72 **Skippen P**, Seear M, Poskitt K, Kestle J, Cochrane D, Annich G, Handel J. Effect of hyperventilation on regional cerebral blood flow in head-injured children. *Crit Care Med* 1997; **25**: 1402-1409 [PMID: 9267957 DOI: 10.1097/00003246-199708000-00031]

73 **Kassell NF**, Hitchon PW, Gerk MK, Sokoll MD, Hill TR. Alterations in cerebral blood flow, oxygen metabolism, and electrical activity produced by high dose sodium thiopental. *Neurosurgery* 1980; **7**: 598-603 [PMID: 6782503 DOI: 10.1097/00006123-198012000-00011]

74 **Chen HI**, Malhotra NR, Oddo M, Heuer GG, Levine JM, LeRoux PD. Barbiturate infusion for intractable intracranial hypertension and its effect on brain oxygenation. *Neurosurgery* 2008; **63**: 880-886 [PMID: 19005378 DOI: 10.1227/01.NEU.0000327882.10629.06]

75 **Pittman T**, Bucholz R, Williams D. Efficacy of barbiturates in the treatment of resistant intracranial hypertension in severely head-injured children. *Pediatr Neurosci* 1989; **15**: 13-17 [PMID: 2635769 DOI: 10.1159/000120433]

76 **Roberts I**, Sydenham E. Barbiturates for acute traumatic brain injury. *Cochrane Database Syst Rev* 2012; **12**: CD000033 [PMID: 23235573 DOI: 10.1002/14651858.CD000033.pub2]

77 **Arndt DH**, Lerner JT, Matsumoto JH, Madikians A, Yudovin S, Valino H, McArthur DL, Wu JY, Leung M, Buxey F, Szeliga C, Van Hirtum-Das M, Sankar R, Brooks-Kayal A, Giza CC. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia* 2013; **54**: 1780-1788 [PMID: 24032982 DOI: 10.1111/epi.12369]

78 **Exo J**, Kochanek PM, Adelson PD, Greene S, Clark RS, Bayir H, Wisniewski SR, Bell MJ. Intracranial pressure-monitoring systems in children with traumatic brain injury: combining therapeutic and diagnostic tools. *Pediatr Crit Care Med* 2011; **12**: 560-565 [PMID: 20625341 DOI: 10.1097/PCC.0b013e3181e8b3ee]

79 **Baldwin HZ**, Rekate HL. Preliminary experience with controlled external lumbar drainage in diffuse pediatric head injury. *Pediatr Neurosurg* 1991; **17**: 115-120 [PMID: 1819324 DOI: 10.1159/000120579]

80 **Cooper DJ**, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; **364**: 1493-1502 [PMID: 21434843 DOI: 10.1056/NEJMoa1102077]

81 **Carrera EC**, Steiner LA, Brady K, Zweifel C, Castellani G, Hiler M, Smielewski P, Czosnyka M. Integration of brain signals in multimodal bedside monitoring after traumatic brain injury. *Open Neurosurg J* 2010; **3**: 17-27 [DOI: 10.2174/1876529701003010017]

82 **Lassen NA**. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959; **39**: 183-238 [PMID: 13645234 DOI: 10.1097/00000542-195903000-00057]

83 **Czosnyka M**, Smielewski P, Lavinio A, Pickard JD, Panerai R. An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: a comparison of two models, index of autoregulation and mean flow index. *Anesth Analg* 2008; **106**: 234-239, table of contents [PMID: 18165583 DOI: 10.1213/01.ane.0000295802.89962.13]

84 **Panerai RB**, Kerins V, Fan L, Yeoman PM, Hope T, Evans DH. Association between dynamic cerebral autoregulation and mortality in severe head injury. *Br J Neurosurg* 2004; **18**: 471-479 [PMID: 15799148 DOI: 10.1080/02688690400012343]

85 **Vavilala MS**, Lee LA, Boddu K, Visco E, Newell DW, Zimmerman JJ, Lam AM. Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004; **5**: 257-263 [PMID: 15115564 DOI: 10.1097/01.pcc.0000123545.69133.c3]

86 **Figaji AA**, Zwane E, Fieggen AG, Argent AC, Le Roux PD, Siesjo P, Peter JC. Pressure autoregulation, intracranial pressure, and brain tissue oxygenation in children with severe traumatic brain injury.

J Neurosurg Pediatr 2009; **4**: 420-428 [PMID: 19877773 DOI: 10.3171/2009.6.PEDS096]

87 **Czosnyka M**, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery* 1997; **41**: 11-17; discussion 17-19 [PMID: 9218290 DOI: 10.1097/00006123-199707000-00005]

88 **Budohoski KP**, Czosnyka M, de Riva N, Smielewski P, Pickard JD, Menon DK, Kirkpatrick PJ, Lavinio A. The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. *Neurosurgery* 2012; **71**: 652-660; discussion 660-661 [PMID: 22653390 DOI: 10.1227/neu.0b013e318260feb1]

89 **Aries MJ**, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, Hutchinson PJ, Brady KM, Menon DK, Pickard JD, Smielewski P. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med* 2012; **40**: 2456-2463 [PMID: 22622398 DOI: 10.1097/CCM.0b013e3182514eb6]

90 **Depreitere B**, Güiza F, Van den Berghe G, Schuhmann MU, Maier G, Piper I, Meyfroidt G. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. *J Neurosurg* 2014; **120**: 1451-1457 [PMID: 24745709 DOI: 10.3171/2014.3.JNS131500]

91 **Jaeger M**, Dengl M, Meixensberger J, Schuhmann MU. Effects of cerebrovascular pressure reactivity-guided optimization of cerebral perfusion pressure on brain tissue oxygenation after traumatic brain injury. *Crit Care Med* 2010; **38**: 1343-1347 [PMID: 20154598 DOI: 10.1097/CCM.0b013e3181d45530]

92 **Jaeger M**, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. *Crit Care Med* 2006; **34**: 1783-1788 [PMID: 16625135 DOI: 10.1097/01.ccm.0000218413.51546.9e]

93 **Lewis PM**, Czosnyka M, Carter BG, Rosenfeld JV, Paul E, Singhal N, Butt W. Cerebrovascular Pressure Reactivity in Children With Traumatic Brain Injury. *Pediatr Crit Care Med* 2015; **16**: 739-749 [PMID: 26132743 DOI: 10.1097/PCC.0000000000000471]

94 **Brady KM**, Shaffner DH, Lee JK, Easley RB, Smielewski P, Czosnyka M, Jallo GI, Guerguerian AM. Continuous monitoring of cerebrovascular pressure reactivity after traumatic brain injury in children. *Pediatrics* 2009; **124**: e1205-e1212 [PMID: 19948619 DOI: 10.1542/peds.2009-0550]

95 **Ract C**, Le Moigno S, Bruder N, Vigué B. Transcranial Doppler ultrasound goal-directed therapy for the early management of severe traumatic brain injury. *Intensive Care Med* 2007; **33**: 645-651 [PMID: 17325830 DOI: 10.1007/s00134-007-0558-6]

96 **Bellner J**, Romner B, Reinstrup P, Kristiansson KA, Ryding E, Brandt L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surg Neurol* 2004; **62**: 45-51; discussion 51 [PMID: 15226070 DOI: 10.1016/j.surneu.2003.12.007]

97 **Splavski B**, Radanović B, Vranković D, Has B, Muzević D, Janculjak D, Legcević J. Transcranial doppler ultrasonography as an early outcome forecaster following severe brain injury. *Br J Neurosurg* 2006; **20**: 386-390 [PMID: 17439090 DOI: 10.1080/02688690601048104]

98 **Paulson OB**, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; **2**: 161-192 [PMID: 2201348]

99 **Oddo M**, Levine JM, Mackenzie L, Frangos S, Feihl F, Kasner SE, Katsnelson M, Pukenas B, Macmurtrie E, Maloney-Wilensky E, Kofke WA, LeRoux PD. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery* 2011; **69**: 1037-1045; discussion 1045 [PMID: 21673608 DOI: 10.1227/NEU.0b013e3182287ca7]

100 **Stippler M**, Ortiz V, Adelson PD, Chang YF, Tyler-Kabara EC, Wisniewski SR, Fink EL, Kochanek PM, Brown SD, Bell MJ. Brain tissue oxygen monitoring after severe traumatic brain injury in children: relationship to outcome and association with other clinical parameters. *J Neurosurg Pediatr* 2012; **10**: 383-391 [PMID: 22978637 DOI: 10.3171/2012.8.PEDS12165]

101 **Maas AI**, Fleckenstein W, de Jong DA, van Santbrink H. Monitoring cerebral oxygenation: experimental studies and preliminary clinical results of continuous monitoring of cerebrospinal fluid and brain tissue oxygen tension. *Acta Neurochir Suppl* (Wien) 1993; **59**: 50-57 [PMID: 8310863 DOI: 10.1007/978-3-7091-9302-0_9]

102 **Maloney-Wilensky E**, Gracias V, Itkin A, Hoffman K, Bloom S, Yang W, Christian S, LeRoux PD. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med* 2009; **37**: 2057-2063 [PMID: 19384213 DOI: 10.1097/CCM.0b013e3181a009f8]

103 **Cormio M**, Valadka AB, Robertson CS. Elevated jugular venous oxygen saturation after severe head injury. *J Neurosurg* 1999; **90**: 9-15 [PMID: 10413150 DOI: 10.1097/00008506-199907000-00020]

104 **Jaeger M**, Soehle M, Schuhmann MU, Winkler D, Meixensberger J. Correlation of continuously monitored regional cerebral blood flow and brain tissue oxygen. *Acta Neurochir* (Wien) 2005; **147**: 51-56; discussion 56 [PMID: 15565486 DOI: 10.1007/s00701-004-0408-z]

105 **Hillered L**, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. *J Neurotrauma* 2005; **22**: 3-41 [PMID: 15665601 DOI: 10.1089/neu.2005.22.3]

106 **Vespa P**, Bergsneider M, Hattori N, Wu HM, Huang SC, Martin NA, Glenn TC, McArthur DL, Hovda DA. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005; **25**: 763-774 [PMID: 15716852 DOI: 10.1038/sj.jcbfm.9600073]

107 **Vespa PM**, O'Phelan K, McArthur D, Miller C, Eliseo M, Hirt D, Glenn T, Hovda DA. Pericontusional brain tissue exhibits persistent elevation of lactate/pyruvate ratio independent of cerebral perfusion pressure. *Crit Care Med* 2007; **35**: 1153-1160 [PMID: 17334254 DOI: 10.1097/01.ccm.0000259466.66310.4f]

108 **Timofeev I**, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, Smielewski P, Pickard JD, Menon DK, Kirkpatrick PJ, Gupta AK, Hutchinson PJ. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. *Brain* 2011; **134**: 484-494 [PMID: 21247930 DOI: 10.1093/brain/awq353]

P- Reviewer: Demirci H, Tanriverdi F **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.47

World J Crit Care Med 2016 February 4; 5(1): 47-56
ISSN 2220-3141 (online)

REVIEW

Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock

Jihad Mallat, Malcolm Lemyze, Laurent Tronchon, Benoît Vallet, Didier Thevenin

Jihad Mallat, Malcolm Lemyze, Laurent Tronchon, Benoît Vallet, Didier Thevenin, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, 62300 Lens, France

Author contributions: Mallat J contributed to conception, designed and wrote the paper; Lemyze M, Tronchon L, Vallet B and Thevenin D revised the manuscript critically for important intellectual content.

Conflict-of-interest statement: Authors declare no conflicts of interests for this article.

Correspondence to: Jihad Mallat, MD, Department of Anesthesiology and Critical Care Medicine, Centre Hospitalier du Dr. Schaffner de Lens, 99 route de La Bassée, 62300 Lens, France. mallatjihad@gmail.com
Telephone: +33-321-691088
Fax: +33-321-691839

Received: August 5, 2015
Peer-review started: August 6, 2015
First decision: September 16, 2015
Revised: October 12, 2015
Accepted: December 3, 2015
Article in press: December 4, 2015
Published online: February 4, 2016

Abstract

The mixed venous-to-arterial carbon dioxide (CO_2) tension difference [P (v-a) CO_2] is the difference between carbon dioxide tension (PCO_2) in mixed venous blood (sampled from a pulmonary artery catheter) and the PCO_2 in arterial blood. P (v-a) CO_2 depends on the cardiac output and the global CO_2 production, and on the complex relationship between PCO_2 and CO_2 content. Experimental and clinical studies support the evidence that P (v-a) CO_2 cannot serve as an indicator of tissue hypoxia, and should be regarded as an indicator of the adequacy of venous blood to wash out the total CO_2 generated by the peripheral tissues. P (v-a) CO_2 can be replaced by the central venous-to-arterial CO_2 difference (ΔPCO_2), which is calculated from simultaneous sampling of central venous blood from a central vein catheter and arterial blood and, therefore, more easy to obtain at the bedside. Determining the ΔPCO_2 during the resuscitation of septic shock patients might be useful when deciding when to continue resuscitation despite a central venous oxygen saturation ($ScvO_2$) > 70% associated with elevated blood lactate levels. Because high blood lactate levels is not a discriminatory factor in determining the source of that stress, an increased ΔPCO_2 (> 6 mmHg) could be used to identify patients who still remain inadequately resuscitated. Monitoring the ΔPCO_2 from the beginning of the reanimation of septic shock patients might be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy. In this respect, it can aid to titrate inotropes to adjust oxygen delivery to CO_2 production, or to choose between hemoglobin correction or fluid/inotrope infusion in patients with a too low $ScvO_2$ related to metabolic demand. The combination of P (v-a) CO_2 or ΔPCO_2 with oxygen-derived parameters through the calculation of the P (v-a) CO_2 or ΔPCO_2/arteriovenous oxygen content difference ratio can detect the presence of global anaerobic metabolism.

Key words: Venous-to-arterial carbon dioxide tension difference; Carbon dioxide production; Oxygen supply dependency; Cardiac output; tissue hypoxia; Anaerobic metabolism; Oxygen consumption; Resuscitation; Septic shock

Core tip: Early recognition and correction of tissue hypoperfusion are cornerstones in the management of septic shock patients. The venous-to-arterial carbon dioxide tension difference, which is a marker of the adequacy of cardiac output to global metabolic demand, is a helpful additional means to detect patients who stay under-resuscitated after optimization of O_2-derived parameters. In this regard, its monitoring should help the clinicians for the decision of giving therapy targeting at increasing cardiac output.

Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. *World J Crit Care Med* 2016; 5(1): 47-56 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/47.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.47

INTRODUCTION

A shock is a form of acute circulatory failure associated with an inequality between systemic oxygen delivery (DO_2) and oxygen consumption (VO_2), which result in tissue hypoxia[1]. Early recognition and adequate resuscitation of tissue hypoperfusion are of particular importance in the management of septic shock to avoid the development of tissue hypoxia and multi-organ failure. Assessment of mixed venous oxygen saturation (SvO_2) from a pulmonary artery catheter has been proposed as an indirect marker of global tissue oxygenation[2]. SvO_2 reflects the balance between oxygen demand and supply. A low SvO_2 represents a high oxygen extraction (O_2ER) in order to maintain aerobic metabolism and VO_2 constant in response to an acute decrease in DO_2. However, when DO_2 drops under a critical value, O_2ER is no longer capable of upholding VO_2, and global tissue hypoxia appears, as indicated by the occurrence of lactic acidosis[3-5].

Since the assessment of central venous oxygen saturation ($ScvO_2$) can be achieved more easily, and is less risky than from pulmonary artery catheter, it would be useful if $ScvO_2$ could function as an accurate reflection of SvO_2. In fact, SvO_2 is not similar to $ScvO_2$ because the latter primarily reflects the oxygenation of the upper side of the body. In normal patients, $ScvO_2$ is lower than SvO_2 by about 2% to 3%, largely because of the less rate of oxygen extraction by the kidneys[6]. In shock state, the absolute value of $ScvO_2$ was more often reported to be higher than $ScvO_2$, probably due to the oxygen extraction increases in splanchnic and renal tissues[7-11]. This suggests that the existence of a decreased $ScvO_2$ implies an even smaller SvO_2. Because of the lack of agreement regarding absolute values, some authors questioned the clinical utility of $ScvO_2$[12,13]. However, despite absolute values differ, trends in $ScvO_2$ closely mirror trends in SvO_2[8,9], suggesting that monitoring $ScvO_2$ makes sense in critically ill patients.

It has been shown that an early hemodynamic optimization using a resuscitation bundle aimed at increasing $ScvO_2$ > 70% was related to an important reduction in septic shock mortality[14]. Since that, monitoring $ScvO_2$ has become widely recommended[1,14,15]. Recently, three large multicenter studies[16-18] failed to demonstrate any benefits of the early goal-directed therapy approach. Nevertheless, the design of these trials was not to answer the question of whether targeting an $ScvO_2$ > 70% was effective. Also, in these studies, the mean baseline $ScvO_2$ values were already above 70%. Thus, these findings do not indicate that clinicians should stop monitoring $ScvO_2$ and adjust DO_2 by optimizing $ScvO_2$ levels, particularly in septic shock patients with low $ScvO_2$, who are at the highest risk of death[19].

On the other hand, normalization of $ScvO_2$ does not rule out persistent tissue hypoperfusion and does not preclude evolution to multi-organ dysfunction and death[20]. The obvious limitation of $ScvO_2$ is that normal/high values cannot distinguish if DO_2 is sufficient or in excess to demand. In septic conditions, normal/high $ScvO_2$ values might be due to the heterogeneity of the microcirculation that generates capillary shunting and/or mitochondrial damage responsible of disturbances in tissue oxygen extraction. Because $ScvO_2$ is measured downstream from tissues, when a given tissue receives inadequate DO_2, the resulting low local oxygen venous saturations may be "masked" by admixture with highly saturated venous blood from tissues with better perfusion and DO_2, resulting overall in normal or even high $ScvO_2$. Although $ScvO_2$ may thus not miss any global DO_2 dysfunction, it may stay "blind" to local perfusion disturbances, which exist in abundance in sepsis due to damaged microcirculation. Indeed, high $ScvO_2$ values have been associated with increased mortality in septic shock patients[21,22]. Thus, in some circumstances the use of $ScvO_2$ might erroneously drive a clinician to conclude that the physiologic state of the patient has ameliorated when, in fact, it may not have improved.

Lactate has also been proposed as a resuscitation endpoint[23,24]. However, no benefits have been observed for lactate decrease-guided therapy over resuscitation guided by $ScvO_2$ in septic shock patients[25]. Moreover, given the nonspecific nature of lactate level elevation, hyperlactatemia alone is not a discriminatory factor in establishing the source of the circulatory failure. Hence, additional circulatory parameters such as the venous-to-arterial carbon dioxide tension difference are needed to identify patients with septic shock who presently may still insufficiently reanimated, especially when $ScvO_2$ values are normal/high in the context of hyperlactatemia. The purpose of this review is to discuss the physiologic background and the potential clinical usefulness of the venous-to-arterial carbon dioxide tension difference in septic shock.

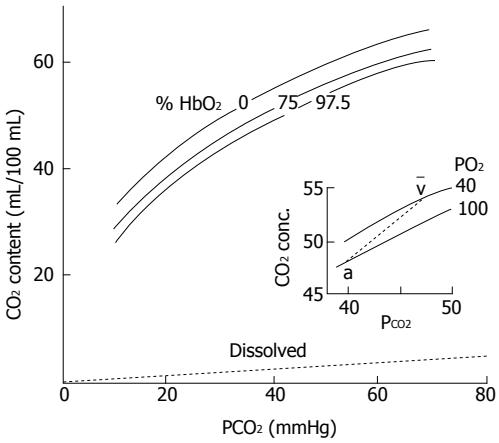


Figure 1 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Differences between the curves result in higher CO_2 content in the blood, and smaller PCO_2 differences between arterial and venous blood. Hemoglobin-O_2 saturation affects the position of the CO_2 dissociation curve (Haldane effect).

PHYSIOLOGICAL BACKGROUND

CO_2 transport in the blood

CO_2 is transported in the blood in three figures[26]: Dissolved, in combination with proteins as carbamino compounds, and as bicarbonate. Physically dissolved CO_2 is a function of CO_2 solubility in blood, which is about 20 times that of oxygen (O_2); therefore, considerably more CO_2 than O_2 is present in simple solution at equal partial pressures. However, dissolved CO_2 shares only around 5% of the whole CO_2 concentration in arterial blood.

Carbamino compounds comprise the second form of CO_2 in the blood. These compounds occur when CO_2 combines with terminal amine groups in blood proteins, especially with the globin of hemoglobin. However, this chemical combination between CO_2 and hemoglobin is much less important than haemoglobin-O_2 binding, so carbamino compounds comprise only 5% of the total CO_2 in the arterial blood.

The bicarbonate ion (HCO_3^-) is the most significant form of the CO_2 carriage in the blood. CO_2 combines with water (H_2O) to form carbonic acid (H_2CO_3), and this dissociates to HCO_3^- and hydrogen ion (H^+): $CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$. Carbonic anhydrase is the enzyme that catalyzes the first reaction, making it almost instantaneous. Carbonic anhydrase occurs mainly in red blood cells (RBC), but it also occurs on pulmonary capillary endothelial cells, and it accelerates the reaction in plasma in the lungs. The uncatalyzed reaction will occur in plasma, but at a much slower rate. The second reaction happens immediately inside RBC and does not require any enzyme. The H_2CO_3 dissociates to H^+ and HCO_3^-, and the H^+ is buffered primarily by hemoglobin while the excess HCO_3^- is transported out the RBC into plasma by an electrically neutral bicarbonate-chloride exchanger. The fast conversion of CO_2 to HCO_3^- results in nearly 90% of the CO_2 in arterial blood being transported in that manner.

Hemoglobin-O_2 saturation is the major factor affecting the capacity of hemoglobin to fix CO_2 (Haldane effect). Consequently, CO_2 concentration increases when blood is deoxygenated, or CO_2 concentration diminishes when blood is oxygenated, at any assumed carbon dioxide tension (PCO_2)[26] (Figure 1). H^+ ions from CO_2 can be deemed as competing with O_2 for hemoglobin binding. Accordingly, rising oxygen reduces the affinity of hemoglobin for H^+ and blood CO_2 concentration (Haldane effect). The physiological assets of the Haldane effect are that it promotes removing of CO_2 in the lungs when blood is oxygenated and CO_2 filling in the blood when oxygen is delivered to tissues. Additionally, the Haldane effect leads to a sharper physiologic CO_2 blood equilibrium curve that has the physiologic interest of rising CO_2 concentration differences for a given PCO_2 difference.

CO_2 is rapidly excreted from the circulation by the lungs by passive diffusion from the capillaries to the alveoli, and its production approximately matches excretion.

The relationship between PCO_2 and the total blood CO_2 content (CCO_2) is curvilinear even though more linear than the oxygen dissociation curve[26]. Oxygen saturation, hematocrit, temperature, and the degree of metabolic acidosis influence the PCO_2/CCO_2 relationship[26]. Hence, for a given value of CCO_2, PCO_2 is higher in the case of metabolic acidosis than in the case of normal pH (Figure 2).

Determinant of venous-to-arterial CO_2 tension difference

The venous-to-arterial CO_2 tension difference [P (v-a) CO_2] is the gradient between PCO_2 in mixed venous blood ($PvCO_2$) and PCO_2 in arterial blood ($PaCO_2$): P (v-a) $CO_2 = PvCO_2 - PaCO_2$; $PvCO_2$ and $PaCO_2$ are partial pressures of the dissolved CO_2 in the mixed venous and arterial blood, respectively.

The application of Fick equation to CO_2 shows that the CO_2 elimination (identical to CO_2 generation in a stable condition) equals the product of the difference between mixed venous blood CO_2 content ($CvCO_2$) and arterial blood CO_2 content ($CaCO_2$) and cardiac output: Total CO_2 production (VCO_2) = cardiac output × ($CvCO_2$ - $CaCO_2$). In spite of a global curvilinear shape of the relation between PCO_2 and the total CCO_2, there is a rather linear association between CCO_2 and PCO_2 over the general physiological range of CO_2 content so that CCO_2 can be substituted by PCO_2 ($PCO_2 = k \times CCO_2$)[27-29]. Therefore, VCO_2 can be calculated from a modified Fick equation as: VCO_2 = cardiac output × k × P (v-a) CO_2 so that P (v-a) $CO_2 = k \times VCO_2$/cardiac output, where k is the pseudo-linear coefficient supposed to be constant in physiological states[27]. Therefore, P (v-a) CO_2 would be linearly linked to CO_2 generation and inversely associated to cardiac output. Under normal conditions, P (v-a) CO_2 values range between 2 and 6 mmHg[30].

Influence of CO_2 production on P (v-a) CO_2

Aerobic CO_2 production: Oxidative phosphorylation proceeds with the formation of energy-laden molecules, CO_2 and water. Total CO_2 production is directly related to VO_2: $VCO_2 = R \times VO_2$, where R is the respiratory

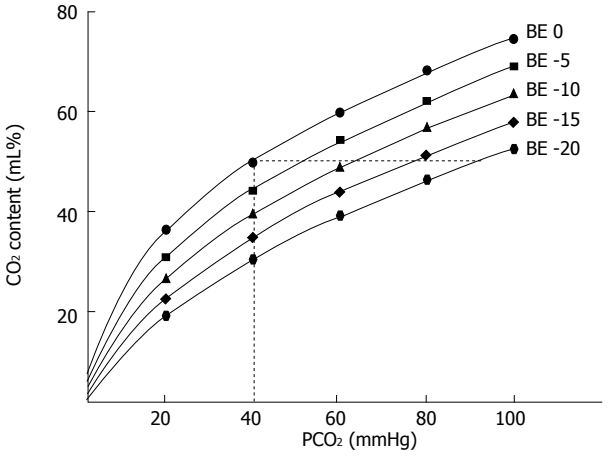


Figure 2 CO_2 dissociation curve. CO_2 content (mL/100 mL) *vs* CO_2 partial tension (PCO_2). Each curve is described at constant base excess (BE). As displayed, for the same CO_2 content, changing the BE results in a great change in PCO_2.

quotient varying among 0.7 and 1.0 according to the energy intake. Under circumstances of important carbohydrate consumption, R becomes close to 1.0. Thus, CO_2 generation should increase either with elevated oxidative metabolism or for a constant VO_2 when a balanced alimentation regime is substituted by a high carbohydrate consumption regime[31]. Under both situations of increased VCO_2, P (v-a) CO_2 should increase unless cardiac output can increase to the same extent.

Anaerobic CO_2 production: Under conditions of tissue hypoxia, there is an increased generation of H^+ ions from an excessive generation of lactic acid due to an acceleration of anaerobic glycolysis, and the hydrolysis of high-energy phosphates[32]. These H^+ ions will then be buffered by the bicarbonate existing in the cells so that CO_2 will be produced. Decarboxylation of metabolic intermediates such as α-ketoglutarate and oxaloacetate during hypoxia is, also, a possible but trivial cause of anaerobic CO_2 generation[32].

Anaerobic CO_2 generation in hypoxic tissues is not simple to identify. Indeed, the effluent venous blood flow can be sufficiently high to wash out the CO_2 generated under these conditions of a significant decline in aerobic CO_2 production[33]. Consequently, PCO_2 could be not increased in the efferent vein, and anaerobic CO_2 generation not recognized from the calculation of P (v-a) CO_2. Nevertheless, if afferent and efferent blood flows are artificially arrested, hypoxia will happen inside the organ and the sustained CO_2 production would then be disclosed by measuring an augmented PCO_2 in the sluggish efferent blood flow, in spite of the drop in CO_2 generation from the aerobic pathway[34,35].

Influence of cardiac output on P (v-a) CO_2

According to the modified Fick equation, P (v-a) CO_2 is related to VCO_2 and inversely linked to cardiac output. Under steady states of both VO_2 and VCO_2, P (v-a) CO_2 was observed to increase in parallel with the reduction in cardiac output[33,36,37]. In other words, when cardiac output is adapted to VO_2, P (v-a) CO_2 should not increase due to increased clearance of CO_2, whereas P (v-a) CO_2 should be high following cardiac output reduction because of a low flow-induced tissue CO_2 stagnation phenomenon. Due to the decreasing of transit time a higher than usual addition of CO_2 per unit of blood passing the efferent microvessels leads to produce hypercapnia in the venous blood. As long as alveolar respiration is sufficient, a gradient will occur between $PvCO_2$ and $PaCO_2$. However, under spontaneous breathing situations, hyperventilation, stimulated by the decreased blood flow, may reduce $PaCO_2$ and thus may prevent the CO_2 stagnation-induced rise in $PvCO_2$[38]. This finding underscores the utility of calculating P (v-a) CO_2 rather than simply assessing $PvCO_2$, particularly in the case of spontaneous breathing[39].

Can P (v-a) CO_2 be used as a marker of tissue hypoxia?

Marked increases in P (v-a) CO_2 were reported in patients during cardiopulmonary resuscitation[40]. Furthermore, higher P (v-a) CO_2 values were observed in patients with circulatory failure compared with those without circulatory failure[41]. These observations were attributed to the decrease of blood flow and the development of anaerobic metabolism with anaerobic CO_2 production. Thus, it has been suggested that P (v-a) CO_2can be used to detect the presence of tissue hypoxia in patients with acute circulatory failure[33,36]. In fact, under conditions of tissue hypoxia with a decreased VO_2, the relationship between changes in cardiac output and P (v-a) CO_2 are much more complex. Indeed, in these circumstances, the increase in CO_2 production related to the anaerobic pathway is counterbalanced by a reduced aerobic CO_2 production, so that VCO_2 and hence P (v-a) CO_2 could be at best unchanged or decreased[37]. Nevertheless, since the k factor should rise during tissue hypoxia[33] while VCO_2 must decrease, the resultant effect on P (v-a) CO_2 depends mainly on the flow state (cardiac output)[27].

Tissue hypoxia with low blood flow

Experimental studies in which blood flow was progressively reduced, an elevation in P (v-a) CO_2 following the reduction in DO_2 was reported, while a constant VO_2 was measured[33,36,37,42]. In this state of O_2 supply-independency and steady CO_2 generation, rising of P (v-a) CO_2 after flow decrease can be explained clearly by CO_2 stagnation.

In those studies, when DO_2 was more diminished under its critical value, a drop in VO_2 was noticed, insinuating O_2 supply-dependency and occurrence of anaerobic metabolism. The progressive widening of P (v-a) CO_2 seen before DO_2 had achieved the critical point, was amplified by an acute rise in $PvCO_2$ when DO_2 declined below that point. The authors[33,36,42] assumed that this brisk increase in P (v-a) CO_2 can be utilized as a good indicator of tissue dysoxia. However, since both VCO_2 (aerobic production) and venous efferent blood flow decrease, P (v-a) CO_2 should not be considerably

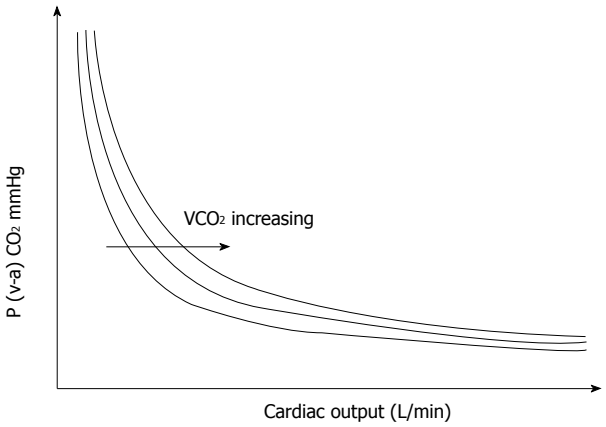


Figure 3 Relationship between the mixed venous-to-arterial PCO_2 difference P (v-a) CO_2 and cardiac output. For a constant total CO_2 production (VCO_2), changes in cardiac output result in large changes in P (v-a) CO_2 in the low values of cardiac output, whereas changes in cardiac output will not result in significant changes in P (v-a) CO_2 in the high values of cardiac output.

changed unless very low values of blood flow were achieved during the supply dependent period. Therefore, from the analysis of the data of these experimental studies[33,36,37,42], it can be reasonably supposed that an abrupt increase in P (v-a) CO_2 should not be easily attributed to the outset of hypoxia but rather to an additional decrease in cardiac output. This fact can be explained by the two following reasons.

Since the association between P (v-a) CO_2 and cardiac output is curvilinear (Fick equation), an enormous rise in P (v-a) CO_2 must be noticed for a reduction in cardiac output in its lowest scale. In fact, even if this mathematical phenomenon may be robust under conditions of maintained VCO_2, it should be moderated in hypoxic states because the decline in VCO_2 leftward shift the isopleth which describes the P (v-a) CO_2/cardiac output relationship (Figure 3).

The curvilinearity of the relationship between $CvCO_2$ and $PvCO_2$ may be another cause for this sharp increase in P (v-a) CO_2. Indeed, due to this particular relationship, $PvCO_2$ changes are greater than $CvCO_2$ changes at the highest range of CCO_2[29]. Furthermore, the disproportions between CCO_2 and PCO_2 at high values of CCO_2 are magnified in the presence of an elevated O_2 saturation and by the decrease in venous pH[29], which is frequently associated with the increase in $PvCO_2$ and may be of greater significance if metabolic acidosis coexists (Figure 2). Therefore, in the case of low flow states, P[v-a]CO_2 can substantially increase resulting from CO_2 stagnation in spite of the decrease in VCO_2 as reported in those experimental studies[33,36,37,42].

Tissue hypoxia with maintained or high blood flow

Under conditions of tissue hypoxia with maintained flow state, venous blood flow should be sufficiently elevated to assure adequate clearance of the CO_2 generated by the hypoxic cells, so that P (v-a) CO_2 should not increase even if the CO_2 production is not decreased. Conversely, low flow states can result in a widening of P (v-a) CO_2 due to the tissue CO_2 stagnation phenomenon[43] even if no additional CO_2 production occurs. This point was nicely demonstrated by Vallet *et al*[44] in a canine model of isolated limb in which a diminished DO_2 by reducing blood flow (ischemic hypoxia) was related to a rise in P (v-a) CO_2. On the other hand, when blood flow was preserved, but arterial PO_2 was decreased by lowering the input oxygen concentration (hypoxic hypoxia), P (v-a) CO_2 did not rise despite a significant decline in VO_2. This because the preserved blood flow was sufficient to clear the generated CO_2[40]. Accordingly, Nevière *et al*[45] demonstrated that for the same level of induced oxygen supply dependency, P (v-a) CO_2 was risen only in ischemic hypoxia but not in hypoxic hypoxia, indicating that augmented P (v-a) CO_2 was mostly linked to the reduction in cardiac output. These studies clearly show that the absence of elevated P (v-a) CO_2 does not preclude the presence of tissue hypoxia and hence underline the good value of P (v-a) CO_2 to detect inadequate tissue perfusion related to its metabolic production but also its poor sensitivity to detect tissue hypoxia. A mathematical model analysis also established that cardiac output plays the key role in the widening of P (v-a) CO_2[46].

Clinical studies

Results from clinical investigations in septic shock patients have also supported that the decreased cardiac output is the major determinant in the elevation of P (v-a) CO_2[37,38]. Mecher *et al*[47] observed that septic shock patients with P (v-a) CO_2 > 6 mmHg had a significantly lower mean cardiac output when compared to patients with P (v-a) CO_2 $\leqslant$ 6 mmHg. No differences in blood lactate levels were found between the two subgroups. Interestingly, the volume expansion engendered a reduction in P (v-a) CO_2 associated with an increase in cardiac output only in patients with elevated P (v-a) CO_2. Moreover, the changes in cardiac output induced by volume expansion were correlated with changes in P (v-a) CO_2 ($R = 0.46$, $P < 0.01$). The authors rightly concluded that in patients with septic shock, an elevated P (v-a) CO_2 is related to a decreased systemic blood flow. In septic shock patients, Bakker *et al*[48] similarly found a significant negative correlation between cardiac output and P (v-a) CO_2. Thus, a strong association between cardiac output and P (v-a) CO_2 is also well documented in septic shock. Furthermore, increased P (v-a) CO_2 was found merely in patients with lower cardiac output. In that study, the dissimilarities in P (v-a) CO_2 cannot be explained by the inequalities in CO_2 production, as implied by the identical VO_2 and lactate concentration found in the two groups of patients[48]. On the other hand, many patients in those studies[47,48] had normal P (v-a) CO_2 despite the presence of tissue hypoxia, presumably since their elevated cardiac output had simply washed out the CO_2 generated in the peripheral circulation.

Creteur *et al*[49] examined the association between impairment in microcirculatory perfusion and tissue PCO_2. They showed that the reperfusion of damaged

microcirculation (assessed using orthogonal polarized spectroscopy) was associated with normalized sublingual tissue PCO_2 levels. Thus, there is a clear relation between tissue CO_2 accumulation and blood flow leading to increasing venous-arterial CO_2 gradients.

In short, altogether, these results strengthen the conception that low flow situations act a crucial part in the enlargement of P (v-a) CO_2 in states of tissue hypoxia. Elevated P (v-a) CO_2 might imply that: (1) cardiac output is not enough under states of supposed tissue hypoxia; and (2) microcirculatory flow is not sufficiently high or adequately distributed to remove the additional CO_2 in spite of the existence of normal/high cardiac output.

The P (v-a) CO_2 should, therefore, be regarded as an indicator of the ability of an adequate venous blood flow return to clear the CO_2 excess rather than as a marker of tissue hypoxia.

Recently, Ospina-Tascon *et al*[50] have shown that the persistence of high P (v-a) CO_2 ($\geqslant$ 6 mmHg) during the first six hours of reanimation of septic shock patients was linked to more severe multiple organ failure and higher mortality rate (Relative Risk = 2.23, P = 0.01). However, further studies are required to test if P (v-a) CO_2 used as a resuscitation endpoint would be associated with improved outcomes.

Central venous-to-arterial PCO_2 difference as a target in resuscitation of septic shock

The measurement of P (v-a) CO_2 requires the presence of a pulmonary artery catheter, which is rarely practiced nowadays[51]. Since the central venous catheter is implanted in most septic shock patients, the usage of central venous-arterial carbon dioxide partial pressure difference (ΔPCO_2) is greatly easier and similarly helpful. Interestingly, a strong agreement between P (v-a) CO_2 and ΔPCO_2, calculated as the difference between central venous PCO_2 sampled from a central vein catheter and arterial PCO_2, was reported in critically ill patients[52] and severe sepsis and septic shock patients[53].

As emphasized above, high values of $ScvO_2$ do not preclude the presence of tissue hypoperfusion and hypoxia in cases of impaired O_2ER capabilities that can occur in septic shock[21,22]. Since the solubility of CO_2 is very high (around 20 times than O_2), its capability of spreading out of ischemic tissues into the efferent veins is phenomenal, making it an extremely sensitive indicator of hypoperfusion. Consequently, in conditions where there are O_2 diffusion difficulties (resulting from shunted and obstructed capillaries), "covering" reduced O_2ER and increased tissue O_2 debt, CO_2 still diffuses to the efferent veins, "uncovering" the hypoperfusion situation for the clinician when ΔPCO_2 is evaluated[54]. Accordingly, Vallée *et al*[55] tested the hypothesis that the ΔPCO_2 can be used as a global indicator of tissue hypoperfusion in reanimated septic shock patients in whom $ScvO_2$ was already greater than 70%. They showed that despite a normalized DO_2/VO_2 ratio, patients who had impaired tissue perfusion with blood lactate concentration > 2 mmol/L remained with an elevated ΔPCO_2 (> 6 mmHg). Also, patients with low ΔPCO_2 values had greater lactate decrease and cardiac index values and exhibited a significantly higher reduction in SOFA score than patients with high ΔPCO_2. In a prospective study that included 80 patients, we recently examined the usefulness of measuring ΔPCO_2 during the initial resuscitation period of septic shock[56]. We found that during the very early period of septic shock, patients who reached a normal ΔPCO_2 ($\leqslant$ 6 mmHg) after six hours of resuscitation had greater decreases in blood lactate and in SOFA score than those who failed to normalize ΔPCO_2 (> 6 mmHg). Interestingly, patients who achieved the goals of both $\Delta PCO_2 \leqslant$ 6 mmHg and $ScvO_2$ > 70% after the first six hours of resuscitation had the greatest blood lactate decrease, which was found to be an independent prognostic factor of ICU mortality[56]. In addition, Du *et al*[57], in a retrospective study, showed that the normalization of both $ScvO_2$ and ΔPCO_2 seems to be a better prognostic factor of outcome after reanimation from septic shock than $ScvO_2$ only. Patients who achieved both targets seemed to clear blood lactate more efficiently[57].

Taken all these studies together[55-57], we believe that monitoring the ΔPCO_2 from the beginning of the reanimation of patients with septic shock may be a valuable means to evaluate the adequacy of cardiac output in tissue perfusion and, thus, guiding the therapy (Figure 4). Indeed, in patients with decreased $ScvO_2$, an augmented ΔPCO_2 is suggestive of the involvement of low cardiac output, and assessing ΔPCO_2 could assist in expediting treatments intended at increasing cardiac output, rather than the arterial O_2 saturation and hemoglobin concentration. When $ScvO_2$ is normal/high ($\geqslant$ 70%), the presence of elevated ΔPCO_2 is indicative of the persisting impaired perfusion. ΔPCO_2 provides further assistance in making the relevant choices about inotropes and fluids. Randomized clinical trial, however, is required to validate this hypothesis.

How to interpret ΔPCO_2 in septic shock sates?

As developed extensively above, the ΔPCO_2 should be considered as a marker of tissue perfusion (*i.e.,* the adequacy of blood flow to wash out the CO_2 generated by the tissues) rather than a marker of tissue hypoxia.

The clinical inferences of this approach can be outlined as follows: (1) in a patient with an initially increased ΔPCO_2 ($\geqslant$ 6 mmHg), clinicians should be aware that blood flow might not be sufficient despite apparent normal macrocirculatory parameters, including $ScvO_2$. Thus, with respect to the metabolic states, an elevated ΔPCO_2 could encourage clinicians to rise cardiac output in order to improve tissue perfusion, especially under suspected hypoxic conditions (elevated blood lactate levels). Nevertheless, we should stress out that, in the absence of suspected conditions of tissue ischemia, increasing cardiac output to supranormal

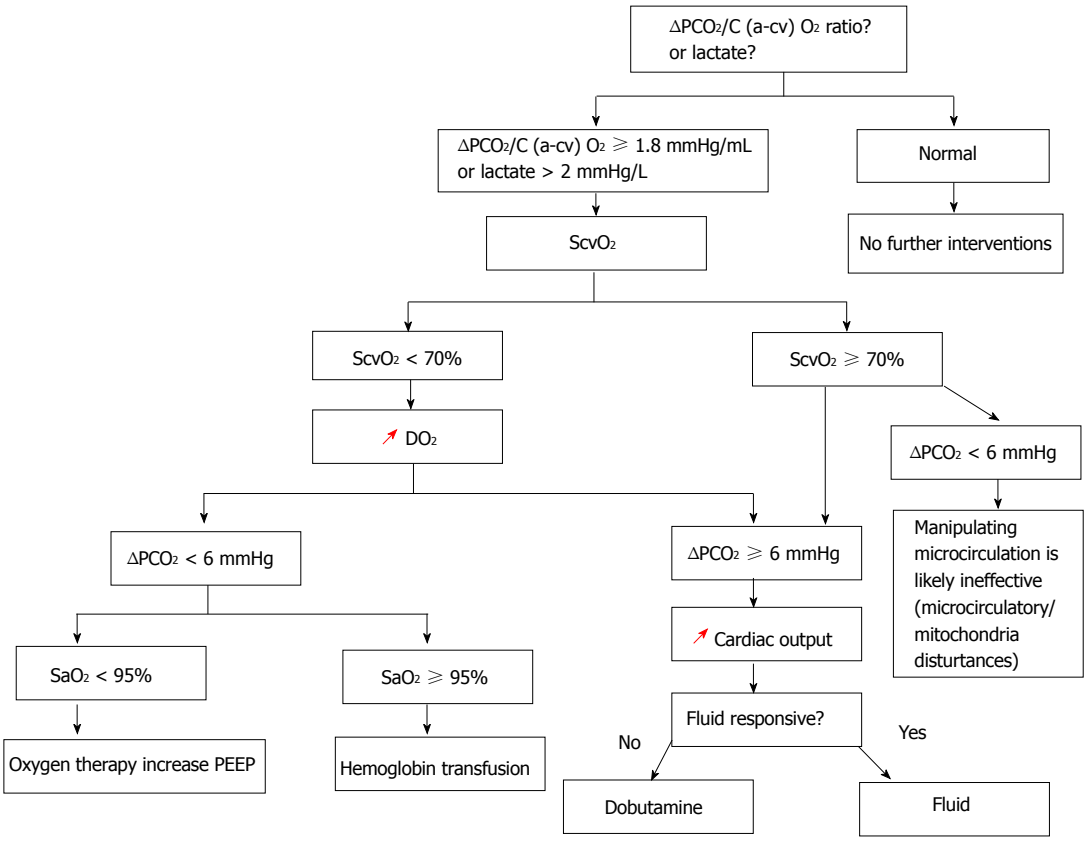


Figure 4 $ScvO_2$-ΔPCO_2 guided protocol. $ScvO_2$: Central venous oxygen saturation; ΔPCO_2: Central venous-to-arterial carbon dioxide tension difference; SaO_2: Arterial oxygen saturation; C (a-cv) O_2: Central arteriovenous oxygen content difference; DO_2: Oxygen delivery; PEEP: Positive end expiratory pressure; red arrows: Increasing.

values not only failed to demonstrate any benefit but could also be potentially harmful in septic shock patients[58,59]; and (2) A normal ΔPCO_2 (< 6 mmHg) would suggest that blood flow is sufficiently high to remove the global CO_2 production from the peripheral circulation, and increasing cardiac output could not be a first concern in the management approach even in the presence of tissue hypoxia. On the other hand, clinicians should keep in mind that a normal ΔPCO_2 with high cardiac output did not preclude the inadequacy of regional blood flow.

The change in ΔPCO_2 - as an index of VCO_2/cardiac output ratio - should be interpreted in line with changes in cardiac output and VCO_2. Under aerobic conditions, ΔPCO_2 along with $ScvO_2$ and O_2ER can serve to guide therapy with dobutamine better than cardiac output in septic shock patients[60]. Indeed, dobutamine in parallel to its effects on systemic hemodynamics may increase VO_2, and therefore VCO_2, through its potential thermogenic effects related to its β_1-adrenergic properties[61]. Recently, we showed that during the stepwise increase of dobutamine dose from 0-10 μg/kg per minute, ΔPCO_2 decreased in parallel with an increase in cardiac output. However, an unchanged ΔPCO_2 was observed when dobutamine was increased from 10-15 μg/kg per minute in spite of the further increase in cardiac output because of the thermogenic effects of the drug at that rate[60]. Thus, ΔPCO_2 can assist the clinician in distinguishing between the hemodynamic and the metabolic effects of dobutamine. Similar results were reported in stable chronic heart failure patients, but with P (v-a) CO_2[43].

Otherwise, the increase in systemic blood flow can affect VCO_2 production under situations of tissue hypoxia. Indeed, under conditions of O_2 supply dependency, an increase in cardiac output may lead to an increase in aerobic VCO_2 production through the supply-dependent increase in VO_2. In this situation, the changes in cardiac output may have no effect on the time-course of ΔPCO_2. Accordingly, almost unaffected ΔPCO_2 with treatment would not indicate that the treatment has been unsuccessful. In such situation, the therapeutic approach would be preferably kept until achieving a significant drop in ΔPCO_2 that would imply that the critical value of DO_2 has been overcome.

Moreover, the clinicians should be aware that because the relationship between ΔPCO_2 and cardiac output is curvilinear, large variations in cardiac output will not necessary engender important variations in ΔPCO_2 (Figure 3). In other words, the interpretation should be cautious in case of high flow states.

Limitations of ΔPCO_2

There are many pre-analytical sources of errors in PCO_2 measurement that should be avoided to interpret ΔPCO_2 correctly: inappropriate sample container, insufficient

sample volume compared to anticoagulant volume, and contaminated sample with resident fluid in the line or with air or venous blood, *etc*. Even after have taken all precautions to minimize the pre-analytical and analytical errors, we, recently, found, in a prospective study[62], that the measurement error for ΔPCO_2 was ± 1.4 mmHg and the smallest detectable difference, which is the least change that requires to be measured by a laboratory analyzer to identify a genuine change of measurement, was ± 2 mmHg. This means that the changes in ΔPCO_2 should be more than ± 2 mmHg to be considered as real changes and not due to natural variation[62].

Combined analysis of P (v-a) CO2 or ΔPCO_2 and O_2-derived parameters

Under situations of tissue hypoxia, a drop in VO_2 is associated with a decline in aerobic CO_2 generation while an anaerobic CO_2 generation can still arise[36,37]. Therefore, the VCO_2 being reduced less than the VO_2, a rise of the respiratory quotient (VCO_2/VO_2 ratio) can be observed[37,63]. Therefore, the rise in the respiratory quotient was suggested to identify global tissue hypoxia[63]. Because VO_2 is equal to the product of cardiac output by the difference between arterial and mixed venous O_2 content C (a-mv) O_2, and VCO_2 is proportional to the product of cardiac output and P (v-a) CO_2 the P (v-a) CO_2/C (a-mv) O_2 ratio could be utilized as indicator of the presence of global tissue hypoxia in critically ill patients. Accordingly, Mekontso-Dessap *et al*[64] tested this hypothesis in a retrospective study of critically ill patients with normalized cardiac output values and DO_2. The authors found a good correlation between P (v-a) CO_2/C (a-mv) O_2 ratio, presented as a substitute of the respiratory quotient, and arterial blood lactate level, while no correlation was found between blood lactate and P (v-a) CO_2 alone and between blood lactate and C (a-mv) O_2 alone. Moreover, for a threshold value > 1.4 the P (v-a) CO_2/C (a-mv) O_2 ratio was able to predict with reliability the presence of hyperlactatemia[64]. The authors concluded that this ratio could be utilized as a reliable indicator of the presence of global anaerobic metabolism in critically ill patients. In a more recent study, Monnet *et al*[65] found that this ratio, calculated from central venous blood [ΔPCO_2/C (a-cv) O_2], predicted an increase in VO_2 after a fluid-induced increase in DO_2 (VO_2/DO_2 dependency), and thus, can be able to detect the presence of global tissue hypoxia as accurately as the blood lactate level and far better than $ScvO_2$. In a series of 60 fluid-responder patients, we recently found that ΔPCO_2/C (a-cv) O_2 ratio at baseline predicted accurately the presence of VO_2/DO_2 dependency phenomenon and better than blood lactate (unpublished data).

In a population of 35 septic shock patients with normalized mean arterial pressure and $ScvO_2$, Mesquida *et al*[66] showed that the presence of elevated ΔPCO_2/C (a-cv) O_2 values at baseline was associated with the absence of lactate clearance within the following hours, and this condition was also associated with mortality. However, this was a retrospective study and it was not powered to explore the prognostic value of the ΔPCO_2/C (a-cv) O_2 ratio. In a recent prospective study that included 135 septic shock patients[67], Ospina-Tascon *et al*[50] found that the mixed venous-to-arterial CCO_2 difference/C (a-mv) O_2 ratio at baseline and six hours after resuscitation was an independent prognostic factor of 28 d mortality, but not P (v-a) CO_2/C (a-mv) O_2 ratio. The authors attributed this discrepancy to the fact that the PCO_2/CCO_2 relationship is curvilinear rather than linear and is influenced by many factors such as pH and oxygen saturation (Haldane effect), and under these conditions, the mixed venous-to-arterial CCO_2 difference/C (a-mv) O_2 ratio might not be equivalent to P (v-a) CO_2/C (a-mv) O_2 ratio.

From the results of those above studies[64-67], we believe that we can reasonably admit that the ΔPCO_2/C (a-cv) O_2 ratio can be used as an indicator of the presence of global tissue hypoxia in critically ill patients. Further clinical trials are needed to assess its prognostic value in patients with septic shock.

CONCLUSION

Early identification and improvement of tissue hypoperfusion are critical factors in the treatment of septic shock patients. The deficit in tissue perfusion with reduced blood flow should be considered as the primary determinant of an increase in ΔPCO_2. ΔPCO_2 should be seen as an indicator of the adequacy of venous blood flow (cardiac output) to clear the CO_2 generated by the peripheral tissues rather than as a marker of tissue hypoxia. Thus, monitoring ΔPCO_2 could be a useful complementary tool to guide the resuscitation in the early phase of septic shock (Figure 4). It can also be combined with the O_2-derived parameters in order to calculate the ΔPCO_2/C (a-cv) O_2, which can be used to detect the presence of global anaerobic metabolism. In such situation, the presence of low $ScvO_2$ (< 70%) should push the physician to increase DO_2, and if ΔPCO_2 is increased (⩾ 6 mmHg), that indicates that increasing cardiac output is the rational choice to achieve this target (Figure 4). In the presence of a normal/high $ScvO_2$ (⩾ 70%), an elevated ΔPCO_2 still suggests that rising cardiac output can be indicated with the purpose of reducing global tissue hypoxia (Figure 4). However, if both $ScvO_2$ and ΔPCO_2 are normal in a state of global anaerobic metabolism, manipulating the microcirculation will probably be ineffective to reduce oxygen deficit (Figure 4).

REFERENCES

1 **Cecconi M**, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL, Vincent JL, Rhodes A. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med* 2014; **40**: 1795-1815 [PMID: 25392034 DOI: 10.1007/s00134-014-3525-z]

2 **Krafft P**, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF. Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest* 1993; **103**: 900-906 [PMID: 8449089]
3 **Schumacker PT**, Cain SM. The concept of a critical oxygen delivery. *Intensive Care Med* 1987; **13**: 223-229 [PMID: 3301969]
4 **Nelson DP**, Samsel RW, Wood LD, Schumacker PT. Pathological supply dependence of systemic and intestinal O2 uptake during endotoxemia. *J Appl Physiol* (1985) 1988; **64**: 2410-2419 [PMID: 3136126]
5 **Zhang H**, Vincent JL. Oxygen extraction is altered by endotoxin during tamponade-induced stagnant hypoxia in the dog. *Circ Shock* 1993; **40**: 168-176 [PMID: 8348680]
6 **Bloos F**, Reinhart K. Venous oximetry. *Intensive Care Med* 2005; **31**: 911-913 [PMID: 15937678]
7 **Chawla LS**, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M. Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 2004; **126**: 1891-1896 [PMID: 15596689]
8 **Reinhart K**, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med* 2004; **30**: 1572-1578 [PMID: 15197435]
9 **Dueck MH**, Klimek M, Appenrodt S, Weigand C, Boerner U. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology* 2005; **103**: 249-257 [PMID: 16052106]
10 **Varpula M**, Karlsson S, Ruokonen E, Pettilä V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Med* 2006; **32**: 1336-1343 [PMID: 16826387]
11 **van Beest PA**, van Ingen J, Boerma EC, Holman ND, Groen H, Koopmans M, Spronk PE, Kuiper MA. No agreement of mixed venous and central venous saturation in sepsis, independent of sepsis origin. *Crit Care* 2010; **14**: R219 [PMID: 21114844 DOI: 10.1186/cc9348]
12 **Martin C**, Auffray JP, Badetti C, Perrin G, Papazian L, Gouin F. Monitoring of central venous oxygen saturation versus mixed venous oxygen saturation in critically ill patients. *Intensive Care Med* 1992; **18**: 101-104 [PMID: 1613187]
13 **Edwards JD**, Mayall RM. Importance of the sampling site for measurement of mixed venous oxygen saturation in shock. *Crit Care Med* 1998; **26**: 1356-1360 [PMID: 9710094]
14 **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169]
15 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]
16 **Yealy DM**, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683-1693 [PMID: 24635773 DOI: 10.1056/NEJMoa1401602]
17 **Peake SL**, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371**: 1496-1506 [PMID: 25272316 DOI: 10.1056/NEJMoa1404380]
18 **Mouncey PR**, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301-1311 [PMID: 25776532 DOI: 10.1056/NEJMoa1500896]
19 **Boulain T**, Garot D, Vignon P, Lascarrou JB, Desachy A, Botoc V, Follin A, Frat JP, Bellec F, Quenot JP, Mathonnet A, Dequin PF. Prevalence of low central venous oxygen saturation in the first hours of intensive care unit admission and associated mortality in septic shock patients: a prospective multicentre study. *Crit Care* 2014; **18**: 609 [PMID: 25529124 DOI: 10.1186/s13054-014-0609-7]
20 **Puskarich MA**, Trzeciak S, Shapiro NI, Heffner AC, Kline JA, Jones AE. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. *Resuscitation* 2011; **82**: 1289-1293 [PMID: 21752522 DOI: 10.1016/j.resuscitation.2011.06.015]
21 **Pope JV**, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; **55**: 40-46.e1 [PMID: 19854541 DOI: 10.1016/j.annemergmed.2009.08.014]
22 **Textoris J**, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, Leone M. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. *Crit Care* 2011; **15**: R176 [PMID: 21791065 DOI: 10.1186/cc10325]
23 **Gu WJ**, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med* 2015; **41**: 1862-1863 [PMID: 26154408 DOI: 10.1007/s00134-015-3955-2]
24 **Zhang Z**, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis*. *Crit Care Med* 2014; **42**: 2118-2125 [PMID: 24797375 DOI: 10.1097/CCM.0000000000000405]
25 **Jones AE**, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739-746 [PMID: 20179283 DOI: 10.1001/jama.2010.158]
26 **West JB**. Gas transport to the periphery: how gases are moved to the peripheral tissues? In: West JB, editor. Respiratory physiology. The essential. 4th ed. Williams & Wilkins: Baltimore, 1990: 69-85
27 **Lamia B**, Monnet X, Teboul JL. Meaning of arterio-venous PCO2 difference in circulatory shock. *Minerva Anestesiol* 2006; **72**: 597-604 [PMID: 16682934]
28 **Giovannini I**, Chiarla C, Boldrini G, Castagneto M. Calculation of venoarterial CO2 concentration difference. *J Appl Physiol* (1985) 1993; **74**: 959-964 [PMID: 8458820]
29 **McHardy GJ**. The relationship between the differences in pressure and content of carbon dioxide in arterial and venous blood. *Clin Sci* 1967; **32**: 299-309 [PMID: 6022823]
30 **Groeneveld AB**. Interpreting the venous-arterial PCO2 difference. *Crit Care Med* 1998; **26**: 979-980 [PMID: 9635634]
31 **Herve P**, Simonneau G, Girard P, Cerrina J, Mathieu M, Duroux P. Hypercapnic acidosis induced by nutrition in mechanically ventilated patients: glucose versus fat. *Crit Care Med* 1985; **13**: 537-540 [PMID: 3924480]
32 **Randall HM**, Cohen JJ. Anaerobic CO2 production by dog kidney in vitro. *Am J Physiol* 1966; **211**: 493-505 [PMID: 4288380]
33 **Zhang H**, Vincent JL. Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. *Am Rev Respir Dis* 1993; **148**: 867-871 [PMID: 8214940]
34 **von Planta M**, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Myocardial acidosis associated with CO2 production during cardiac arrest and resuscitation. *Circulation* 1989; **80**: 684-692 [PMID: 2504512]
35 **Kette F**, Weil MH, Gazmuri RJ, Bisera J, Rackow EC. Intramyocardial hypercarbic acidosis during cardiac arrest and resuscitation. *Crit Care Med* 1993; **21**: 901-906 [PMID: 8504660]
36 **Van der Linden P**, Rausin I, Deltell A, Bekrar Y, Gilbart E, Bakker J, Vincent JL. Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. *Anesth Analg* 1995; **80**: 269-275 [PMID: 7818112]
37 **Groeneveld AB**, Vermeij CG, Thijs LG. Arterial and mixed venous blood acid-base balance during hypoperfusion with incremental positive end-expiratory pressure in the pig. *Anesth Analg* 1991; **73**:

576-582 [PMID: 1952138]
38 **Rackow EC**, Astiz ME, Mecher CE, Weil MH. Increased venous-arterial carbon dioxide tension difference during severe sepsis in rats. *Crit Care Med* 1994; **22**: 121-125 [PMID: 8124954]
39 **Benjamin E**. Venous hypercarbia: a nonspecific marker of hypoperfusion. *Crit Care Med* 1994; **22**: 9-10 [PMID: 8124982]
40 **Weil MH**, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI. Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. *N Engl J Med* 1986; **315**: 153-156 [PMID: 3088448]
41 **Adrogué HJ**, Rashad MN, Gorin AB, Yacoub J, Madias NE. Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood. *N Engl J Med* 1989; **320**: 1312-1316 [PMID: 2535633]
42 **Bowles SA**, Schlichtig R, Kramer DJ, Klions HA. Arteriovenous pH and partial pressure of carbon dioxide detect critical oxygen delivery during progressive hemorrhage in dogs. *J Crit Care* 1992; **7**: 95-105
43 **Teboul JL**, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. *Crit Care Med* 1998; **26**: 1007-1010 [PMID: 9635647]
44 **Vallet B**, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol* (1985) 2000; **89**: 1317-1321 [PMID: 11007564]
45 **Nevière R**, Chagnon JL, Teboul JL, Vallet B, Wattel F. Small intestine intramucosal PCO(2) and microvascular blood flow during hypoxic and ischemic hypoxia. *Crit Care Med* 2002; **30**: 379-384 [PMID: 11889315]
46 **Gutierrez G**. A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. *Am J Respir Crit Care Med* 2004; **169**: 525-533 [PMID: 14656752]
47 **Mecher CE**, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. *Crit Care Med* 1990; **18**: 585-589 [PMID: 2111753]
48 **Bakker J**, Vincent JL, Gris P, Leon M, Coffernils M, Kahn RJ. Veno-arterial carbon dioxide gradient in human septic shock. *Chest* 1992; **101**: 509-515 [PMID: 1735281]
49 **Creteur J**, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 2006; **32**: 516-523 [PMID: 16485092]
50 **Ospina-Tascón GA**, Bautista-Rincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, Bermúdez W, Granados M, Arango-Dávila C, Hernández G. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. *Crit Care* 2013; **17**: R294 [PMID: 24330804 DOI: 10.1186/cc13160]
51 **Richard C**, Monnet X, Teboul JL. Pulmonary artery catheter monitoring in 2011. *Curr Opin Crit Care* 2011; **17**: 296-302 [PMID: 21499096 DOI: 10.1097/MCC.0b013e3283466b85]
52 **Cuschieri J**, Rivers EP, Donnino MW, Katilius M, Jacobsen G, Nguyen HB, Pamukov N, Horst HM. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med* 2005; **31**: 818-822 [PMID: 15803301]
53 **van Beest PA**, Lont MC, Holman ND, Loef B, Kuiper MA, Boerma EC. Central venous-arterial pCO2 difference as a tool in resuscitation of septic patients. *Intensive Care Med* 2013; **39**: 1034-1039 [PMID: 23559077 DOI: 10.1007/s00134-013-2888-x]
54 **Vallet B**, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please "mind the gap"! *Intensive Care Med* 2013; **39**: 1653-1655 [PMID: 23812340 DOI: 10.1007/s00134-013-2998-5]
55 **Vallée F**, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii K, Fourcade O, Genestal M. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med* 2008; **34**: 2218-2225 [PMID: 18607565 DOI: 10.1007/s00134-008-1199-0]
56 **Mallat J**, Pepy F, Lemyze M, Gasan G, Vangrunderbeeck N, Tronchon L, Vallet B, Thevenin D. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. *Eur J Anaesthesiol* 2014; **31**: 371-380 [PMID: 24625464 DOI: 10.1097/EJA.0000000000000064]
57 **Du W**, Liu DW, Wang XT, Long Y, Chai WZ, Zhou X, Rui X. Combining central venous-to-arterial partial pressure of carbon dioxide difference and central venous oxygen saturation to guide resuscitation in septic shock. *J Crit Care* 2013; **28**: 1110.e1-1110.e5 [PMID: 24216336 DOI: 10.1016/j.jcrc.2013.07.049]
58 **Hayes MA**, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; **330**: 1717-1722 [PMID: 7993413]
59 **Gattinoni L**, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med* 1995; **333**: 1025-1032 [PMID: 7675044]
60 **Mallat J**, Benzidi Y, Salleron J, Lemyze M, Gasan G, Vangrunderbeeck N, Pepy F, Tronchon L, Vallet B, Thevenin D. Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine. *Intensive Care Med* 2014; **40**: 404-411 [PMID: 24306082 DOI: 10.1007/s00134-013-3170-y]
61 **Ruffolo RR**. The pharmacology of dobutamine. *Am J Med Sci* 1987; **294**: 244-248 [PMID: 3310640]
62 **Mallat J**, Lazkani A, Lemyze M, Pepy F, Meddour M, Gasan G, Temime J, Vangrunderbeeck N, Tronchon L, Thevenin D. Repeatability of blood gas parameters, PCO2 gap, and PCO2 gap to arterial-to-venous oxygen content difference in critically ill adult patients. *Medicine* (Baltimore) 2015; **94**: e415 [PMID: 25621691 DOI: 10.1097/MD.0000000000000415]
63 **Cohen IL**, Sheikh FM, Perkins RJ, Feustel PJ, Foster ED. Effect of hemorrhagic shock and reperfusion on the respiratory quotient in swine. *Crit Care Med* 1995; **23**: 545-552 [PMID: 7874908]
64 **Mekontso-Dessap A**, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, Teboul JL. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. *Intensive Care Med* 2002; **28**: 272-277 [PMID: 11904655]
65 **Monnet X**, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, Persichini R, Anguel N, Richard C, Teboul JL. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. *Crit Care Med* 2013; **41**: 1412-1420 [PMID: 23442986 DOI: 10.1097/CCM.0b013e318275cece]
66 **Mesquida J**, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, Artigas A. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. *Crit Care* 2015; **19**: 126 [PMID: 25888382 DOI: 10.1186/s13054-015-0858-0]
67 **Ospina-Tascón GA**, Umaña M, Bermúdez W, Bautista-Rincón DF, Hernandez G, Bruhn A, Granados M, Salazar B, Arango-Dávila C, De Backer D. Combination of arterial lactate levels and venous-arterial CO2 to arterial-venous O 2 content difference ratio as markers of resuscitation in patients with septic shock. *Intensive Care Med* 2015; **41**: 796-805 [PMID: 25792204 DOI: 10.1007/s00134-015-3720-6]

P- Reviewer: Zhang ZH **S- Editor**: Qiu S **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.57

World J Crit Care Med 2016 February 4; 5(1): 57-64
ISSN 2220-3141 (online)

REVIEW

Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis

Lukas Buendgens, Alexander Koch, Frank Tacke

Lukas Buendgens, Alexander Koch, Frank Tacke, Department of Medicine Ⅲ, University Hospital Aachen, 52074 Aachen, Germany

Author contributions: Buendgens L, Koch A and Tacke F wrote this review.

Supported by The German Research Foundation, No. DFG Ta434/5-1; and the Interdisciplinary Center for Clinical Research (IZKF) Aachen.

Conflict-of-interest statement: The authors declare no conflict of interest.

Correspondence to: Frank Tacke, MD, PhD, Department of Medicine Ⅲ, University Hospital Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. frank.tacke@gmx.net
Telephone: +49-241-8035848
Fax: +49-241-8082455

Received: October 4, 2015
Peer-review started: October 9, 2015
First decision: November 4, 2015
Revised: November 13, 2015
Accepted: January 5, 2016
Article in press: January 7, 2016
Published online: February 4, 2016

Abstract

Stress-related mucosal disease is a typical complication of critically ill patients in the intensive care unit (ICU). It poses a risk of clinically relevant upper gastrointestinal (GI) bleeding. Therefore, stress ulcer prophylaxis (SUP) is recommended in high-risk patients, especially those mechanically ventilated > 48 h and those with a manifest coagulopathy. Proton pump inhibitors (PPI) and, less effectively, histamine 2 receptor antagonists (H2RA) prevent GI bleeding in critically ill patients in the ICU. However, the routine use of pharmacological SUP does not reduce overall mortality in ICU patients. Moreover, recent studies revealed that SUP in the ICU might be associated with potential harm such as an increased risk of infectious complications, especially nosocomial pneumonia and *Clostridium difficile*-associated diarrhea. Additionally, special populations such as patients with liver cirrhosis may even have an increased mortality rate if treated with PPI. Likewise, PPI can be toxic for both the liver and the bone marrow, and some PPI show clinically relevant interactions with important other drugs like clopidogrel. Therefore, the agent of choice, the specific balance of risks and benefits for individual patients as well as the possible dose of PPI has to be chosen carefully. Alternatives to PPI prophylaxis include H2RA and/or sucralfate. Instead of routine SUP, further trials should investigate risk-adjusted algorithms, balancing benefits and threats of SUP medication in the ICU.

Key words: Proton pump inhibitors; *Clostridium difficile*; Intensive care unit; Gastrointestinal hemorrhage; Stress; Histamine H2 antagonists; Risk assessment; Pneumonia; Physiological; Sucralfate

Core tip: To prevent gastrointestinal (GI) bleeding due to stress-related mucosal disease, critically ill patients are often routinely treated with proton pump inhibitors (PPI) or histamine 2 receptor antagonists (H2RA) for stress ulcer prophylaxis (SUP) in the intensive care unit (ICU). While major GI bleeding is currently rare in the ICU, SUP has not improved the overall survival of ICU patients in large clinical trials. Moreover, PPI and H2RA pose significant risks including toxicity, drug-drug-interactions

and infectious complications (*e.g.*, nosocomial pneumonia or *Clostridium difficile*-associated diarrhea). Instead of routine SUP, risk-adjusted algorithms may better balance benefits and threats of SUP in the ICU.

Buendgens L, Koch A, Tacke F. Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis. *World J Crit Care Med* 2016; 5(1): 57-64 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/57.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.57

INTRODUCTION

The gastric mucosa is sensitive to both hemodynamic changes and inflammatory signals in critical illness. The term stress-related mucosal disease (SRMD) has been introduced to describe the resulting mucosal damage ranging from single lesions to multiple gastric ulcers that may lead to major bleeding complications in critical ill patients[1].

With proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) potent options for pharmacological prophylaxis of such lesions are available. Both are able to decrease the risk of a bleeding event effectively[2] and are usually well tolerated. However, pharmacological stress ulcer prophylaxis (SUP) in the intensive care unit (ICU) has not translated into a mortality benefit in prospective trials. Thus, recently, some intensivists have expressed concerns about the safety of SUP, especially with respect to infectious complications.

EPIDEMIOLOGY

SRMD, as defined by clinical, endoscopic or histological characteristics, is present in most critically ill patients[3]. However, only a few patients experience overt bleeding complications. The fraction of ICU patients with SMRD-related gastrointestinal (GI) bleeding has been reported to be as high as 17% in earlier trials and in patients without prophylaxis[4,5] but has remarkably decreased at present to rates as low as 1% or below[2,6,7].

PATHOPHYSIOLOGY

In most critically ill patients, the gastric mucosal blood flow is impaired. Reasons include systemic hemodynamic changes (hypotension and/or vasopressor therapy) and/or local alterations, *e.g.,* reduced splanchnic blood flow because of positive end-expiratory pressure in mechanical ventilated patients[8]. In addition to the ischemic tissue damage itself, hypoperfusion leads to a reduced production of several protective mechanisms that exist in a healthy stomach (Figure 1)[4]. The latter include various components such as mucus, phospholipids, bicarbonate, trefoil factor family peptides and heat-shock proteins[9]. For example, gastric ischemia/reperfusion in an experimental rat model led to an inhibition of both cyclooxygenase and lipoxygenase pathways, resulting in lower prostaglandin levels (especially PGE2), lower bicarbonate levels and decreased gastric mucosal defense[10,11]. Moreover, two important molecular regulators of vascular tension are dysregulated in critical illness. While the production of the vasodilator nitric oxide is reduced, the level of endothelin-1, a strong vasoconstrictor, is significantly increased[12,13]. This shift can further harm the mucosa.

While these mechanisms can cause mucosal damage, they are often insufficient by themselves to cause major ulcerations and gastric bleeding. A crucial component for overt damage is the presence of gastric acid. Without acid, mucosal damage is only minimal. In animal models of gastric ischemia, the addition of acid increased the damage by factor of ten[12]. This provides the rationale for the use of acid-suppressive drugs such as PPI or H2RA for pharmacological prophylaxis.

MORTALITY RISK OF STRESS ULCER-RELATED BLEEDING

An acute bleeding episode due to a stress ulcer is associated with an increased risk of death in the ICU. In a large prospective trial by Cook *et al*[14] the mortality of patients with stress ulcer bleeding was 49% compared to 9% in those without an episode of GI bleeding. This latter figure, however, appears unusually low for a general ICU population, raising the concern that related co-factors (*e.g.,* co-morbidities, medication) might have affected the mortality risk of ICU patients who experienced bleeding.

Moreover, the patients in this study mainly underwent cardiovascular surgery and only 1.6% presented with sepsis, provoking the question whether the numbers can be extrapolated to other settings of critical illness[14]. Nonetheless, a more recent study by the same authors using multivariate analysis for adjustment showed an increased relative risk (RR) of 1 to 4 (dependent on the model used) as well as an extension of the ICU stay by up to eight days in ICU patients with GI hemorrhage[15].

In contrast to these findings, in a more recent study including 1034 patients in 97 ICUs, GI bleeding was not associated with an increased mortality in multivariate analysis after adjusting for severity of comorbidity, other organ failure and age[7], in line with two meta-analyses reported in 2012 and 2013[2,16]. However, these recent studies all reported a very low incidence of stress ulcer-related bleeding due to effective pharmacological and non-pharmacological prophylactic measures, which may not allow proper assessment of true mortality risk.

RISK FACTORS FOR STRESS ULCER-RELATED BLEEDING

Multiple investigations have been conducted to identify patients at risk for stress ulcer-related bleeding. A

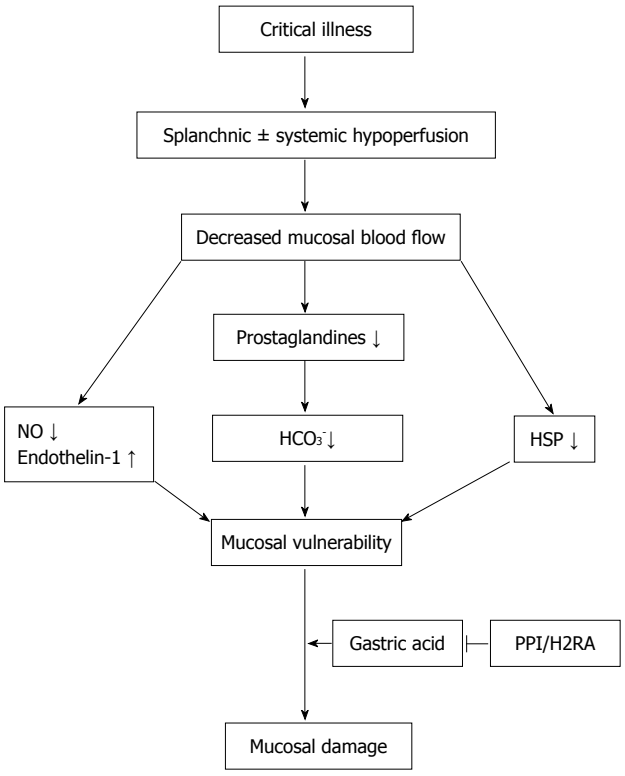


Figure 1 Pathophysiology of stress-related mucosal disease and rationale for the routine use of proton pump inhibitor/histamine 2 receptor antagonists at the intensive care unit. NO: Nitric oxide; PPI: Proton pump inhibitor(s); H2RA: Histamine 2 receptor antagonists; HSP: Heat-shock proteins; HCO_3^-: Bicarbonate.

large, prospective multicenter trial of 2252 ICU patients was able to identify at multiple regression two main risk factors: mechanical ventilation (OR = 15.6; $P < 0.001$) and coagulopathy (OR = 4.3; $P < 0.001$). In the absence of both risk factors the bleeding rate was as low as 0.1%[14]. A smaller, earlier trial came to the same conclusion[17]. A more recent inception cohort study ($n = 1034$) identified the presence of more than three or more comorbidities (OR = 8.9; 95%CI: 2.7-28.8), liver disease (OR = 7.6; 95%CI: 3.3-17.6); use of renal replacement therapy (OR = 6.9; 95%CI: 2.7-17.5); a coexisting (OR = 5.2; 95%CI: 2.3-11.8) or acute coagulopathy (OR = 4.2; 95%CI: 1.7-10.2) and higher SOFA-score (OR = 1.4; 95%CI: 1.2-1.6) as significant risk factors after multivariate analysis. Interestingly, mechanical ventilation was not associated with an increased risk of GI bleeding in this trial[7].

Other risk factors with a lower degree of evidence include patients with severe head trauma, those who have had extended surgeries with operation times exceeding 4 h as well as patients with acute kidney or hepatic failure, sepsis, hypotension, a history of gastrointestinal bleeding, high-dose corticosteroids, burn patients, advanced age and male sex[1,3,17,18]. This wide spectrum of suggested risk factors has prompted the rather unselected use of pharmacological SUP in the ICU setting, resulting in the routine use of PPI and/or H2RAs in > 80% of critically ill patients as reported in in many observational studies[6,7].

INDICATIONS FOR PHARMACOLOGICAL PROPHYLAXIS

While SRMD-related bleeding can have severe clinical impact, acid-suppressive medication effectively decreases bleeding rates as demonstrated by multiple meta-analyses on this topic[19-22]. Although the quality of the available data has been criticized[23], both national and international guidelines recommend stress ulcer prophylaxis (SUP) in critically ill patients with sepsis and other risk factors[24,25].

In our ICU, patients with at least one of the following risk factors are recommended to receive pharmacological ulcer prophylaxis based upon current evidence: Mechanical ventilation, coagulopathy, history of an upper gastrointestinal bleeding within the past 12 mo, severe sepsis or septic shock, or cardiogenic shock. Additionally, we consider ulcer prophylaxis for the following patients based on weaker evidence: burn patients, those with cranio-cerebral injury, acute renal failure, known peptic ulcer disease, those post kidney or liver transplantation and patients taking non-steroidal anti-inflammatory drugs (NSAID) or high-dose glucocorticoids. The algorithm that we propose for SUP in the ICU is presented as Figure 2.

However, it is mandatory to frequently re-evaluate the individual indication both during and after ICU stay. Buckley *et al*[26] could show that 14.4% of patients in an ICU received acid suppression without proper indication, which resulted in unnecessary risk of side effects (see below) and unnecessary costs (> 200000 dollar annually in the study hospital).

While prophylaxis effectively decreases the risk of stress ulcer-related bleeding, it is important to stress that no single trial and/or meta-analysis has been able to convincingly demonstrate a benefit regarding survival. Outside an ICU or even in outpatients, very little evidence supports the use of stress ulcer prophylaxis; for instance, patients with cardiovascular diseases who have concomitant newly prescribed with the oral anticoagulant dabigatran may be at lower risk for severe GI bleedings if PPI are administered[27]. Without a proper indication or a clear high-risk assessment, SUP should be discontinued, because it might cause unnecessary harm (see below) as well as costs[22].

PHARMACOLOGICAL PROPHYLAXIS

If a stress ulcer prophylaxis is necessary, different options are available: Options include the acid-suppressing drugs, PPI and H2RA, or the mucosa-protective agent sucralfate. Sucralfate is a reasonable option and reduces the risk of stress ulcer-related bleeding. However, a large trial revealed its inferiority to H2RA[28], so that an acid-suppressive medication is preferred for SUP.

There are several trials and meta-analyses comparing PPI to H2RA. Most of them favor PPI with respect to reduction of bleeding rates (Table 1). Regarding mortality, no analysis has been able to show a significant difference. Currently, PPI are the agents of choice in SUP.

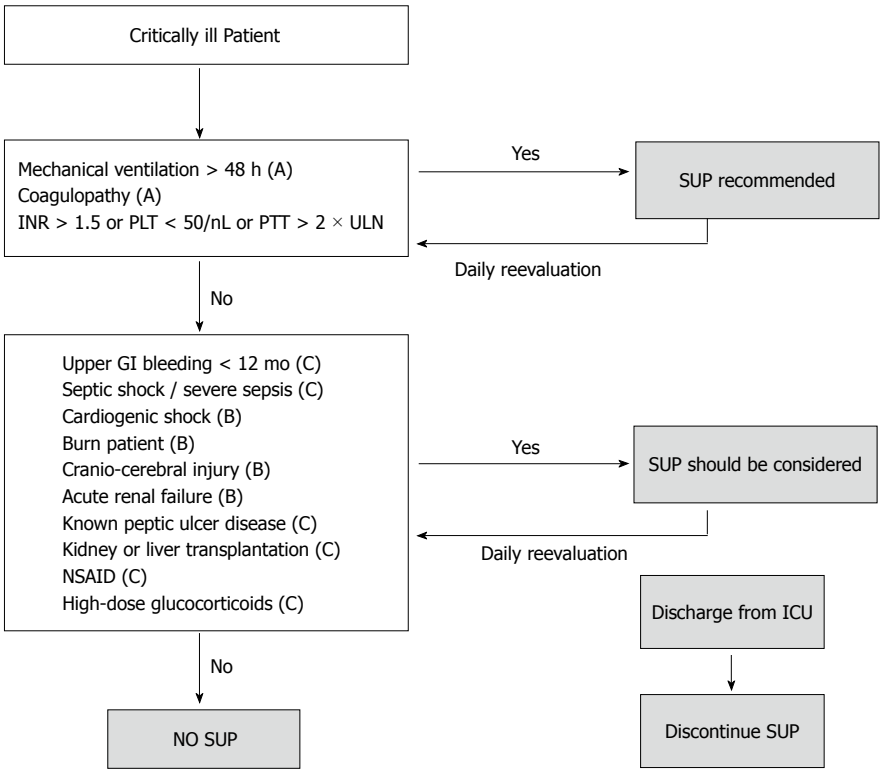


Figure 2 Proposed algorithm for stress ulcer prophylaxis. For the different indications for SUP, the level of evidence is provided [A: Multiple randomized trials or meta-analysis, B: Single randomized or large non-randomized trial(s), C: Expert opinion or retrospective studies]. GI: Gastrointestinal; ICU: Intensive care unit; INR: International normalized ratio; NO: Nitric oxide; NSAID: Nonsteroidal anti-inflammatory drugs; PLT: Platelets; PTT: Partial thromboplastin time; SUP: Stress ulcer prophylaxis.

Table 1 Efficacy of proton pump inhibitor compared to histamine 2 receptor antagonists at the intensive care unit

Meta-analysis	*n*	Risk reduction (bleeding)	Risk reduction (mortality)
Alhazzani *et al*[2]	1720	RR = 0.36 (95%CI: 0.19-0.67)	RR = 1.01 (95%CI: 0.83-1.24)
Pongprasobchai *et al*[59]	569	OR = 0.42 (95%CI: 0.20-0.91)	n/a
Barkun *et al*[60]	1587	OR = 0.30 (95%CI: 0.17-0.54)	OR = 1.19 (95%CI: 0.84-1.68)
Lin *et al*[61]	936	RD = 0.04 (95%CI: 0.09-0.01)	RD = 0.00 (95%CI: 0.04-0.05)

n/a: Not assessed; *n*: Patients included in the meta-analysis; RR: Relative risk; OR: Odds ratio; PPI: Proton pump inhibitor(s); RD: Risk difference.

ADVERSE EVENTS

Gastric acid is a natural physiological barrier against ingested pathogens. Pharmacological acid suppression alters this barrier significantly. Subsequently, it is associated with gastric and duodenal bacterial overgrowth[29]. This effect is stronger in patients receiving PPI than in those taking H2RA[30]. The loss of this natural barrier may lead to intestinal (*e.g., Clostridium difficile*-associated diarrhea), but also to extra-intestinal infections (*e.g.,* pneumonia, possibly *via* retrograde microaspiration). In addition, both PPI and H2RA potentially affect leucocyte function: Experimental studies have shown an effect of these drugs on both phagocytosis by neutrophils itself and the acidification of the phagolysosome in neutrophils necessary to kill its contents[31,32].

As the effects of acid-suppressing drugs may render patients susceptible for infections, two main complications have to be considered: *Clostridium difficile*-associated diarrhea (CDAD) and pneumonia. In outpatients and patients on standard care wards, it has been shown that PPI increase the risk of both significantly[6,33-44]. Additionally, experiments in mice suggest that acid suppression favors intestinal colonization with multi-resistant bacteria such as Vancomycin-resistant *Enterococcus faecium* (VRE) or multi-resistant *Klebsiella pneumonia*[45].

In the setting of SUP in the ICU, the data are controversial (Table 2). Two meta-analyses failed to show any effect on the rate of nosocomial and/or ventilator-associated pneumonia[2,16]. However, only seven of the original studies included reported on pneumonia. In contrast, a small (n = 137) but prospective and randomized trial showed a strong increase in ventilator-associated pneumonia within the PPI group compared to placebo (36.4% *vs* 14.1%, $P < 0.001$)[46].

A retrospective study from our group found a significant association of PPI with pneumonia only by univariate but not by multivariate analysis[6]. A prevalence study including over 10000 patients from 17 countries identified SUP as an independent risk factor for infections[47]. Thus, the role of acid suppression as a risk factor for pneumonia is unclear but remains likely. Larger randomized prospective

Table 2 Acid suppression as a risk factor for pneumonia at the intensive care unit

Acid suppression as a risk factor for		Pneumonia
Barkun *et al*[16]	Meta-analysis	OR = 1.05 (95%CI: 0.69-1.62)
Alhazzani *et al*[2]	Meta-analysis	RR = 1.06 (95%CI: 0.73-1.52)
Khorvash *et al*[6]	Randomized controlled trial	14.1% without *vs* 36.4% with PPI, $P < 0.001$
Buendgens *et al*[6]	Retrospective cohort study	OR = 1.28 (95%CI: 0.95-1.73)

OR: Odds ratio; RR: Relative risk; PPI: Proton pump inhibitor.

trials are warranted to resolve this issue.

The main infection route of *C. difficile* is *via* ingestion of its spores and its vegetative forms. While the spores are naturally resistant to acid, the vegetative form is normally killed by acid in the stomach. If the stomach pH is raised above 5, *Clostridia* species show drastically improved survival. Given that the stool of infected individuals contains tenfold more vegetative forms than spores, this might explain an association of PPI and H2RA with CDAD[48].

Although no prospective data is available on this matter for critically ill patients, studies suggest an association between pharmacological SUP and CDAD in the ICU (Table 3). A small case-control study showed a positive association between the duration of PPI therapy and the risk of CDAD[49]. A retrospective study with 3286 ICU patients demonstrated PPI as an independent risk factor for CDAD by multivariate analysis (OR = 3.11; 95%CI: 1.11-8.74), comparable to the risk for CDAD associated with the use of fluoroquinolones or third-generation cephalosporins. Moreover, in this trial an ICU-onset CDAD was associated with an increased mortality (OR = 1.59; 95%CI: 1.06-2.41)[6]. Another recent study from Canada revealed a significant association with CDAD recurrence rates and continuation of PPI therapy (OR = 1.5; 95%CI: 1.1-2.0), similar to antibiotic reexposure (OR = 1.3; 95%CI: 0.9-1.7)[50].

Patients with liver cirrhosis appear to pose a population particularly prone to adverse effects of SUP. A prospective study including 272 patients with cirrhosis found the use of PPI to be an independent risk factor for overall mortality by multivariate analysis in those patients (HR = 2.3; 95%CI: 1.3-4.3)[51]. Reasons for this might be an increased risk of spontaneous bacterial peritonitis in addition to higher rates of pneumonia and CDAD[52-54].

Drug-drug-interactions are another concern for using PPI, especially in ICU patients. An important possible interaction exists between the antiplatelet agent clopidogrel and various PPI. In 2009, a study reported increased cardiovascular events in patients taking both clopidogrel and PPI[55]. The antiplatelet agent clopidogrel is a prodrug, dependent on the enzyme CYP2C19. *In vitro* PPI inhibit CYP2C19 and potentially inhibit clopidogrel. It remains unclear if this experimental finding is of clinical

Table 3 Proton pump inhibitor as a risk factor for *Clostridium difficile*-associated diarrhea at the intensive care unit

PPI as a risk factor for		*Clostridium difficile*-associated diarrhea (OR, 95%CI)
Barletta *et al*[49]	Case control study	1.14 (1.02-1.27)
Buendgens *et al*[6]	Retrospective cohort study	3.11 (1.11-8.74)

OR: Odds ratio; PPI: Proton pump inhibitor.

importance, since the patients with concomitant use of PPI and clopidogrel might have had a higher intrinsic risk due to greater age and more cardiovascular risk factors. In order to overcome this potential interaction, independent ingestion times, the use of pantoprazole (a PPI with low interaction potential) and/or replacing clopidogrel with ticagrelor, which is not a prodrug, have been suggested.

Other side effects of PPI potentially relevant for critically ill patients include toxicity to liver or bone marrow and hypomagnesaemia. The latter has resulted in a recent warning from the Food and Drug Administration of the United States[56]. Osteopenia, another known association, seems less important acutely in ICU patients[57]. It is currently unknown if those adverse effects affect the prognosis of patients in an ICU.

ENTERAL NUTRITION

With regard to the potential adverse effects of SUP as described above, potential alternatives have been discussed. One should also keep in mind that both PPI and H2RA do not have a direct effect on the SRMD pathophysiology of reduced blood flow and altered balance between vasoconstrictors and dilatators (Figure 1). Enteral nutrition, in contrast, potentially has a positive impact on both[58]. Enteral nutrition could therefore be a viable alternative to pharmacological SUP. However, no prospective data is available on this subject. A meta-analysis of data available on 1836 patients disclosed that in presence of enteral nutrition a pharmacological SUP did not significantly change the risk of stress ulcer-related bleeding. Interestingly, in those patients that were enterally fed and treated with SUP the risk of pneumonia was increased (OR = 2.81; 95%CI: 1.2-6.6) compared to patients on parenteral nutrition. In this subgroup, even an increase in mortality was observed[21]. Therefore, the role of enteral nutrition in SUP should be further explored in randomized prospective trials.

CONCLUSION

Critically ill patients often develop gastrointestinal lesions due to altered perfusion of the gastric mucosa, reduced protective mucosal factors and increased gastric acid, rendering them at risk for GI bleeding due to SRMD or ulcers. Pharmacological SUP is performed in the majority of ICU patients at present, with PPI or H2RA effectively preventing GI bleeding. However, this common practice

is currently debated, due to the fact that SUP does not significantly improve mortality of ICU patients, while acid suppression poses relevant risks. Specifically, nosocomial pneumonia and *Clostridium difficile* associated diarrhea are potential serious complications of SUP. Thus, SUP should follow a clear algorithm balancing risks and benefits (Figure 2). Alternative strategies like enteral feeding or restricting SUP to the early phase of ICU treatment or to patients with an exceptional high-risk profile deserve evaluation in prospective randomized trials.

REFERENCES

1 **Stollman N**, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care* 2005; **20**: 35-45 [PMID: 16015515 DOI: 10.1016/j.jcrc.2004.10.003]

2 **Alhazzani W**, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013; **41**: 693-705 [PMID: 23318494 DOI: 10.1097/CCM.0b013e3182758734]

3 **Bardou M**, Quenot JP, Barkun A. Stress-related mucosal disease in the critically ill patient. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 98-107 [PMID: 25560847 DOI: 10.1038/nrgastro.2014.235]

4 **Laine L**, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology* 2008; **135**: 41-60 [PMID: 18549814 DOI: 10.1053/j.gastro.2008.05.030]

5 **Shuman RB**, Schuster DP, Zuckerman GR. Prophylactic therapy for stress ulcer bleeding: a reappraisal. *Ann Intern Med* 1987; **106**: 562-567 [PMID: 3548524 DOI: 10.7326/0003-4819-106-4-562]

6 **Buendgens L**, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, Tacke F, Koch A. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea. *J Crit Care* 2014; **29**: 696.e11-696.e15 [PMID: 24674763 DOI: 10.1016/j.jcrc.2014.03.002]

7 **Krag M**, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Møller MH. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med* 2015; **41**: 833-845 [PMID: 25860444 DOI: 10.1007/s00134-015-3725-1]

8 **Fujita Y**. Effects of PEEP on splanchnic hemodynamics and blood volume. *Acta Anaesthesiol Scand* 1993; **37**: 427-431 [PMID: 8322573 DOI: 10.1111/j.1399-6576.1993.tb03742.x]

9 **de Foneska A**, Kaunitz JD. Gastroduodenal mucosal defense. *Curr Opin Gastroenterol* 2010; **26**: 604-610 [PMID: 20948371 DOI: 10.1097/MOG.0b013e32833f1222]

10 **Nakagiri A**, Murakami M. Roles of NADPH oxidase in occurrence of gastric damage and expression of cyclooxygenase-2 during ischemia/reperfusion in rat stomachs. *J Pharmacol Sci* 2009; **111**: 352-360 [PMID: 19942802 DOI: 10.1254/jphs.09169FP]

11 **Peskar BM**, Ehrlich K, Schuligoi R, Peskar BA. Role of lipoxygenases and the lipoxin A(4)/annexin 1 receptor in ischemia-reperfusion-induced gastric mucosal damage in rats. *Pharmacology* 2009; **84**: 294-299 [PMID: 19816089 DOI: 10.1159/000244017]

12 **Michida T**, Kawano S, Masuda E, Kobayashi I, Nishimura Y, Tsujii M, Takei Y, Tsuji S, Nagano K, Fusamoto H, Kamada T, Sugimoto T. Endothelin-1 in the gastric mucosa in stress ulcers of critically ill patients. *Am J Gastroenterol* 1997; **92**: 1177-1181 [PMID: 9219794]

13 **Björne H**, Govoni M, Törnberg DC, Lundberg JO, Weitzberg E. Intragastric nitric oxide is abolished in intubated patients and restored by nitrite. *Crit Care Med* 2005; **33**: 1722-1727 [PMID: 16096448 DOI: 10.1097/01.CCM.0000171204.59502.AA]

14 **Cook DJ**, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, Winton TL, Rutledge F, Todd TJ, Roy P. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med* 1994; **330**: 377-381 [PMID: 8284001 DOI: 10.1056/NEJM199402103300601]

15 **Cook DJ**, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001; **5**: 368-375 [PMID: 11737927 DOI: 10.1186/cc1071]

16 **Barkun AN**, Bardou M, Pham CQ, Martel M. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 507-520; quiz 521 [PMID: 22290403 DOI: 10.1038/ajg.2011.474]

17 **Schuster DP**, Rowley H, Feinstein S, McGue MK, Zuckerman GR. Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. *Am J Med* 1984; **76**: 623-630 [PMID: 6608877]

18 **Quenot JP**, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? *Curr Opin Crit Care* 2009; **15**: 139-143 [PMID: 19578324 DOI: 10.1097/MCC.0b013e32832978e0]

19 **Kahn JM**, Doctor JN, Rubenfeld GD. Stress ulcer prophylaxis in mechanically ventilated patients: integrating evidence and judgment using a decision analysis. *Intensive Care Med* 2006; **32**: 1151-1158 [PMID: 16788804 DOI: 10.1007/s00134-006-0244-0]

20 **Cook DJ**, Reeve BK, Guyatt GH, Heyland DK, Griffith LE, Buckingham L, Tryba M. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996; **275**: 308-314 [PMID: 8544272 DOI: 10.1001/jama.1996.03530280060038]

21 **Marik PE**, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med* 2010; **38**: 2222-2228 [PMID: 20711074 DOI: 10.1097/CCM.0b013e3181f17adf]

22 **Messori A**, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials. *BMJ* 2000; **321**: 1103-1106 [PMID: 11061729 DOI: 10.1136/bmj.321.7269.1103]

23 **Krag M**, Perner A, Wetterslev J, Wise MP, Hylander Møller M. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. *Intensive Care Med* 2014; **40**: 11-22 [PMID: 24141808 DOI: 10.1007/s00134-013-3125-3]

24 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165-228 [PMID: 23361625 DOI: 10.1007/s00134-012-2769-8]

25 **Reinhart K**, Brunkhorst FM, Bone HG, Bardutzky J, Dempfle CE, Forst H, Gastmeier P, Gerlach H, Gründling M, John S, Kern W, Kreymann G, Krüger W, Kujath P, Marggraf G, Martin J, Mayer K, Meier-Hellmann A, Oppert M, Putensen C, Quintel M, Ragaller M, Rossaint R, Seifert H, Spies C, Stüber F, Weiler N, Weimann A, Werdan K, Welte T. [Prevention, diagnosis, treatment, and follow-up care of sepsis. First revision of the S2k Guidelines of the German Sepsis Society (DSG) and the German Interdisciplinary Association for Intensive and Emergency Care Medicine (DIVI)]. *Anaesthesist* 2010; **59**: 347-370 [PMID: 20414762 DOI: 10.1007/s00101-010-1719-5]

26 **Buckley MS**, Park AS, Anderson CS, Barletta JF, Bikin DS, Gerkin RD, O'Malley CW, Wicks LM, Garcia-Orr R, Kane-Gill SL. Impact of a clinical pharmacist stress ulcer prophylaxis management program on inappropriate use in hospitalized patients. *Am J Med* 2015; **128**: 905-913 [PMID: 25820164 DOI: 10.1016/j.amjmed.2015.02.014]

27 **Chan EW**, Lau WC, Leung WK, Mok MT, He Y, Tong TS,

Wong IC. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. *Gastroenterology* 2015; **149**: 586-595.e3 [PMID: 25960019 DOI: 10.1053/j.gastro.2015.05.002]

28 **Cook D**, Guyatt G, Marshall J, Leasa D, Fuller H, Hall R, Peters S, Rutledge F, Griffith L, McLellan A, Wood G, Kirby A. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; **338**: 791-797 [PMID: 9504939 DOI: 10.1056/NEJM199803193381203]

29 **Thorens J**, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, Duroux P, Nicolet M, Pignatelli B, Blum AL, Gonvers JJ, Fried M. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut* 1996; **39**: 54-59 [PMID: 8881809 DOI: 10.1136/gut.39.1.54]

30 **Wang K**, Lin HJ, Perng CL, Tseng GY, Yu KW, Chang FY, Lee SD. The effect of H2-receptor antagonist and proton pump inhibitor on microbial proliferation in the stomach. *Hepatogastroenterology* 2004; **51**: 1540-1543 [PMID: 15362796]

31 **Agastya G**, West BC, Callahan JM. Omeprazole inhibits phagocytosis and acidification of phagolysosomes of normal human neutrophils in vitro. *Immunopharmacol Immunotoxicol* 2000; **22**: 357-372 [PMID: 10952036 DOI: 10.3109/08923970009016425]

32 **Zedtwitz-Liebenstein K**, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med* 2002; **30**: 1118-1122 [PMID: 12006811]

33 **Kwok CS**, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; **107**: 1011-1019 [PMID: 22525304 DOI: 10.1038/ajg.2012.108]

34 **Herzig SJ**, Vaughn BP, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for nosocomial gastrointestinal tract bleeding. *Arch Intern Med* 2011; **171**: 991-997 [PMID: 21321285 DOI: 10.1001/archinternmed.2011.14]

35 **Laheij RJ**, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292**: 1955-1960 [PMID: 15507580 DOI: 10.1001/jama.292.16.1955]

36 **Johnstone J**, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. *Aliment Pharmacol Ther* 2010; **31**: 1165-1177 [PMID: 20222914 DOI: 10.1111/j.1365-2036.2010.04284.x]

37 **Aseeri M**, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008; **103**: 2308-2313 [PMID: 18702653 DOI: 10.1111/j.1572-0241.2008.01975.x]

38 **Giuliano C**, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. *Expert Rev Clin Pharmacol* 2012; **5**: 337-344 [PMID: 22697595 DOI: 10.1586/ecp.12.20]

39 **Filion KB**, Chateau D, Targownik LE, Gershon A, Durand M, Tamim H, Teare GF, Ravani P, Ernst P, Dormuth CR. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. *Gut* 2014; **63**: 552-558 [PMID: 23856153 DOI: 10.1136/gutjnl-2013-304738]

40 **Eom CS**, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ* 2011; **183**: 310-319 [PMID: 21173070 DOI: 10.1503/cmaj.092129]

41 **Dial S**, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**: 2989-2995 [PMID: 16414946 DOI: 10.1001/jama.294.23.2989]

42 **Tleyjeh IM**, Bin Abdulhak AA, Riaz M, Alasmari FA, Garbati MA, AlGhamdi M, Khan AR, Al Tannir M, Erwin PJ, Ibrahim T, Allehibi A, Baddour LM, Sutton AJ. Association between proton pump inhibitor therapy and clostridium difficile infection: a contemporary systematic review and meta-analysis. *PLoS One* 2012; **7**: e50836 [PMID: 23236397 DOI: 10.1371/journal.pone.0050836]

43 **Janarthanan S**, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 1001-1010 [PMID: 22710578 DOI: 10.1038/ajg.2012.179]

44 **Pant C**, Madonia P, Minocha A. Does PPI therapy predispose to Clostridium difficile infection? *Nat Rev Gastroenterol Hepatol* 2009; **6**: 555-557 [PMID: 19713988 DOI: 10.1038/nrgastro.2009.128]

45 **Stiefel U**, Rao A, Pultz MJ, Jump RL, Aron DC, Donskey CJ. Suppression of gastric acid production by proton pump inhibitor treatment facilitates colonization of the large intestine by vancomycin-resistant Enterococcus spp. and Klebsiella pneumoniae in clindamycin-treated mice. *Antimicrob Agents Chemother* 2006; **50**: 3905-3907 [PMID: 16940078 DOI: 10.1128/AAC.00522-06]

46 **Khorvash F**, Abbasi S, Meidani M, Dehdashti F, Ataei B. The comparison between proton pump inhibitors and sucralfate in incidence of ventilator associated pneumonia in critically ill patients. *Adv Biomed Res* 2014; **3**: 52 [PMID: 24627860 DOI: 10.4103/2277-9175.125789]

47 **Vincent JL**, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; **274**: 639-644 [PMID: 7637145 DOI: 10.1001/jama.1995.03530080055041]

48 **Jump RL**, Pultz MJ, Donskey CJ. Vegetative Clostridium difficile survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pump inhibitors and C. difficile-associated diarrhea? *Antimicrob Agents Chemother* 2007; **51**: 2883-2887 [PMID: 17562803 DOI: 10.1128/AAC.01443-06]

49 **Barletta JF**, El-Ibiary SY, Davis LE, Nguyen B, Raney CR. Proton Pump Inhibitors and the Risk for Hospital-Acquired Clostridium difficile Infection. *Mayo Clin Proc* 2013; **88**: 1085-1090 [PMID: 24012413 DOI: 10.1016/j.mayocp.2013.07.004]

50 **McDonald EG**, Milligan J, Frenette C, Lee TC. Continuous Proton Pump Inhibitor Therapy and the Associated Risk of Recurrent Clostridium difficile Infection. *JAMA Intern Med* 2015; **175**: 784-791 [PMID: 25730198 DOI: 10.1001/jamainternmed.2015.42]

51 **Dultz G**, Piiper A, Zeuzem S, Kronenberger B, Waidmann O. Proton pump inhibitor treatment is associated with the severity of liver disease and increased mortality in patients with cirrhosis. *Aliment Pharmacol Ther* 2015; **41**: 459-466 [PMID: 25523381 DOI: 10.1111/apt.13061]

52 **Goel GA**, Deshpande A, Lopez R, Hall GS, van Duin D, Carey WD. Increased rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression. *Clin Gastroenterol Hepatol* 2012; **10**: 422-427 [PMID: 22155557 DOI: 10.1016/j.cgh.2011.11.019]

53 **Trikudanathan G**, Israel J, Cappa J, O'Sullivan DM. Association between proton pump inhibitors and spontaneous bacterial peritonitis in cirrhotic patients - a systematic review and meta-analysis. *Int J Clin Pract* 2011; **65**: 674-678 [PMID: 21564440 DOI: 10.1111/j.1742-1241.2011.02650.x]

54 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Mapara S, Hassan S, Rolston DD, Sferra TJ, Hernandez AV. Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. *J Gastroenterol Hepatol* 2013; **28**: 235-242 [PMID: 23190338 DOI: 10.1111/jgh.12065]

55 **Ho PM**, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; **301**: 937-944 [PMID: 19258584 DOI: 10.1001/jama.2009.261]

56 **Tamura T**, Sakaeda T, Kadoyama K, Okuno Y. Omeprazole- and esomeprazole-associated hypomagnesaemia: data mining of the public version of the FDA Adverse Event Reporting System. *Int*

J Med Sci 2012; **9**: 322-326 [PMID: 22745572 DOI: 10.7150/ijms.4397]

57 **Ito T**, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep* 2010; **12**: 448-457 [PMID: 20882439 DOI: 10.1007/s11894-010-0141-0]

58 **MacLaren R**, Jarvis CL, Fish DN. Use of enteral nutrition for stress ulcer prophylaxis. *Ann Pharmacother* 2001; **35**: 1614-1623 [PMID: 11793631 DOI: 10.1345/aph.1A083]

59 **Pongprasobchai S**, Kridkratoke S, Nopmaneejumruslers C. Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: a meta-analysis. *J Med Assoc Thai* 2009; **92**: 632-637 [PMID: 19459523]

60 **Barkun A**, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2003; **139**: 843-857 [PMID: 14623622 DOI: 10.7326/0003-4819-139-10-200311180-00012]

61 **Lin PC**, Chang CH, Hsu PI, Tseng PL, Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med* 2010; **38**: 1197-1205 [PMID: 20173630 DOI: 10.1097/CCM.0b013e3181d69ccf]

P- Reviewer: Kozarek R, Li YY, Manguso F, Rabago L
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.65

World J Crit Care Med 2016 February 4; 5(1): 65-73
ISSN 2220-3141 (online)

REVIEW

Respiratory mechanics in brain injury: A review

Antonia Koutsoukou, Maria Katsiari, Stylianos E Orfanos, Anastasia Kotanidou, Maria Daganou, Magdalini Kyriakopoulou, Nikolaos G Koulouris, Nikoletta Rovina

Antonia Koutsoukou, Maria Daganou, Magdalini Kyriakopoulou, Nikoletta Rovina, ICU, First Department of Respiratory Medicine, University of Athens Medical School, Sotiria Hospital, 11527 Athens, Greece

Maria Katsiari, Intensive Care Unit, "Konstantopouleio" General Hospital of Nea Ionia, 14233 Athens, Greece

Stylianos E Orfanos, Second Department of Critical Care, University of Athens Medical School, Attikon Hospital, 12462 Athens, Greece

Anastasia Kotanidou, First Department of Critical Care and Pulmonary Services, University of Athens Medical School, Evangelismos Hospital, 10676 Athens, Greece

Nikolaos G Koulouris, First Department of Respiratory Medicine, University of Athens Medical School, Sotiria Hospital, 11527 Athens, Greece

Author contributions: All authors contributed to this paper; Koutsoukou A, Katsiari M, Orfanos SE and Rovina N designed the study; Koutsoukou A, Katsiari M, Kyriakopoulou M and Daganou M performed the literature review and analysis; Katsiari M, Koulouris NG and Rovina N wrote the paper; Koutsoukou A, Orfanos SE, Kotanidou A, Koulouris NG and Rovina N performed the critical revision and editing; all authors approved the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Correspondence to: Antonia Koutsoukou, Associate Professor, ICU, First Department of Respiratory medicine, University of Athens Medical School, Sotiria Hospital, Mesogion Av 152, 11527 Athens, Greece. koutsoukou@yahoo.gr

Telephone: +30-21-07763718
Fax: +30-21-07781250

Received: August 6, 2015
Peer-review started: August 10, 2015
First decision: September 16, 2015
Revised: October 8, 2015
Accepted: December 10, 2015
Article in press: December 11, 2015
Published online: February 4, 2016

Abstract

Several clinical and experimental studies have shown that lung injury occurs shortly after brain damage. The responsible mechanisms involve neurogenic pulmonary edema, inflammation, the harmful action of neurotransmitters, or autonomic system dysfunction. Mechanical ventilation, an essential component of life support in brain-damaged patients (BD), may be an additional traumatic factor to the already injured or susceptible to injury lungs of these patients thus worsening lung injury, in case that non lung protective ventilator settings are applied. Measurement of respiratory mechanics in BD patients, as well as assessment of their evolution during mechanical ventilation, may lead to preclinical lung injury detection early enough, allowing thus the selection of the appropriate ventilator settings to avoid ventilator-induced lung injury. The aim of this review is to explore the mechanical properties of the respiratory system in BD patients along with the underlying mechanisms, and to translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

Key words: Brain damage; Respiratory mechanics; Positive end-expiratory pressure; Lung injury; Ventilator-induced lung injury

Core tip: Clinical and experimental evidence supports that preclinical lung injury occurs shortly after brain damage. Brain-damaged patients exhibit altered respiratory system mechanics and hypoxemia, even in the absence of clinically evident lung injury. Measurement of respiratory mechanics in such patients may reveal brain damage related lung injury early enough, and facilitate selection of the appropriate ventilator settings to avoid ventilator induced lung injury. Lung protective ventilation, consisting of low tidal volume and moderate levels of positive end-expiratory pressure, may prevent a further deterioration of respiratory dysfunction, and could be possibly associated with improved outcome.

Koutsoukou A, Katsiari M, Orfanos SE, Kotanidou A, Daganou M, Kyriakopoulou M, Koulouris NG, Rovina N. Respiratory mechanics in brain injury: A review. *World J Crit Care Med* 2016; 5(1): 65-73 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/65.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.65

INTRODUCTION

Brain damage (BD), either due to spontaneous hemorrhage or trauma, represents one of the most important causes of death and disability in modern societies. Although morbidity and mortality of these patients are due principally to their primary disease, medical complications are frequent, with respiratory dysfunction being the most common[1-3]. Up to one third of BD patients develop acute respiratory distress syndrome (ARDS), a complication that has been associated with poor outcome[4,5].

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain damage. Rogers *et al*[6] found a significant increase of the lung weight along with edema, congestion and hemorrhage in 50% of patients who died within 96 h after isolated brain damage.

Ultrastructural changes in type Ⅱ pneumocytes along with an inflammatory response in the lung, similar to that induced by high tidal volume ventilation, have been observed in animals within the first hours of traumatic brain injury[7]. Similarly, alterations in lung architecture, such as alveolar hemorrhage, proteinaceous debris and neutrophilic infiltration were detected by Weber *et al*[8] in experimental traumatic brain damage. In addition, decreased pulmonary tolerance to subsequent mechanical stress due to mechanical ventilation[9], as well as aggravation of preexisting lung injury[10] have been reported after massive brain damage in animals.

Although experimental as well as clinical evidence support the existence of a close interaction between the brain and lungs[11], the mechanisms by which brain damage leads to alterations in pulmonary function are unclear. They may involve neurogenic pulmonary edema, inflammation, neurotransmitter-related engagement, or adverse effects of neuroprotective therapies[12,13].

Mechanical ventilation is an essential component of life support in brain damaged patients. It is well known that, despite being lifesaving, mechanical ventilation may nonetheless cause or perpetuate lung injury if alveolar overdistention and repeated alveolar collapse and re-expansion occurs with each breath [ventilator-induced lung injury (VILI)][14]. Non lung protective mechanical ventilation could thus constitute an additional traumatic factor to the already injured or susceptible to injury lungs of such patients[9,15]. Indeed, recent research has found that a lung protective strategy is an independent predictor of favorable outcome of BD patients[16]. Furthermore, it has been shown that lung protective strategy prevented the decline of pulmonary function consequent to brain death and increased the number of lungs available for transplantation[17], a finding particularly important in the context of lung transplantation because of the scarcity of lung donors. In relation to the latter, it should be noted that preclinical lung injury may be present in BD patients with "normal" chest X-rays; thus it is of paramount importance to have a marker that could detect such an injury.

Measurement of respiratory mechanics in brain damaged patients, as well as assessment of their evolution during mechanical ventilation, may help in the detection of lung injury early enough, but also in selecting the appropriate ventilator settings to avoid VILI.

The aim of this review is to explore the mechanical properties of the respiratory system in brain damaged patients along with the underlying mechanisms, and translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

RESEARCH

The information in this review is based on results of a Medline and OVID search. The key words used were related to brain damage (traumatic brain injury, hemorrhagic stroke, intracranial pressure, brain death), and to acute lung injury/ARDS and mechanical ventilation (pulmonary edema, acute respiratory distress syndrome, ventilator induced lug injury, inflammation, respiratory mechanics, mechanical ventilation, tidal volume, positive end-expiratory pressure, lung transplantation). We read relevant articles in full, searched their reference lists, and chose the most relevant on the basis of findings and clinical significance. Bibliographies of identified articles, guidelines and conference proceedings of professional societies were reviewed for additional references.

FROM THE BRAIN TO THE INJURY OF THE LUNGS

Several nonexclusive mechanisms have been implicated in the brain to lungs' injury process. Pulmonary dysfunction

after brain damage has long been attributed to an increased sympathetic activity. Massive catecholamine release may lead to neurogenic pulmonary edema[18], that is the extravasation of fluid from the blood into the alveolar and interstitial space of the lungs in patients who have suffered an acute neurological event. Several theories have been proposed considering the pathophysiology of this entity. The mostly recognized is the "blast injury" theory, suggesting that the sympathetic storm which follows a sudden increase in intra-cranial pressure induces a transient increase in intravascular pressure and the consequent disruption of the alveolo-capillary membrane[18]. The development of neurogenic pulmonary edema is attributed either to hydrostatic forces, as it is supported by a low pulmonary/plasma protein ratio[19], or to high permeability mechanisms supported by increased accumulation of pulmonary extravascular protein[20]. The association between massive sympathetic discharge and neurogenic pulmonary edema is further supported by a more recent experimental study showing that pretreatment of brain-damaged rats with alpha-adrenergic antagonists prevented the hypertensive response and attenuated the subsequent lung injury[21].

In addition to the "blast injury" theory, a systemic inflammatory response seems to play a critical role in the development of lung injury after brain damage. Clinical studies in acutely brain-damaged patients have suggested an increased intracranial production[22] and release[23] of pro-inflammatory mediators into the systemic circulation along with possible activation of inflammatory cascades. Intracranial production of inflammatory cytokines probably takes place in brain microglia and astrocytes[23], while through the altered blood-brain barrier these mediators can reach peripheral organs leading to multi-organ dysfunction[22,24,25]. Indeed, Fisher *et al*[26] detected an increased concentration of proinflammatory cytokines in the bronchoalveolar lavage fluid (BALF) of patients with fatal BD. The same group later reported that increased levels of BALF interleukin-8 (IL-8) in brain dead lung donors correlated with severe early graft dysfunction and recipient mortality, pointing out to the key role of such a preclinical inflammatory process[27].

Several experimental studies have confirmed the existence of a systemic inflammatory process in BD. In animals with acute brain injury, Kalsotra *et al*[28] detected a significant migration of macrophages and neutrophils into the lungs at 24 h post injury, associated with enhanced pulmonary leukotriene B4 production. Skrabal *et al*[29] investigated the very early organ-specific inflammation responses after brain death in pigs and found an up-regulation of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), IL-1β and IL-6 in the animal lungs. All these substances are mediators that may modulate the expression of adhesion molecules and consequent activity[30]. In fact, an up-regulation of the soluble intercellular adhesion molecule-1 (ICAM-1) was found in the lungs of BD animals[29]. Similarly, Cobelens *et al*[31] found that experimental subarachnoid hemorrhage was associated with neutrophil influx into the lungs as well as increased expression of pulmonary adhesion molecules and chemokines. Adhesion molecules through activation, firm adhesion, and the chemotactic migration of leukocytes[32] may contribute to lung injury. In this respect, a strong association between increased serum levels of ICAM-1 and poor neurological outcome has been found by McKeating *et al*[33] in a cohort of BD patients. Among other molecules that have been linked with the brain to lung injury process are S-100B, E-Selectin and caspase-1[10,34]. Moreover, altered activity of pulmonary capillary endothelial angiotensin converting enzyme is present in brain dead subjects denoting preclinical pulmonary endothelial dysfunction[35]. In a similar respect, the presence of preclinical pulmonary inflammation in mechanically ventilated BD patients was revealed by markers measured in exhaled breath condensate[36].

Very recently, Nicolls *et al*[37] demonstrated that acute lung injury that followed traumatic brain injury in animals was mediated by high-mobility group box-1 (HMGB1), a nuclear protein that serves as an early mediator of inflammation[8]. The authors additionally showed that HMGB1 activates inflammatory responses through binding to receptor for advanced glycation end products (RAGE). The fact that RAGE is highly expressed on lung epithelial cells could partially explain why the lung is so sensitive to damage after brain injury.

Severe brain damage may induce lung injury through modulation of neurokinins since such substances are released in patients with BD[38,39]. Substance P and neurokinin A have been implicated in bronchoconstriction, mucosal edema, increased vascular permeability, pulmonary edema and leukocyte adhesion activation[39]. Chavolla-Calderón *et al*[40] demonstrated that the derangement of the substance P receptor protects against pulmonary inflammation.

Finally, it has been suggested that excessive lung inflammation may be the result of BD-induced impairment of the parasympathetic nervous system leading to loss of the protective cholinergic anti- inflammatory pathway[41,42]. Kox *et al*[43] have suggested that BD-associated increased intracranial pressure (ICP) may alter the immunoregulatory function of the vagus nerve, which may operate as an additional means through which the brain exerts control over cytokine expression[41]. Indeed, it has been reported that vagus nerve stimulation was followed by inhibition of TNF-α, IL-1, IL-6, IL-8 and HMGB1 release[44]. dos Santos *et al*[45] supported the protective role of the cholinergic ant-inflammatory pathway, demonstrating that vagus nerve stimulation attenuated lung injury while in contrast vagotomy exacerbated VILI.

Regardless of the responsible mechanisms, an injurious ventilatory strategy in the presence of an established inflammatory process may act as an additional stimulus that can aggravate lung damage. A "double hit" model could explain the development of organ failure associated

with acute brain injury[15]. "First hit" corresponds to the adrenergic boost and systemic production and release of inflammatory mediators that make the lungs more vulnerable to a subsequent "second hit", such as the mechanical stress induced by mechanical ventilation or the ischemia/reperfusion that may be seen in lung transplants[15].

RESPIRATORY MECHANICS AND GAS EXCHANGE

Although, as already mentioned, pulmonary dysfunction is a well-recognized complication of brain damage, it is surprising that until now very few studies have assessed respiratory mechanics in this group of patients. Moreover, although these patients usually need prolonged mechanical ventilation due to coma, few studies have assessed the impact of ventilatory settings on respiratory mechanics.

Two decades ago, Tantucci *et al*[46] studied a group of BD patients and found increased respiratory system flow resistance (Rmin,rs). Increased respiratory system resistance was also detected by Gamberoni *et al*[47] in BD patients with and, importantly, without respiratory failure. It should be noted that increased Rmin,rs was also found on the first day of mechanical ventilation in BD patients without acute lung injury[48].

Increased Rmin,rs could be attributed to bronchoconstriction, as a result of hyperventilation and consequent hypocapnia that are usually therapeutically applied in these patients. In anesthetized and paralyzed normal subjects (*i.e.*, without apparent lung pathology), D'Angelo *et al*[49] have shown that decreased partial pressure of arterial carbon dioxide ($PaCO_2$) was associated with a significant increase in Rmin,rs. However, additional factors inducing bronchoconstriction and airway mucosal edema, such as neuropeptides, cannot be excluded as potential mechanisms, since such substances appear to be released and circulate in patients with BD[38,39]. Finally, an altered control of airway caliber has been proposed as a likely explanation for the increased respiratory system resistance[47].

Increased respiratory system elastance (Est,rs) has been found in experimental[8,50] as well as in clinical BD without acute lung injury[47,48,51]. Interestingly, only one study[46] reported non increased Est,rs, but this may reflect the high tidal volumes used for ventilation in the past (15 mL/kg).

Increased extravascular lung water, a manifestation of pulmonary edema resulting from the sympathetic hypereactivity elicited by the central nervous system injury, might partially explain the aforementioned increased Est,rs. In this regard, it should be noted that, despite relatively normal chest X-rays, increased lung densities have been detected in CT scans of patients with BD[47]. In a similar respect, increased extravascular lung water along with CT scan lung densities were detected in animals soon after the induction of intracranial hypertension[10].

Finally, atelectasis, associated with anesthesia and paralysis or with impaired production/function of pulmonary surfactant as a result of brain damage, as well as alterations in chest wall mechanics, may be additional potential explanations for the increased Est,rs in this setting[7,47,48,52,53].

Gas exchange

Although hypoxemia is present in a substantial percentage of BD patients[15,47,48,54] and has been recognized as a secondary insult associated with poor neurological outcome[55-57], data on gas exchange in such patients are scarce. A moderate to severe impairment of oxygenation has been noted in patients with isolated brain injury in the absence of abnormal chest X-rays[6,58,59]. Similarly, a ratio of partial pressure of arterial of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) below the normal limit was detected on the first day of mechanical ventilation in BD patients without acute lung injury[48], while oxygenation further deteriorated after 5 d on mechanical ventilation.

Weber *et al*[8] reported that in animals with BD the degree of inflammation, as expressed by serum levels of HMGB1 were correlated with PaO_2/FiO_2. Mascia *et al*[60] found that BD patients who subsequently developed ARDS had at baseline an abnormal PaO_2/FiO_2 ratio (< 300 mmHg), and that hypoxemia was the strongest independent predictor of ARDS development. Ventilation/perfusion (V/Q) mismatch and shunt, the main pathophysiological mechanisms of hypoxemia[61] ensuing from airway closure and atelectasis due to lung surfactant depletion[7,53] and/or increased extravascular lung water[10,47] might explain oxygenation impairment.

Given that brain damage patients are usually hyperventilated for neuroprotection, data on ventilation and $PaCO_2$ disturbances are missing.

VENTILATORY STRATEGIES

Ventilatory management of brain-damaged patients presents a major challenge for physicians since the fragile lung-brain balance must be preserved. The ventilatory strategy on one hand aims at maintaining adequate oxygenation and avoiding hypercapnia in order to protect the intracranial pressure and cerebral blood flow, and thus prevent secondary brain injury; on the other hand though it should avoid VILI. In addition, it should be noted that injurious mechanical ventilation per se may cause brain activation[62] or damage to selected brain areas[63] and thus, the selection of appropriate ventilatory settings becomes of paramount importance.

According to the guidelines for the management of severe traumatic brain injury intense hypocapnia should be avoided, because it may compromise cerebral blood flow and aggravate hypoperfusion[64]. However, traditional ventilatory management of BD patients involves high tidal volumes to maintain mild hypocapnia ($PaCO_2$-30-35 mmHg) for the treatment of intracranial

hypertension accompanied by low levels of positive end-expiratory pressure (PEEP) to optimize oxygenation without impeding cerebral venous drainage[64].

Furthermore, it is well established that this ventilatory strategy can exacerbate the pulmonary and systemic inflammatory response in patients with ARDS[65]. Even in patients without ARDS, ventilation with high tidal volumes proved to have deleterious effects and to induce VILI[66]. Moreover, according to the "double hit" theory, once the lungs are primed from a severe brain injury, they may become more susceptible to the injurious effects of mechanical ventilation[15] making VILI development more probable. In this respect, it was demonstrated that apparently healthy lungs of animals subjected to massive brain-injury developed more alveolar damage under injurious mechanical ventilation[9].

In clinical settings, high tidal volume and low PEEP have been implicated in deterioration of respiratory mechanics and unfavorable outcome in BD patients. A recent clinical study reported that in patients with severe brain injury, high tidal volumes, high respiratory rates, and hypoxemia were the stronger independent predictors of ARDS development[60]. Similarly, in mechanically ventilated patients with intracerebral hemorrhage, Elmer *et al*[16] showed that high tidal volumes were among the factors associated with ARDS development. High mechanical stretch with consequent alveolar distention, alveolar epithelial and vascular endothelial disruption and inflammation[14] may have contributed to the exacerbation of lung injury and ARDS in the already primed lungs of these patients[16].

Furthermore, in BD patients without acute lung injury, application of moderate levels of PEEP for 5 d prevented lung damage, as assessed by the increased Est,rs, present in the group of patients ventilated on zero end-expiratory pressure (ZEEP)[48]. In a later study, BD patients with no apparent lung pathology ventilated with ZEEP exhibited early and sustained increases of circulating inflammatory indices as compared to patients on 8 cmH_2O of PEEP[36]. Avoiding end-expiratory collapse and maintenance of recruited alveoli by applying PEEP, may protect against "low volume" injury, that is the lung damage attributable to airway closure or heterogeneous constriction[67-72]. Atelectasis in the dependent lung zones and peripheral airway closure usually develop during general anesthesia even in normal lungs[52]. In BD patients, abnormal surfactant production due to injury of pneumocytes Ⅱ[7] or release of inflammatory mediators could enhance peripheral airway closure and atelectasis formation. Under these disorders, opening and closing of peripheral airways during tidal breathing would be possible, leading to the development of shear stresses that can damage peripheral airways[67]. In the presence of airway closure there is heterogeneous lung filling and emptying, conditions which might contribute to lung injury[73-75].

Application of PEEP in mechanically ventilated brain-injured patients has been considered controversial. Although PEEP can optimize oxygen delivery to the brain[54,76], it may result in raised mean intrathoracic pressure and therefore might increase ICP through reducing venous drainage. Additionally, the increased intrathoracic pressure could lead to a decrease in arterial pressure, which in turn may decrease cerebral blood flow in patients with impaired cerebral autoregulation[77].

Clinical studies addressing the effect of PEEP in BD patients have mainly focused on the ICP and cerebral perfusion pressure (CPP) showing conflicting results[78-80]. The Starling resistor model serves the most suitable interpretation of the PEEP effect on the ICP[81]. Luce *et al*[81] documented in an animal study that the consequences of PEEP on ICP were more evident whenever the applied PEEP was higher than ICP. Later, McGuire *et al*[82], in a clinical study, provided evidence that PEEP levels up to 15 mH_2O were not transmitted to central nervous system if baseline ICP values were higher than the applied PEEP.

Unexpected findings have been reported by Huynch *et al*[83] who have shown that increases in PEEP up to 15 cmH_2O, in 5 cmH_2O increments, correlated with reduction in ICP and augmented CPP. Nevertheless, no physiologic explanations have been provided for these findings.

Decrease in mean arterial pressure as a consequence of increased intrathoracic pressure has been implicated as a responsible mechanism of PEEP-induced decrease in CPP. An observational study involving patients with subarachnoid hemorrhage demonstrated that restoration of mean arterial pressure returned CPP to baseline, supporting a PEEP-dependent decrease of the former as the underlying mechanism of CPP reduction post PEEP application, rather than an increase in ICP[84]. In this regard, Doblar *et al*[85] showed that euvolemia, achieved with hypertonic volume expanders, averted an undesired reduction in arterial and cerebral perfusion pressure after application of various levels of PEEP.

The elastic properties of the respiratory system and its components could have an impact on the PEEP effect on ICP. In cases of low chest wall compliance or normal lung compliance, PEEP may increase intrathoracic pressure. On the contrary, reduced lung compliance could exert a protective role by minimizing airway pressure transmission[86]. However, clinical studies investigating the influence of respiratory system mechanics on the transmission of PEEP to the intracranial compartment have reported conflicting results[78,87]. Caricato *et al*[51] found that PEEP application resulted in reduction of CPP only in patients with normal respiratory system compliance, but had no effect on ICP regardless of the latter. Recently, a clinical study in patients with hemorrhagic stroke and respiratory system compliance within normal range displayed that, although PEEP up to 14 cmH_2O significantly increased ICP, arterial and cerebral perfusion pressures were not affected and thus the observed increases in ICP were not clinically meaningful[88].

Application of PEEP may affect cerebral circulation through CO_2-mediated mechanisms[89]. An increase in

$PaCO_2$ directly causes vasodilation of cerebral arteries and a consequent increase in cerebral blood volume, which might result in a rise in ICP if intracranial compliance is reduced. In patients with severe brain injury and acute lung injury, Mascia *et al*[60] studied the cerebro-pulmonary interactions during the application of low PEEP levels. In brain-damaged patients with "relatively normal" ICP, these investigators found that when the application of PEEP induced hyperinflation with consequent increase in $PaCO_2$, the ICP increased; in contrast when PEEP resulted in alveolar recruitment there were no effects on ICP and cerebral perfusion.

Despite the aforementioned clinical and experimental studies, the ideal ventilation strategy for patients with massive brain damage has not been clarified. The "open lung" approach which integrates the use of low tidal volumes with high PEEP, despite its beneficial effect on morbidity and/or mortality in ARDS patients, has not been extensively studied in brain-injured patients. Wolf *et al*[93] found that an "open lung" approach, consisting of low tidal volumes and elevated PEEP levels after performing recruiting maneuvers, improved respiratory function in neurosurgical patients with severe respiratory failure without generating negative effects on cerebral physiology. A recent animal study demonstrated that an "open lung" approach, consisting of low tidal volumes and PEEP set according to the minimal Est,rs, attenuated lung injury in rats with massive brain damage[90]; however neurological parameters and therefore the potential impact of the open lung strategy on brain damage were not evaluated in this study.

At present, it seems that the use of low tidal volume to avoid overdistention, and of moderate levels of PEEP to improve oxygenation and to avoid "low volume" injury, may be appropriate in patients with brain damage; however mean arterial pressure should be preserved and close attention to ICP and CPP alterations should be given.

CONCLUSION

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain injury. Brain-damaged patients without acute lung injury exhibit alterations of respiratory system mechanics, mainly increased respiratory system elastance and airway resistance, and hypoxemia. Ventilatory management of such patients should aim at optimizing neurologic protection, but at the same time at preventing further deterioration of respiratory dysfunction. Modifiable ventilator parameters possibly associated with improved outcome include low tidal volumes and moderate levels of PEEP. Nevertheless, more studies are needed to elucidate the potential beneficial role of an "open lung"approach in brain-damaged patients with respiratory compromise.

REFERENCES

1 **Solenski NJ**, Haley EC, Kassell NF, Kongable G, Germanson T, Truskowski L, Torner JC. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Crit Care Med* 1995; **23**: 1007-1017 [PMID: 7774210]

2 **Zygun DA**, Kortbeek JB, Fick GH, Laupland KB, Doig CJ. Non-neurologic organ dysfunction in severe traumatic brain injury. *Crit Care Med* 2005; **33**: 654-660 [PMID: 15753760]

3 **Plötz FB**, Slutsky AS, van Vught AJ, Heijnen CJ. Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. *Intensive Care Med* 2004; **30**: 1865-1872 [PMID: 15221129]

4 **Holland MC**, Mackersie RC, Morabito D, Campbell AR, Kivett VA, Patel R, Erickson VR, Pittet JF. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma* 2003; **55**: 106-111 [PMID: 12855888]

5 **Kahn JM**, Caldwell EC, Deem S, Newell DW, Heckbert SR, Rubenfeld GD. Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors, and outcome. *Crit Care Med* 2006; **34**: 196-202 [PMID: 16374174]

6 **Rogers FB**, Shackford SR, Trevisani GT, Davis JW, Mackersie RC, Hoyt DB. Neurogenic pulmonary edema in fatal and nonfatal head injuries. *J Trauma* 1995; **39**: 860-866 [PMID: 7474001]

7 **Yildirim E**, Kaptanoglu E, Ozisik K, Beskonakli E, Okutan O, Sargon MF, Kilinc K, Sakinci U. Ultrastructural changes in pneumocyte type II cells following traumatic brain injury in rats. *Eur J Cardiothorac Surg* 2004; **25**: 523-529 [PMID: 15037266]

8 **Weber DJ**, Gracon AS, Ripsch MS, Fisher AJ, Cheon BM, Pandya PH, Vittal R, Capitano ML, Kim Y, Allette YM, Riley AA, McCarthy BP, Territo PR, Hutchins GD, Broxmeyer HE, Sandusky GE, White FA, Wilkes DS. The HMGB1-RAGE axis mediates traumatic brain injury-induced pulmonary dysfunction in lung transplantation. *Sci Transl Med* 2014; **6**: 252ra124 [PMID: 25186179 DOI: 10.1126/scitranslmed.3009443]

9 **López-Aguilar J**, Villagrá A, Bernabé F, Murias G, Piacentini E, Real J, Fernández-Segoviano P, Romero PV, Hotchkiss JR, Blanch L. Massive brain injury enhances lung damage in an isolated lung model of ventilator-induced lung injury. *Crit Care Med* 2005; **33**: 1077-1083 [PMID: 15891339]

10 **Kant IJ**, de Jong LC, van Rijssen-Moll M, Borm PJ. A survey of static and dynamic work postures of operating room staff. *Int Arch Occup Environ Health* 1992; **63**: 423-428 [PMID: 1544692 DOI: 10.1007/s00134-011-2232-2]

11 **Masek K**, Slánský J, Petrovický P, Hadden JW. Neuroendocrine immune interactions in health and disease. *Int Immunopharmacol* 2003; **3**: 1235-1246 [PMID: 12860179]

12 **Robertson CS**, Valadka AB, Hannay HJ, Contant CF, Gopinath SP, Cormio M, Uzura M, Grossman RG. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; **27**: 2086-2095 [PMID: 10548187]

13 **Gonzalvo R**, Martí-Sistac O, Blanch L, López-Aguilar J. Bench-to-bedside review: brain-lung interaction in the critically ill--a pending issue revisited. *Crit Care* 2007; **11**: 216 [PMID: 17581271]

14 **Dreyfuss D**, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998; **157**: 294-323 [PMID: 9445314]

15 **Mascia L**. Acute lung injury in patients with severe brain injury: a double hit model. *Neurocrit Care* 2009; **11**: 417-426 [PMID: 19548120 DOI: 10.1007/s12028-009-9242-8]

16 **Elmer J**, Hou P, Wilcox SR, Chang Y, Schreiber H, Okechukwu I, Pontes-Neto O, Bajwa E, Hess DR, Avery L, Duran-Mendicuti MA, Camargo CA, Greenberg SM, Rosand J, Pallin DJ, Goldstein JN. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage*. *Crit Care Med* 2013; **41**: 1992-2001 [PMID: 23760151 DOI: 10.1097/CCM.0b013e31828a3f4d]

17 **Mascia L**, Pasero D, Slutsky AS, Arguis MJ, Berardino M, Grasso S, Munari M, Boifava S, Cornara G, Della Corte F, Vivaldi N, Malacarne P, Del Gaudio P, Livigni S, Zavala E, Filippini C, Martin EL, Donadio PP, Mastromauro I, Ranieri VM. Effect of a lung

protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA* 2010; **304**: 2620-2627 [PMID: 21156950 DOI: 10.1001/jama.2010.1796]
18 **Theodore J**, Robin ED. Pathogenesis of neurogenic pulmonary oedema. *Lancet* 1975; **2**: 749-751 [PMID: 52777]
19 **Smith WS**, Matthay MA. Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. *Chest* 1997; **111**: 1326-1333 [PMID: 9149590]
20 **McClellan MD**, Dauber IM, Weil JV. Elevated intracranial pressure increases pulmonary vascular permeability to protein. *J Appl Physiol* (1985) 1989; **67**: 1185-1191 [PMID: 2793711]
21 **Avlonitis VS**, Wigfield CH, Kirby JA, Dark JH. The hemodynamic mechanisms of lung injury and systemic inflammatory response following brain death in the transplant donor. *Am J Transplant* 2005; **5**: 684-693 [PMID: 15760391]
22 **Ott L**, McClain CJ, Gillespie M, Young B. Cytokines and metabolic dysfunction after severe head injury. *J Neurotrauma* 1994; **11**: 447-472 [PMID: 7861440]
23 **McKeating EG**, Andrews PJ, Signorini DF, Mascia L. Transcranial cytokine gradients in patients requiring intensive care after acute brain injury. *Br J Anaesth* 1997; **78**: 520-523 [PMID: 9175965]
24 **Habgood MD**, Bye N, Dziegielewska KM, Ek CJ, Lane MA, Potter A, Morganti-Kossmann C, Saunders NR. Changes in blood-brain barrier permeability to large and small molecules following traumatic brain injury in mice. *Eur J Neurosci* 2007; **25**: 231-238 [PMID: 17241284]
25 **Morganti-Kossmann MC**, Rancan M, Stahel PF, Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care* 2002; **8**: 101-105 [PMID: 12386508]
26 **Fisher AJ**, Donnelly SC, Hirani N, Burdick MD, Strieter RM, Dark JH, Corris PA. Enhanced pulmonary inflammation in organ donors following fatal non-traumatic brain injury. *Lancet* 1999; **353**: 1412-1413 [PMID: 10227229]
27 **Fisher AJ**, Donnelly SC, Hirani N, Haslett C, Strieter RM, Dark JH, Corris PA. Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. *Am J Respir Crit Care Med* 2001; **163**: 259-265 [PMID: 11208654]
28 **Kalsotra A**, Zhao J, Anakk S, Dash PK, Strobel HW. Brain trauma leads to enhanced lung inflammation and injury: evidence for role of P4504Fs in resolution. *J Cereb Blood Flow Metab* 2007; **27**: 963-974 [PMID: 16985506]
29 **Skrabal CA**, Thompson LO, Potapov EV, Southard RE, Joyce DL, Youker KA, Noon GP, Loebe M. Organ-specific regulation of pro-inflammatory molecules in heart, lung, and kidney following brain death. *J Surg Res* 2005; **123**: 118-125 [PMID: 15652959]
30 **Kelley BJ**, Lifshitz J, Povlishock JT. Neuroinflammatory responses after experimental diffuse traumatic brain injury. *J Neuropathol Exp Neurol* 2007; **66**: 989-1001 [PMID: 17984681]
31 **Cobelens PM**, Tiebosch IA, Dijkhuizen RM, van der Meide PH, Zwartbol R, Heijnen CJ, Kesecioglu J, van den Bergh WM. Interferon-β attenuates lung inflammation following experimental subarachnoid hemorrhage. *Crit Care* 2010; **14**: R157 [PMID: 20731855 DOI: 10.1186/cc9232]
32 **Walzog B**, Gaehtgens P. Adhesion Molecules: The Path to a New Understanding of Acute Inflammation. *News Physiol Sci* 2000; **15**: 107-113 [PMID: 11390891]
33 **McKeating EG**, Andrews PJ, Mascia L. Leukocyte adhesion molecule profiles and outcome after traumatic brain injury. *Acta Neurochir Suppl* 1998; **71**: 200-202 [PMID: 9779183]
34 **Suzuki H**, Sozen T, Hasegawa Y, Chen W, Zhang JH. Caspase-1 inhibitor prevents neurogenic pulmonary edema after subarachnoid hemorrhage in mice. *Stroke* 2009; **40**: 3872-3875 [PMID: 19875734]
35 **Glynos C**, Athanasiou C, Kotanidou A, Korovesi I, Kaziani K, Livaditi O, Dimopoulou I, Maniatis NA, Tsangaris I, Roussos C, Armaganidis A, Orfanos SE. Preclinical pulmonary capillary endothelial dysfunction is present in brain dead subjects. *Pulm Circ* 2013; **3**: 419-425 [PMID: 24015344 DOI: 10.4103/2045-8932.113189]
36 **Korovesi I**, Papadomichelakis E, Orfanos SE, Giamarellos-Bourboulis EJ, Livaditi O, Pelekanou A, Sotiropoulou C, Koutsoukou A, Dimopoulou I, Ekonomidou F, Psevdi E, Armaganidis A, Roussos C, Marczin N, Kotanidou A. Exhaled breath condensate in mechanically ventilated brain-injured patients with no lung injury or sepsis. *Anesthesiology* 2011; **114**: 1118-1129 [PMID: 21521967 DOI: 10.1097/ALN.0b013e31820d84db]
37 **Nicolls MR**, Laubach VE. Traumatic brain injury: lungs in a RAGE. *Sci Transl Med* 2014; **6**: 252fs34 [PMID: 25186173 DOI: 10.1126/scitranslmed.3010259]
38 **Rall JM**, Matzilevich DA, Dash PK. Comparative analysis of mRNA levels in the frontal cortex and the hippocampus in the basal state and in response to experimental brain injury. *Neuropathol Appl Neurobiol* 2003; **29**: 118-131 [PMID: 12662320]
39 **Campos MM**, Calixto JB. Neurokinin mediation of edema and inflammation. *Neuropeptides* 2000; **34**: 314-322 [PMID: 11049735]
40 **Chavolla-Calderón M**, Bayer MK, Fontán JJ. Bone marrow transplantation reveals an essential synergy between neuronal and hemopoietic cell neurokinin production in pulmonary inflammation. *J Clin Invest* 2003; **111**: 973-980 [PMID: 12671046]
41 **Hoeger S**, Bergstraesser C, Selhorst J, Fontana J, Birck R, Waldherr R, Beck G, Sticht C, Seelen MA, van Son WJ, Leuvenink H, Ploeg R, Schnuelle P, Yard BA. Modulation of brain dead induced inflammation by vagus nerve stimulation. *Am J Transplant* 2010; **10**: 477-489 [PMID: 20055812 DOI: 10.1111/j.1600-6143.2009.02951]
42 **Tracey KJ**. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 2007; **117**: 289-296 [PMID: 17273548]
43 **Kox M**, Vrouwenvelder MQ, Pompe JC, van der Hoeven JG, Pickkers P, Hoedemaekers CW. The effects of brain injury on heart rate variability and the innate immune response in critically ill patients. *J Neurotrauma* 2012; **29**: 747-755 [PMID: 22111862 DOI: 10.1089/neu.2011.2035]
44 **Wang H**, Liao H, Ochani M, Justiniani M, Lin X, Yang L, Al-Abed Y, Wang H, Metz C, Miller EJ, Tracey KJ, Ulloa L. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med* 2004; **10**: 1216-1221 [PMID: 15502843]
45 **dos Santos CC**, Shan Y, Akram A, Slutsky AS, Haitsma JJ. Neuroimmune regulation of ventilator-induced lung injury. *Am J Respir Crit Care Med* 2011; **183**: 471-482 [PMID: 20870758 DOI: 10.1164/rccm.201002-0314OC]
46 **Tantucci C**, Corbeil C, Chassé M, Braidy J, Matar N, Milic-Emili J. Flow resistance in mechanically ventilated patients with severe neurological injury. *J Crit Care* 1993; **8**: 133-139 [PMID: 8275157]
47 **Gamberoni C**, Colombo G, Aspesi M, Mascheroni C, Severgnini P, Minora G, Pelosi P, Chiaranda M. Respiratory mechanics in brain injured patients. *Minerva Anestesiol* 2002; **68**: 291-296 [PMID: 12024102]
48 **Koutsoukou A**, Perraki H, Raftopoulou A, Koulouris N, Sotiropoulou C, Kotanidou A, Orfanos S, Roussos C. Respiratory mechanics in brain-damaged patients. *Intensive Care Med* 2006; **32**: 1947-1954 [PMID: 17053881]
49 **D'Angelo E**, Calderini IS, Tavola M. The effects of CO2 on respiratory mechanics in anesthetized paralyzed humans. *Anesthesiology* 2001; **94**: 604-610 [PMID: 11379680]
50 **López-Aguilar J**, Quilez ME, Martí-Sistac O, García-Martín C, Fuster G, Puig F, Flores C, Villar J, Artigas A, Blanch L. Early physiological and biological features in three animal models of induced acute lung injury. *Intensive Care Med* 2010; **36**: 347-355 [PMID: 19841895 DOI: 10.1007/s00134-009-1695-x]
51 **Caricato A**, Conti G, Della Corte F, Mancino A, Santilli F, Sandroni C, Proietti R, Antonelli M. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. *J Trauma* 2005; **58**: 571-576 [PMID: 15761353]

52 **Hedenstierna G**, Lundquist H, Lundh B, Tokics L, Strandberg A, Brismar B, Frostell C. Pulmonary densities during anaesthesia. An experimental study on lung morphology and gas exchange. *Eur Respir J* 1989; **2**: 528-535 [PMID: 2744136]

53 **Glumoff V**, Väyrynen O, Kangas T, Hallman M. Degree of lung maturity determines the direction of the interleukin-1- induced effect on the expression of surfactant proteins. *Am J Respir Cell Mol Biol* 2000; **22**: 280-288 [PMID: 10696064]

54 **Miller JD**, Sweet RC, Narayan R, Becker DP. Early insults to the injured brain. *JAMA* 1978; **240**: 439-442 [PMID: 660888]

55 **Gentleman D**, Jennett B. Hazards of inter-hospital transfer of comatose head-injured patients. *Lancet* 1981; **2**: 853-854 [PMID: 6116963]

56 **Jones PA**, Andrews PJ, Midgley S, Anderson SI, Piper IR, Tocher JL, Housley AM, Corrie JA, Slattery J, Dearden NM. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol* 1994; **6**: 4-14 [PMID: 8298263]

57 **Wald SL**, Shackford SR, Fenwick J. The effect of secondary insults on mortality and long-term disability after severe head injury in a rural region without a trauma system. *J Trauma* 1993; **34**: 377-381; discussion 381-382 [PMID: 8483178]

58 **Simmons RL**, Martin AM, Heisterkamp CA, Ducker TB. Respiratory insufficiency in combat casualties. II. Pulmonary edema following head injury. *Ann Surg* 1969; **170**: 39-44 [PMID: 5789528]

59 **Corral L**, Javierre CF, Ventura JL, Marcos P, Herrero JI, Mañez R. Impact of non-neurological complications in severe traumatic brain injury outcome. *Crit Care* 2012; **16**: R44 [PMID: 22410278 DOI: 10.1186/cc11243]

60 **Mascia L**, Zavala E, Bosma K, Pasero D, Decaroli D, Andrews P, Isnardi D, Davi A, Arguis MJ, Berardino M, Ducati A. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. *Crit Care Med* 2007; **35**: 1815-1820 [PMID: 17568331]

61 **Roussos C**, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl* 2003; **47**: 3s-14s [PMID: 14621112]

62 **Quilez ME**, Fuster G, Villar J, Flores C, Martí-Sistac O, Blanch L, López-Aguilar J. Injurious mechanical ventilation affects neuronal activation in ventilated rats. *Crit Care* 2011; **15**: R124 [PMID: 21569477 DOI: 10.1186/cc10230]

63 **González-López A**, López-Alonso I, Aguirre A, Amado-Rodríguez L, Batalla-Solís E, Astudillo A, Tomás-Zapico C, Fueyo A, dos Santos CC, Talbot K, Albaiceta GM. Mechanical ventilation triggers hippocampal apoptosis by vagal and dopaminergic pathways. *Am J Respir Crit Care Med* 2013; **188**: 693-702 [PMID: 23962032]

64 **Bratton SL**, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. *J Neurotrauma* 2007; **24** Suppl 1: S87-S90 [PMID: 17511553]

65 **Ranieri VM**, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999; **282**: 54-61 [PMID: 10404912]

66 **Gajic O**, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; **32**: 1817-1824 [PMID: 15343007]

67 **D'Angelo E**, Pecchiari M, Baraggia P, Saetta M, Balestro E, Milic-Emili J. Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. *J Appl Physiol* (1985) 2002; **92**: 949-956 [PMID: 11842025]

68 **D'Angelo E**, Pecchiari M, Della Valle P, Koutsoukou A, Milic-Emili J. Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits. *J Appl Physiol* (1985) 2005; **99**: 433-444 [PMID: 15761084]

69 **D'Angelo E**, Pecchiari M, Saetta M, Balestro E, Milic-Emili J. Dependence of lung injury on inflation rate during low-volume ventilation in normal open-chest rabbits. *J Appl Physiol* (1985) 2004; **97**: 260-268 [PMID: 15020576]

70 **Muscedere JG**, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; **149**: 1327-1334 [PMID: 8173774]

71 **Slutsky AS**. Lung injury caused by mechanical ventilation. *Chest* 1999; **116**: 9S-15S [PMID: 10424561]

72 **Nucci G**, Suki B, Lutchen K. Modeling airflow-related shear stress during heterogeneous constriction and mechanical ventilation. *J Appl Physiol* (1985) 2003; **95**: 348-356 [PMID: 12651864]

73 **Turner JM**, Mead J, Wohl ME. Elasticity of human lungs in relation to age. *J Appl Physiol* 1968; **25**: 664-671 [PMID: 5727191]

74 **Mead J**, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970; **28**: 596-608 [PMID: 5442255]

75 **Koutsoukou A**, Koulouris N, Bekos B, Sotiropoulou C, Kosmas E, Papadima K, Roussos C. Expiratory flow limitation in morbidly obese postoperative mechanically ventilated patients. *Acta Anaesthesiol Scand* 2004; **48**: 1080-1088 [PMID: 15352952]

76 **Nemer SN**, Caldeira JB, Santos RG, Guimarães BL, Garcia JM, Prado D, Silva RT, Azeredo LM, Faria ER, Souza PCP. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: a pilot study. *J Crit Care* 2015; In Press

77 **Rosner MJ**, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. *J Neurosurg* 1995; **83**: 949-962 [PMID: 7490638]

78 **Burchiel KJ**, Steege TD, Wyler AR. Intracranial pressure changes in brain-injured patients requiring positive end-expiratory pressure ventilation. *Neurosurgery* 1981; **8**: 443-449 [PMID: 7017452]

79 **Shapiro HM**, Marshall LF. Intracranial pressure responses to PEEP in head-injured patients. *J Trauma* 1978; **18**: 254-256 [PMID: 351206]

80 **Frost EA**. Effects of positive end-expiratory pressure on intracranial pressure and compliance in brain-injured patients. *J Neurosurg* 1977; **47**: 195-200 [PMID: 327031]

81 **Luce JM**, Huseby JS, Kirk W, Butler J. A Starling resistor regulates cerebral venous outflow in dogs. *J Appl Physiol Respir Environ Exerc Physiol* 1982; **53**: 1496-1503 [PMID: 6759493]

82 **McGuire G**, Crossley D, Richards J, Wong D. Effects of varying levels of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure. *Crit Care Med* 1997; **25**: 1059-1062 [PMID: 9201061]

83 **Huynh T**, Messer M, Sing RF, Miles W, Jacobs DG, Thomason MH. Positive end-expiratory pressure alters intracranial and cerebral perfusion pressure in severe traumatic brain injury. *J Trauma* 2002; **53**: 488-492; discussion 492-493 [PMID: 12352486]

84 **Muench E**, Bauhuf C, Roth H, Horn P, Phillips M, Marquetant N, Quintel M, Vajkoczy P. Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation. *Crit Care Med* 2005; **33**: 2367-2372 [PMID: 16215394]

85 **Doblar DD**, Santiago TV, Kahn AU, Edelman NH. The effect of positive end-expiratory pressure ventilation (PEEP) on cerebral blood flow and cerebrospinal fluid pressure in goats. *Anesthesiology* 1981; **55**: 244-250 [PMID: 6791528]

86 **Chapin JC**, Downs JB, Douglas ME, Murphy EJ, Ruiz BC. Lung expansion, airway pressure transmission, and positive end-expiratory pressure. *Arch Surg* 1979; **114**: 1193-1197 [PMID: 384964]

87 **Cooper KR**, Boswell PA, Choi SC. Safe use of PEEP in patients with severe head injury. *J Neurosurg* 1985; **63**: 552-555 [PMID: 3897477]

88 **Lima WA**, Campelo AR, Gomes RL, Brandão DC. The impact of positive end-expiratory pressure on cerebral perfusion pressure in adult patients with hemorrhagic stroke. *Rev Bras Ter Intensiva* 2011; **23**: 291-296 [PMID: 23949400]

89 **Blanch L**, Fernández R, Benito S, Mancebo J, Net A. Effect of PEEP on the arterial minus end-tidal carbon dioxide gradient. *Chest*

1987; **92**: 451-454 [PMID: 3113834 DOI: 10.1186/cc13813]
90 **Wolf S**, Schürer L, Trost HA, Lumenta CB. The safety of the open lung approach in neurosurgical patients. *Acta Neurochir* 2002; **81**: 99-101 [PMID: 12168369]

P- Reviewer: Rocco P **S- Editor**: Qiu S **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.74

World J Crit Care Med 2016 February 4; 5(1): 74-82
ISSN 2220-3141 (online)

MINIREVIEWS

Preemptive mechanical ventilation can block progressive acute lung injury

Benjamin Sadowitz, Sumeet Jain, Michaela Kollisch-Singule, Joshua Satalin, Penny Andrews, Nader Habashi, Louis A Gatto, Gary Nieman

Benjamin Sadowitz, the Southeastern Center for Digestive Disorders and Pancreatic Cancer, Advanced Minimally Invasive and Robotic Surgery, Florida Hospital Tampa, Tampa, FL 33613, United States

Sumeet Jain, Michaela Kollisch-Singule, Joshua Satalin, Gary Nieman, Department of Surgery, Upstate Medical University, Syracuse, NY 13210, United States

Penny Andrews, Nader Habashi, Critical Care Medicine, Surgical Critical Care, Trauma Critical Care Medicine, The R Adams Cowley Shock Trauma Center, University of Maryland, Baltimore, MD 21201, United States

Louis A Gatto, Biological Sciences Department, SUNY Cortland, Cortland, NY 13045, United States

Author contributions: Sadowitz B contributed to acquisition of data, data interpretation and analysis, drafting the manuscript; Jain S, Kollisch-Singule M, Satalin J, Andrews P, Habashi N, Gatto LA and Nieman G contributed to data interpretation and analysis, critical revision of the manuscript.

Conflict-of-interest statement: We have no conflict of interests to disclose.

Correspondence to: Joshua Satalin, Lab Manager (Cardio-pulmonary Critical Care Lab), Department of Surgery, Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, United States. satalinj@upstate.edu
Telephone: +1-315-4641696

Received: June 10, 2015
Peer-review started: June 11, 2015
First decision: August 16, 2015
Revised: October 15, 2015
Accepted: December 29, 2015
Article in press: January 4, 2016
Published online: February 4, 2016

Abstract

Mortality from acute respiratory distress syndrome (ARDS) remains unacceptable, approaching 45% in certain high-risk patient populations. Treating fulminant ARDS is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventing this syndrome from ever occurring. Clinical studies were examined to determine why ARDS has remained resistant to treatment over the past several decades. In addition, both basic science and clinical studies were examined to determine the impact that early, protective mechanical ventilation may have on preventing the development of ARDS in at-risk patients. Fulminant ARDS is highly resistant to both pharmacologic treatment and methods of mechanical ventilation. However, ARDS is a progressive disease with an early treatment window that can be exploited. In particular, protective mechanical ventilation initiated before the onset of lung injury can prevent the progression to ARDS. Airway pressure release ventilation (APRV) is a novel mechanical ventilation strategy for delivering a protective breath that has been shown to block progressive acute lung injury (ALI) and prevent ALI from progressing to ARDS. ARDS mortality currently remains as high as 45% in some studies. As ARDS is a progressive disease, the key to treatment lies with preventing the disease from ever occurring while it remains subclinical. Early protective mechanical ventilation with APRV appears to offer substantial benefit in this regard and may be the prophylactic treatment of choice for preventing ARDS.

Key words: Mechanical ventilation; Acute lung injury;

Acute respiratory distress syndrome; Airway pressure release ventilation

Core tip: Mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high. Treating fulminant ARDS, however, is currently relegated to supportive care measures only. Thus, the best treatment for ARDS may lie with preventive measures. Indeed, since ARDS is a progressive disease, treating this disease in its subclinical phases may prevent the disease from ever occurring. In this regard, early protective mechanical ventilation with airway pressure release ventilation appears to offer substantial benefit and may be the prophylactic treatment of choice for preventing ARDS.

Sadowitz B, Jain S, Kollisch-Singule M, Satalin J, Andrews P, Habashi N, Gatto LA, Nieman G. Preemptive mechanical ventilation can block progressive acute lung injury. *World J Crit Care Med* 2016; 5(1): 74-82 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/74.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.74

ACUTE RESPIRATORY DISTRESS SYNDROME AND ITS SEQUELAE REMAIN A MAJOR AND COSTLY PUBLIC HEALTH CARE BURDEN

Acute respiratory distress syndrome (ARDS) and its sequelae remain a significant public health care burden in North America and worldwide[1-3]. The mean hospital costs for a patient with ARDS can easily cross the $100000 mark before discharge; this figure does not include the cost of subsequent hospital visits for complications from ARDS or any outpatient services including physical therapy, in-home nursing, or pharmaceuticals[1].

Compounding this significant cost is the broad spectrum of disability suffered by ARDS patients[2-6]. These disabilities are both physical and psychological, and they can last for at lease 5 years after the initial ARDS insult[1-6]. Most importantly, the sum total of these disabilities ultimately leads to a quality of life for ARDS patients that is significantly reduced compared to both the general population and other patients without ARDS who survived a critical illness[4,6].

It would appear that the most effective way to reduce the economic, physical, and psychological burden of ARDS would be *via* prevention of the disease process from ever occurring. Fulminant ARDS is resistant to all current treatment therapies, be they pharmacologic, mechanical, or a combination of the two[7-9]. We believe, however, that employment of a protective ventilation strategy early in the course of acute lung injury (ALI) or in patients at risk for ALI can block progression of this disease and prevent ARDS. Thus, our goal with this review is to detail the longstanding futility of treating established ARDS while examining the evidence that preemptive protective mechanical ventilation can reduce ARDS incidence. Furthermore, we will examine both the basic science and clinical studies demonstrating that airway pressure release ventilation (APRV) is the premier mode of ventilation for delivering an optimal protective breath with a specific mechanical breath profile (MBP) that prevents progression to ARDS for those patients at risk.

ONCE ESTABLISHED, THERE ARE NO EFFECTIVE TREATMENTS FOR ARDS

The landmark ARDSnet trial in 2000 marked the first time in decades that a significant, positive treatment effect was noted in patients with ALI and ARDS. In this trial, patients with ALI or ARDS were randomized to a "traditional", high-tidal volume (12 cc/kg) ventilation group or a low-tidal volume (6 cc/kg) ventilation group. The trial was terminated after enrollment of 861 patients, as mortality was significantly lower in the low-tidal volume ventilation group compared to the high-tidal volume ventilation group (31% *vs* 38.9%, P = 0.007)[10].

Although this certainly was a step forward in ARDS treatment, the optimism of this study should be tempered with the following considerations. First, the patient population studied in this trial underrepresents certain patient groups at high risk for ARDS. In particular, trauma patients only accounted for 13% of the patients in the low-tidal volume group and 9% of the patients in the high-tidal volume group[10]. Many trauma patients have well-known risk factors for ARDS development including: Injury severity scores > 16, thoracic injury or pulmonary contusions with abbreviated injury scale score of > 3, longbone and/or pelvic fractures, and transfusion of > 2 units of blood products within the first 24 h of injury[11]. Second, although the results of the study were statistically significant, in-hospital mortality from ARDS remained quite high at 31%. Lastly, and perhaps most importantly, the overall mortality of ARDS worldwide has not substantially changed since the original ARDSnet study was published and remains static at approximately 40%[12-14].

ARDS is a progressive disease, and there is a treatment window early in this progression that can be exploited

Why has ARDS remained a vexing clinical entity, highly resistant to all of our attempts at effective treatment? The answer to this question may lie in the way we view the disease process itself. For decades, ARDS has been viewed through the lens of a binary construct: the disease is either present or it is not. However, this

paradigm has started shifting in recent years, and this shift may hold the key to effectively combating ALI and ARDS. In particular, ARDS is now being viewed as a progressive disease with an early treatment window that can be targeted[15-25]. To that end, ARDS investigators are turning their attention toward identifying patients at-risk for developing ALI/ARDS and investigating preventive treatment strategies.

Unfortunately, identifying at-risk patients for ALI has proven difficult. The complexity of this process is highlighted by a recent prospective observational study in three Spanish teaching hospitals. In this study, 815 patients were identified with at least one clinical insult, the most common being sepsis, pneumonia, and pancreatitis[26]. However, the majority of patients in this study with risk factors for developing ALI/ARDS never developed lung injury at all[26]. What is clear across multiple studies, however, is the fact that ALI is rarely present on initial presentation and develops over hours to days while patients are in the hospital[27-30]. Thus, there is a window of opportunity early in the progression of developing lung injury that can be exploited with the following caveat: whatever intervention is used, it must be benign and without deleterious side effects so it can be applied to all patients at high-risk for developing lung injury.

What is clinically needed to make this a reality is a reliable risk factor model that accurately identifies, with a high sensitivity and specificity, those patients who will develop ALI/ARDS. One model that may prove helpful in this regard is the Lung Injury Prediction score (LIPS). The LIPS score is calculated based on a set of predisposing conditions and risk modifiers that are catalogued before the onset of ALI including the presence of shock, sepsis, pneumonia, acute abdomen, smoke inhalation, lung contusion, multiple fractures and acidosis[31]. Benefits of the LIPS score include the use of clinical variables closely associated with lung injury that are easily available on hospital admission and are a usual part of the patient chart[31]. In addition, this model identifies at-risk patients before they are admitted to the intensive care unit (ICU) or suffer a "second hit" that can hasten the progression to ALI[31].

The only successful treatments thus far are those involving methods of protective mechanical ventilation instituted early in the disease course

Although a clinical predictive tool like the LIPS score may ultimately prove useful for identifying those patients at risk for developing ALI/ARDS, successfully preventing progression to lung injury has proven equally difficult to solve. To be sure, maximizing supportive care measures and following a standardized bundle of lung injury prevention measures is an important part of this process[15,22]. However, there is no clearly defined treatment to date, either pharmacologic or mechanical, that definitively prevents lung injury.

With this in mind, there is an increasing body of literature demonstrating the beneficial effects of early protective mechanical ventilation on halting the progression toward lung injury. For example, patients undergoing major abdominal, cardiac, or thoracic surgery represent a large patient population at risk for developing ALI[32-34]. The method and technique of mechanical ventilation during surgery, therefore, represent a potential therapeutic intervention for preventing the development of ALI/ARDS in these at-risk surgery patients. One constant across these studies is the following: Protective ventilation strategies in the operating room, using low tidal volume ventilation strategies (6-8 cc/kg), lower the risk of lung injury and pulmonary complications as compared to conventional mechanical ventilation with higher tidal volumes[34]. Employing selective positive end-expiratory pressure (PEEP) levels and using recruitment maneuvers in the operating room may provide further lung protection as well. For example, Futier *et al*[35] (add 35 here as well) demonstrated a 69% decrease in the number of patients requiring ventilatory support within the first seven days after major abdominal surgery. The ventilation strategy used in the operating room was low tidal volume ventilation (tidal volume 6-8 cc/kg) along with a PEEP of 6-8 cmH_2O and recruitment maneuvers every 30 min after intubation[35].

It is important to remember that these preemptive strategies of protective mechanical ventilation are not restricted to surgical patients or those patients undergoing major abdominal or thoracic surgery. For those patients with critical illness who are in the ICU setting, protective mechanical ventilation strategies may be of utmost importance as well. Specifically, Determann *et al*[36] compared the effect of conventional tidal volume ventilation (10 cc/kg of predicted body weight) *vs* low tidal volume ventilation (6 cc/kg of predicted body weight) in critically ill patients without ALI at the onset of mechanical ventilation. This trial was stopped prematurely as the development of lung injury was significantly higher in the conventional tidal volume group[36].

PREEMPTIVE, PROTECTIVE MECHANICAL VENTILATION INSTITUTED BEFORE THE DEVELOPMENT OF CLINICAL MANIFESTATIONS HAS THE POTENTIAL TO REDUCE THE INCIDENCE OF ARDS

It seems clear, therefore, that mechanical ventilation and the way it is implemented are key factors in determining whether or not patients at-risk for lung injury progress to ALI/ARDS. Thus, if used correctly, mechanical ventilation has the potential to dramatically decrease the incidence of ARDS. This brings up another important question: What method of mechanical ventilation provides the optimal protective breath-to-

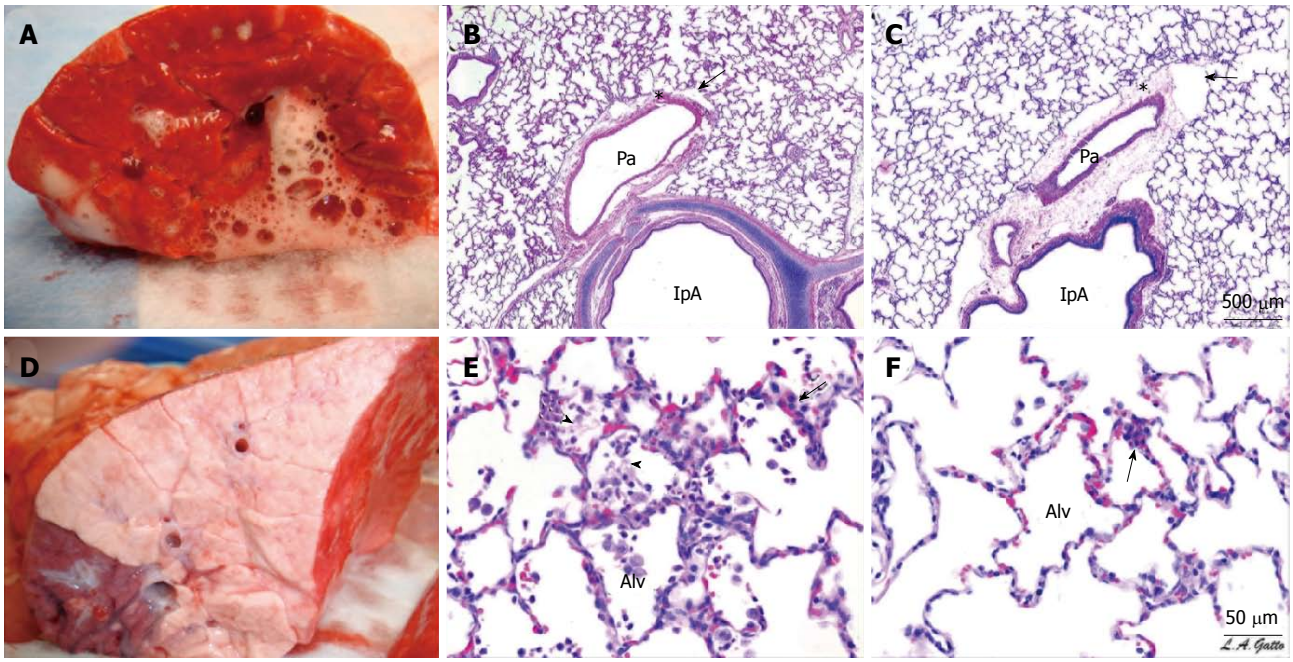


Figure 1 A gross and histological comparison between airway pressure release ventilation and nonpreventative ventilation. A and D: Gross pathology of the cut surface of the right lower lobe of the lung of representative animals from (A) the NPV and (D) the APRV group. The NPV shows severe inflammation, bronchial edema, and areas of hemorrhage. The APRV group demonstrates normal, pink, homogenously inflated lungs with little injury on gross appearance; B, C, E, F: Histological comparison of four pigs, two NPV (B and E) and two APRV (C and F) at low (B and C) and high (E and F) magnification. The NPV animals show classic stigmata of ARDS including atelectasis, fibrinous exudates, intra-alveolar hemorrhage, congested capillaries, thickened alveolar walls, and leukocytic infiltrates. The APRV animals demonstrate preservation of nearly normal pulmonary architecture. Published with permssion from Ref[38]. APRV: Airway pressure release ventilation; NPV: Nonpreventative ventilation; ARDS: Acute respiratory distress syndrome; Alv: Alveoli.

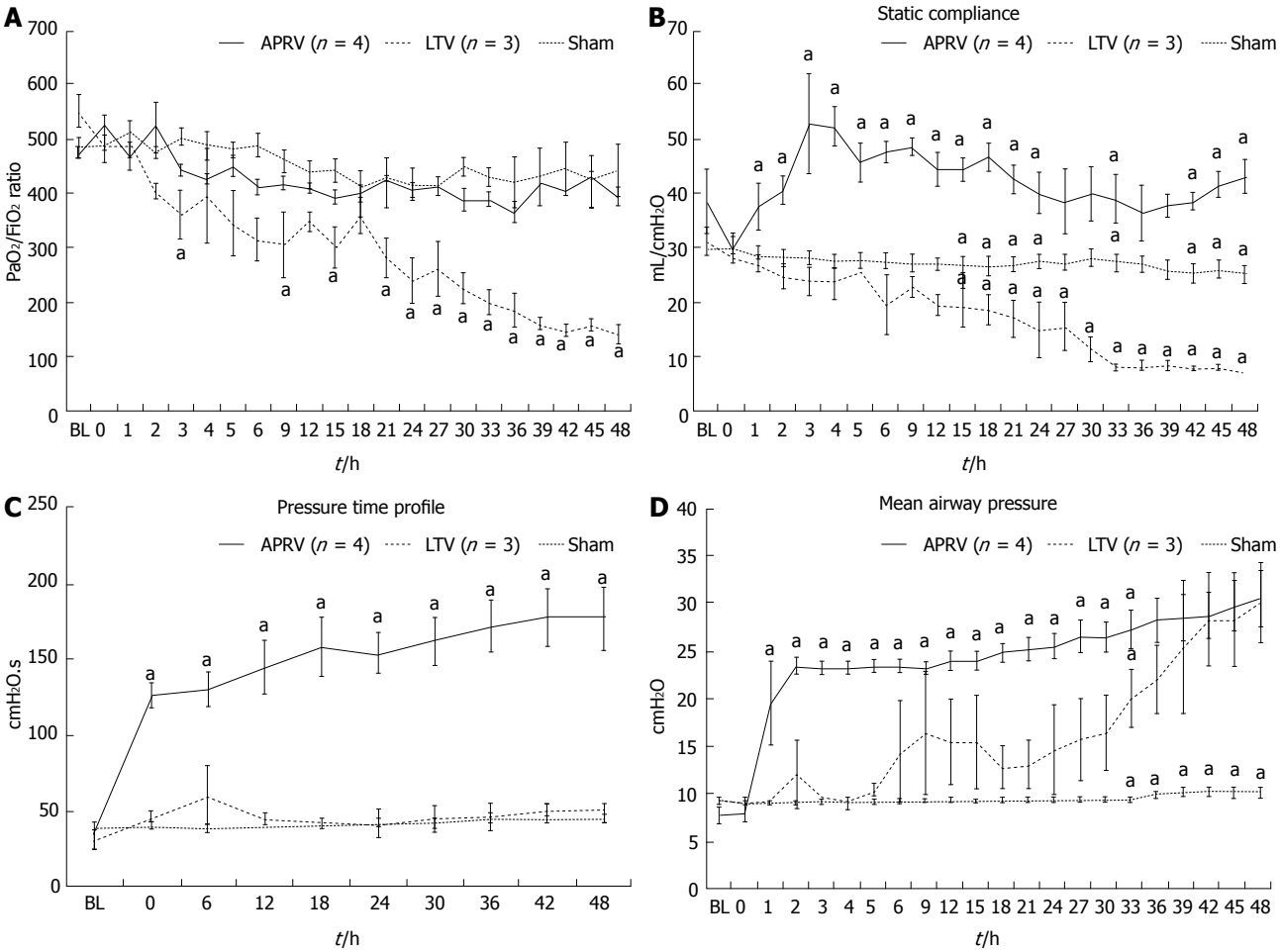
breath strategy for preventing lung injury?

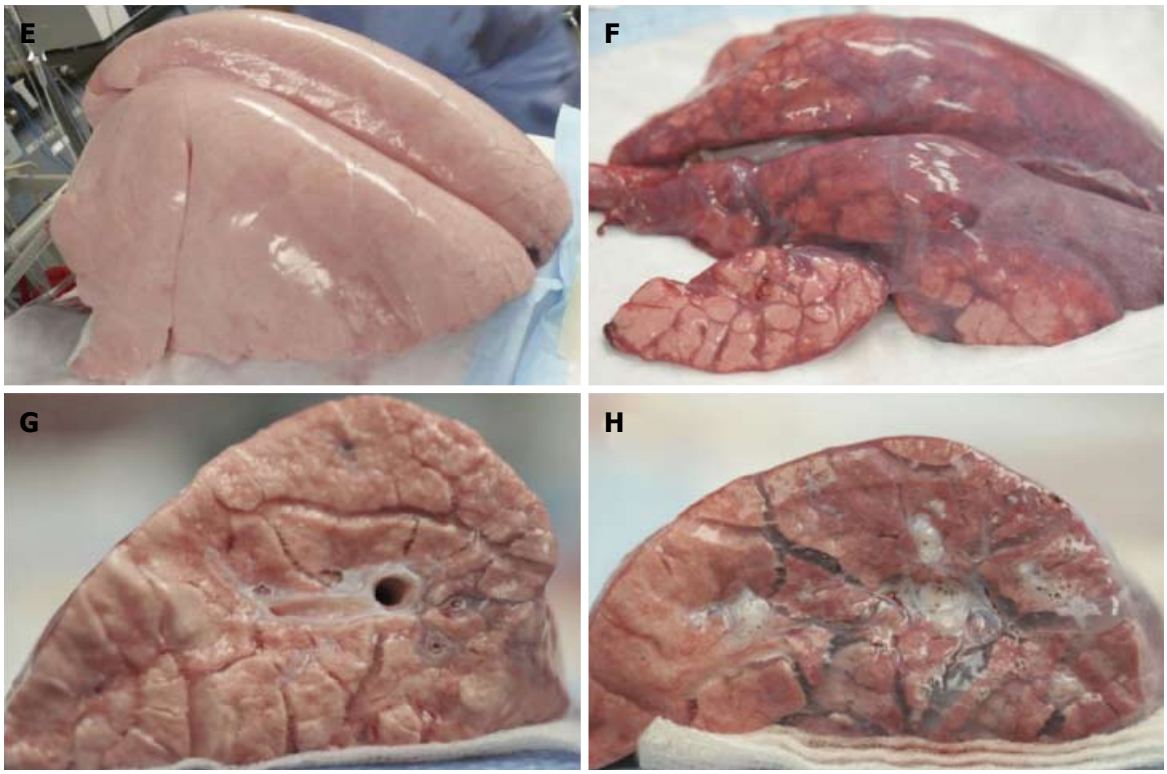
Both basic science and clinical studies suggest that APRV is the ideal ventilation strategy for delivering the optimal protective breath

Work in our laboratory over the past several years has led us to the conclusion that APRV, using a specific MBP, may be the best method of mechanical ventilation for providing the optimal protective breath and ultimately preventing the progression to ALI/ARDS. Our laboratory specializes in a porcine model of secondary ARDS caused by an intestinal ischemia/reperfusion injury and peritoneal sepsis[37]. In 2012 we undertook a study to evaluate the effectiveness of APRV in preventing lung injury in this animal model. Yorkshire pigs were randomized to two mechanical ventilation groups: APRV (10-15 cc/kg tidal volume) and non-preventative ventilation (10 cc/kg tidal volume)[38]. Despite similar markers of systemic inflammation, the APRV group did not develop ARDS and displayed decreased pulmonary inflammation with increased preservation of surfactant proteins[38]. In addition, both the gross and histological appearance of the lungs demonstrated minimal lung injury in the APRV group, while the control group demonstrated significant lung injury and inflammation and progressed to fulminant ARDS (Figure 1)[38].

The significant difference in lung injury between groups prompted us to further evaluate APRV and its effectiveness in preventing lung injury. As the ARDSnet guidelines are the current standard of care for patients with ARDS, we decided to do a comparison study between APRV and the ARDSnet low tidal volume ventilation strategy with our porcine model of ARDS. As with our initial APRV experience, the APRV group in this study did not develop ARDS[39]. In addition, the APRV group demonstrated preservation of lung E-cadherin and surfactant protein A, suggesting APRV can attenuate lung permeability, edema, and surfactant degradation[39]. The ARDSnet ventilation group, on the other hand, developed significant lung injury and ARDS, based on pulmonary parameters along with both the gross and histological appearance of the lungs (Figure 2)[39]. It is important to keep in mind that in this study, low tidal volume protective ventilation was applied after lung injury had developed, similar to current clinical practice. We are currently conducting a study in which low tidal volume ventilation and APRV are both applied preemptively in an attempt to identify the optimally protective breath to block progressive ALI.

The results of these two former studies were clearly dramatic and prompted us to evaluate the mechanical breath profile of APRV to further elucidate its potential for lung protection. To examine the mechanical breath profile of APRV, we used a rat model of lung injury induced by polysorbate lavage[40]. Animals were randomized to one of two groups: A controlled mandatory ventilation group and an APRV group[40]. In the controlled mandatory ventilation group, different levels of PEEP (5, 10, 16,


A
APRV (n = 4)
LTV (n = 3)
Sham
PaO2/FiO2 ratio
t/h
B
Static compliance
mL/cmH2O
C
Pressure time profile
cmH2O.s
D
Mean airway pressure
cmH2O


E
F
G
H

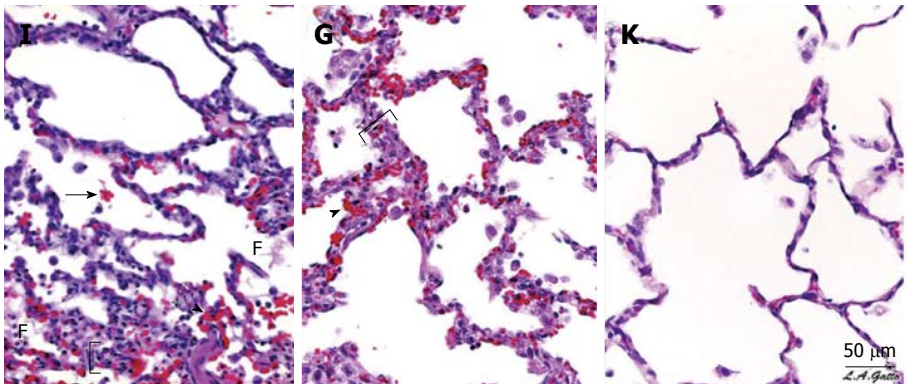


Figure 2 Pulmonary, gross and histologic representation between airway pressure release ventilation, LTV and sham animals. Top: Pulmonary data: A: P/F Ratio: APRV maintains a normal P/F ratio throughout the 48-h study with no significant difference from uninjured sham animals. Low tidal volume ventilation develops ALI (P/F G 300) by 19 h and ARDS (P/F G 250) by 33 h; ventilation strategy does not alter steady progression of increasing hypoxemia (P G 0.001 *vs* APRV and sham); B: Static compliance (Cstat): the APRV shows significant increase in Cstat after transition from volume- cycled mode to APRV (P G 0.001 *vs* sham and LTV ventilation). Sham maintained a normal Cstat level throughout the course of the study. In contrast, the LTV ventilation group developed progressive decreases in Cstat to less than 50% of BL; C: Mean airway pressure: sham group maintained normal Pmean throughout 48-h significantly different from both APRV and LTV ventilation (P G 0.001). Pmean was significantly higher in APRV than in both sham and LTV ventilation after transition from conventional ventilation at 1 h. Because of stepwise increases in PEEP per the ARDSnet protocol, the Pmean was identical from 39 to 48 h for LTV ventilation and APRV; D: Pressure-time profile (P/TP): APRV group had significantly higher P/TP than did both other groups as soon as the transition was made from volume-cycled ventilation (P G 0.001 *vs* sham and LTV ventilation). In the LTV ventilation group, P/TP remained low and did not change over the 48-h course of the study. Sham group animals also had low P/TP, which was not significantly different from the LTV ventilation group throughout the study; Middle: Gross appearance. Representative specimens of gross lungs and cut surface of gross lungs from LTV ventilation (F and H) and APRV (E and G) groups are shown. Bottom I-K: Histological appearance. Photomicrographs of representative lung sections of specimens from each treatment group at 40 × magnification are shown. F: Fibrinous deposit in the air compartment; arrow: Blood in alveolus; arrowhead: Congested alveolar capillary; bracket: Thickened alveolar wall. A: Sham: Animals received 48 h of mechanical ventilation and no injury. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, and thickened alveolar walls; B: Low tidal volume ventilation: animals received aforementioned ischemic injury along with peritoneal sepsis and LTV ventilation after onset of ALI. Specimen exhibits stigmata of lung injury including fibrinous deposits, blood in alveolus, congested capillaries, leukocyte infiltration, and thickened alveolar walls; C: Airway pressure release ventilation: animals received APRV 1 h following aforementioned ischmic injury and peritoneal sepsis. Specimen shows normal pulmonary architecture, alveoli are well expanded and thin walled, and there are no exudates. Republished with permission from Ref[39]. APRV: Airway pressure release ventilation; PEEP: Positive end-expiratory pressure; ALI: Acute lung injury.

20, 24 cmH_2O) were tested; in the APRV group, the T_{low} was set to achieve ratios of the end-expiratory flow rate to peak expiratory flow rate (EEFR to PEFR) of 10%, 25%, 50%, and 75% - the smaller this ratio is, the more time the lung is exposed to low pressure during the release phase[40]. A PEEP of 16 cmH_2O in the controlled mandatory ventilation group and an EEFR to PEFR ratio of 75% in the APRV group both minimized alveolar microstrain (*i.e.*, the dynamic change in alveolar size during tidal ventilation) in this study. However, alveolar recruitment was greater in the APRV group with an EEFR to PEFR ratio of 75% (Figure 3)[40].

From a purely clinical perspective, APRV has demonstrated tremendous potential in preventing ALI/ARDS as well. In particular, Dr. Nader Habashi's clinical work with APRV has demonstrated the benefits of utilizing APRV in trauma patients at risk for developing lung injury. In a systematic review published in 2013, outcomes for patients with early application of APRV at the R Adams Cowley Shock Trauma Center in Maryland from 2002 to 2005 were compared to patient populations at other trauma centers to evaluate rates of ARDS development and in-hospital mortality[11]. Relevant studies were identified through PubMed and MEDLINE searches from 1995 to 2012 using the keywords trauma and acute respiratory distress syndrome or ARDS and trauma and acute lung injury or ALI[11]. Sixteen studies met the inclusion criteria of being a prospective or retrospective observational studies or cohort studies enrolling 100 or more adult trauma patients with reported ALI/ARDS incidence and in-hospital mortality data[11]. Although the patients at the Shock Trauma Center were in the upper quartile for their injury severity scores, both the incidence of ARDS (1.3%) and the in-hospital mortality (3.9%) were the lowest for this group of patients in whom early APRV was applied (Figure 4)[11]. Although a prospective randomized controlled trial is needed to confirm these results, this systematic review provided convincing evidence that APRV may be precisely the protective mechanical ventilation mode that may be applied prophylactically to all patients as soon as they are intubated to prevent the progression to lung injury or ARDS. In addition, since APRV is a comfortable mode of mechanical ventilation with minimal negative side effects in patients with normal lungs, it can be applied prophylactically to all patients as soon as they are intubated (unpublished observations).

CONCLUSION

ARDS remains a troubling clinical entity with an unacceptably high mortality. Treating fulminant ARDS has proven futile for decades; there are currently no effective pharmacologic or mechanical ventilation strategies for curing ARDS, and treatment is relegated to aggressive supportive care measures. Thus, the key to

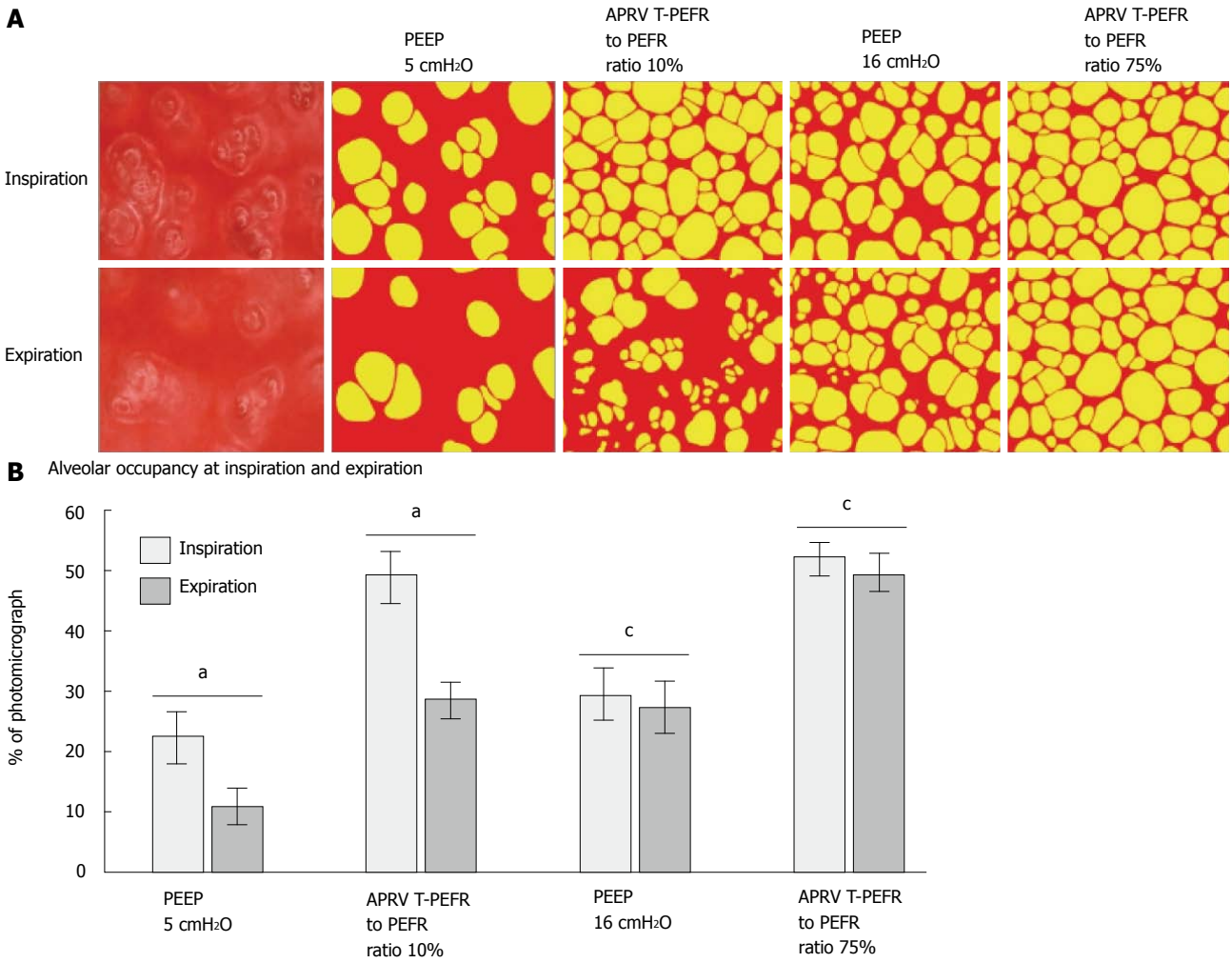


Figure 3 ***In vivo*** **photomicrographs and percentage of alveolar air space occupancy at inspiration and expiration.** A: *In vivo* photomicrographs at inspiration and expiration prior to coloring and for positive end-expiratory pressure (PEEP) of 5 cm H_2O, airway pressure release ventilation (APRV) ratio of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10%, PEEP of 16 cm H_2O, and APRV T-PEFR to PEFR ratio of 75% (original magnification × 10). Alveoli are colored in yellow; nonalveolar tissue, red; B: Alveolar air space occupancy is expressed as a percentage of the photomicrograph containing inflated alveoli (yellow in A) at inspiration and expiration. Data are shown as the mean; error bars indicate standard error of the mean. $^{a}P < 0.05$ for PEEP of 5 cmH_2O *vs* APRVT-PEFR to PEFR ratio of 10%; $^{c}P < 0.05$ for PEEP of 16 cmH_2O *vs* APRV T-PEFR to PEFR ratio of 75%. Republished with permission from Ref[40].

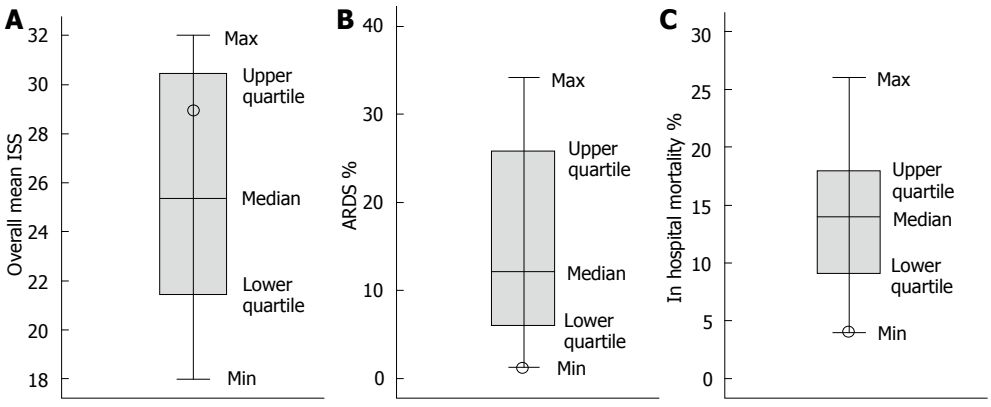


Figure 4 Boxplots for mean individual severity score (A), acute respiratory distress syndrome % (B), and in-hospital mortality % (C). Mean ISS shows the range and distribution of ISS scores reported by 16 authors; 50% of them reported ISS between 30.5 and 23.2, with the middle score of 25.4 (median). The mean ISS of 29 for the preemptive APRV group belonged to the upper quartile of the boxplot. ARDS incidence % shows the range and distribution of scores reported by 16 authors; 50% of them reported ARDS incidence between 22.5% and 6%, with the middle score of 11.95% (median). The incidence of ARDS in the preemptive APRV group represented the minimum score at 1.3%. Mortality % shows the range and distribution of mortality scores reported by 16 authors; 50% of them reported mortality between 18.2% and 9.2%, with the middle score of 13.9% (median). The preemptive APRV group scored the minimum mortality rate of 3.9%. Republished with permission from Ref[11]. ARDS: Acute respiratory distress syndrome; APRV: Airway pressure release ventilation; ISS: Individual severity score.

treating this highly morbid disease lies with preventing the disease from ever occurring. Indeed protective mechanical ventilation strategies are being employed in the operating room and in the intensive care unit before the development of lung injury. Moreover, data from both our laboratory and the clinical realm indicate that appropriately setting APRV generates a protective MBP that may be the most viable and accessible method of preventing lung injury and the subsequent progression to ARDS.

REFERENCES

1 **Cheung AM**, Tansey CM, Tomlinson G, Diaz-Granados N, Matté A, Barr A, Mehta S, Mazer CD, Guest CB, Stewart TE, Al-Saidi F, Cooper AB, Cook D, Slutsky AS, Herridge MS. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; **174**: 538-544 [PMID: 16763220 DOI: 10.1164/rccm.200505-693OC]

2 **Herridge MS**, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011; **364**: 1293-1304 [PMID: 21470008 DOI: 10.1056/NEJMoa1011802]

3 **Rubenfeld GD**, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005; **353**: 1685-1693 [PMID: 16236739 DOI: 10.1056/NEJMoa050333]

4 **Davidson TA**, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA* 1999; **281**: 354-360 [PMID: 9929089 DOI: 10.1001/jama.281.4.354]

5 **Angus DC**, Musthafa AA, Clermont G, Griffin MF, Linde-Zwirble WT, Dremsizov TT, Pinsky MR. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001; **163**: 1389-1394 [PMID: 11371406 DOI: 10.1164/ajrccm.163.6.2005123]

6 **Weinert CR**, Gross CR, Kangas JR, Bury CL, Marinelli WA. Health-related quality of life after acute lung injury. *Am J Respir Crit Care Med* 1997; **156**: 1120-1128 [PMID: 9351611 DOI: 10.1164/ajrccm.156.4.9611047]

7 **Matthay MA**, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, Holets S, Kallet RH, Liu KD, MacIntyre N, Moss M, Schoenfeld D, Steingrub J, Thompson BT. Randomized, placebo-controlled clinical trial of an aerosolized β-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011; **184**: 561-568 [PMID: 21562125 DOI: 10.1164/rccm.201012-2090OC]

8 **Rice TW**, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011; **306**: 1574-1581 [PMID: 21976613 DOI: 10.1001/jama.2011.1435]

9 **Spragg RG**, Taut FJ, Lewis JF, Schenk P, Ruppert C, Dean N, Krell K, Karabinis A, Günther A. Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med* 2011; **183**: 1055-1061 [PMID: 21148720 DOI: 10.1164/rccm.201009-1424OC]

10 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]

11 **Andrews PL**, Shiber JR, Jaruga-Killeen E, Roy S, Sadowitz B, O'Toole RV, Gatto LA, Nieman GF, Scalea T, Habashi NM. Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: a systematic review of observational trauma ARDS literature. *J Trauma Acute Care Surg* 2013; **75**: 635-641 [PMID: 24064877 DOI: 10.1097/TA.0b013e31829d3504]

12 **Villar J**, Sulemanji D, Kacmarek RM. The acute respiratory distress syndrome: incidence and mortality, has it changed? *Curr Opin Crit Care* 2014; **20**: 3-9 [PMID: 24309954 DOI: 10.1097/MCC.0000000000000057]

13 **Phua J**, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med* 2009; **179**: 220-227 [PMID: 19011152 DOI: 10.1164/rccm.200805-722OC]

14 **Villar J**, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, Gandía F, Carriedo D, Mosteiro F, Basaldúa S, Fernández RL, Kacmarek RM. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011; **37**: 1932-1941 [PMID: 21997128 DOI: 10.1007/s00134-011-2380-4]

15 **Beitler JR**, Schoenfeld DA, Thompson BT. Preventing ARDS: progress, promise, and pitfalls. *Chest* 2014; **146**: 1102-1113 [PMID: 25288000 DOI: 10.1378/chest.14-0555]

16 **Biehl M**, Kashiouris MG, Gajic O. Ventilator-induced lung injury: minimizing its impact in patients with or at risk for ARDS. *Respir Care* 2013; **58**: 927-937 [PMID: 23709192 DOI: 10.4187/respcare.02347]

17 **Festic E**, Kor DJ, Gajic O. Prevention of acute respiratory distress syndrome. *Curr Opin Crit Care* 2015; **21**: 82-90 [PMID: 25501020 DOI: 10.1097/MCC.0000000000000174]

18 **Ortiz-Diaz E**, Festic E, Gajic O, Levitt JE. Emerging pharmacological therapies for prevention and early treatment of acute lung injury. *Semin Respir Crit Care Med* 2013; **34**: 448-458 [PMID: 23934714 DOI: 10.1055/s-0033-1351118]

19 **Hou PC**, Elie-Turenne MC, Mitani A, Barry JM, Kao EY, Cohen JE, Frendl G, Gajic O, Gentile NT. Towards prevention of acute lung injury: frequency and outcomes of emergency department patients at-risk - a multicenter cohort study. *Int J Emerg Med* 2012; **5**: 22 [PMID: 22632126 DOI: 10.1186/1865-1380-5-22]

20 **Litell JM**, Gong MN, Talmor D, Gajic O. Acute lung injury: prevention may be the best medicine. *Respir Care* 2011; **56**: 1546-1554 [PMID: 22008396 DOI: 10.4187/respcare.01361]

21 **Thakur SJ**, Trillo-Alvarez CA, Malinchoc MM, Kashyap R, Thakur L, Ahmed A, Reriani MK, Cartin-Ceba R, Sloan JA, Gajic O. Towards the prevention of acute lung injury: a population based cohort study protocol. *BMC Emerg Med* 2010; **10**: 8 [PMID: 20420711 DOI: 10.1186/1471-227X-10-8]

22 **Levitt JE**, Matthay MA. Clinical review: Early treatment of acute lung injury--paradigm shift toward prevention and treatment prior to respiratory failure. *Crit Care* 2012; **16**: 223 [PMID: 22713281 DOI: 10.1186/cc11144]

23 **Yilmaz M**, Keegan MT, Iscimen R, Afessa B, Buck CF, Hubmayr RD, Gajic O. Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med* 2007; **35**: 1660-1666; quiz 1667 [PMID: 17507824]

24 **Shari G**, Kojicic M, Li G, Cartin-Ceba R, Alvarez CT, Kashyap R, Dong Y, Poulose JT, Herasevich V, Garza JA, Gajic O. Timing of the onset of acute respiratory distress syndrome: a population-based study. *Respir Care* 2011; **56**: 576-582 [PMID: 21276315 DOI: 10.4187/respcare.00901]

25 **Fuller BM**, Mohr NM, Hotchkiss RS, Kollef MH. Reducing the burden of acute respiratory distress syndrome: the case for early intervention and the potential role of the emergency department. *Shock* 2014; **41**: 378-387 [PMID: 24469236 DOI: 10.1097/SHK.0000000000000142]

26 **Ferguson ND**, Frutos-Vivar F, Esteban A, Gordo F, Honrubia T, Peñuelas O, Algora A, García G, Bustos A, Rodríguez I. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. *Crit Care* 2007; **11**: R96 [PMID: 17784960 DOI: 10.1186/cc6113]

27 **Gajic O**, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman

OB, O'Byrne MM, Evenson LK, Malinchoc M, DeGoey SR, Afessa B, Hubmayr RD, Moore SB. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med* 2007; **176**: 886-891 [PMID: 17626910 DOI: 10.1164/rccm.200702-271OC]

28 **Gajic O**, Moore SB. Transfusion-related acute lung injury. *Mayo Clin Proc* 2005; **80**: 766-770 [PMID: 15945528 DOI: 10.4065/80.6.766]

29 **Gajic O**, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? *Crit Care Med* 2006; **34**: S170-S173 [PMID: 16617262 DOI: 10.1097/01.CCM.0000214288.88308.26]

30 **Gajic O**, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; **32**: 1817-1824 [PMID: 15343007 DOI: 10.1097/01.CCM.0000133019.52531.30]

31 **Gajic O**, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med* 2011; **183**: 462-470 [PMID: 20802164 DOI: 10.1164/rccm.201004-0549OC]

32 **Futier E**, Godet T, Millot A, Constantin JM, Jaber S. Mechanical ventilation in abdominal surgery. *Ann Fr Anesth Reanim* 2014; **33**: 472-475 [PMID: 25153670 DOI: 10.1016/j.annfar.2014.07.007]

33 **Futier E**, Jaber S. Lung-protective ventilation in abdominal surgery. *Curr Opin Crit Care* 2014; **20**: 426-430 [PMID: 24927044 DOI: 10.1097/MCC.0000000000000121]

34 **Gu WJ**, Wang F, Liu JC. Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials. *CMAJ* 2015; **187**: E101-E109 [PMID: 25512653 DOI: 10.1503/cmaj.141005]

35 **Futier E**, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013; **369**: 428-437 [PMID: 23902482 DOI: 10.1056/NEJMoa1301082]

36 **Determann RM**, Royakkers A, Wolthuis EK, Vlaar AP, Choi G, Paulus F, Hofstra JJ, de Graaff MJ, Korevaar JC, Schultz MJ. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care* 2010; **14**: R1 [PMID: 20055989 DOI: 10.1186/cc8230]

37 **Kubiak BD**, Albert SP, Gatto LA, Vieau CJ, Roy SK, Snyder KP, Maier KG, Nieman GF. A clinically applicable porcine model of septic and ischemia/reperfusion-induced shock and multiple organ injury. *J Surg Res* 2011; **166**: e59-e69 [PMID: 21193206 DOI: 10.1016/j.jss.2010.10.014]

38 **Roy S**, Sadowitz B, Andrews P, Gatto LA, Marx W, Ge L, Wang G, Lin X, Dean DA, Kuhn M, Ghosh A, Satalin J, Snyder K, Vodovotz Y, Nieman G, Habashi N. Early stabilizing alveolar ventilation prevents acute respiratory distress syndrome: a novel timing-based ventilatory intervention to avert lung injury. *J Trauma Acute Care Surg* 2012; **73**: 391-400 [PMID: 22846945 DOI: 10.1097/TA.0b013e31825c7a82]

39 **Roy S**, Habashi N, Sadowitz B, Andrews P, Ge L, Wang G, Roy P, Ghosh A, Kuhn M, Satalin J, Gatto LA, Lin X, Dean DA, Vodovotz Y, Nieman G. Early airway pressure release ventilation prevents ARDS-a novel preventive approach to lung injury. *Shock* 2013; **39**: 28-38 [PMID: 23247119 DOI: 10.1097/shk.0b013e31827b47bb]

40 **Kollisch-Singule M**, Emr B, Smith B, Roy S, Jain S, Satalin J, Snyder K, Andrews P, Habashi N, Bates J, Marx W, Nieman G, Gatto LA. Mechanical breath profile of airway pressure release ventilation: the effect on alveolar recruitment and microstrain in acute lung injury. *JAMA Surg* 2014; **149**: 1138-1145 [PMID: 25230047 DOI: 10.1001/jamasurg.2014.1829]

P- Reviewer: Chen XL, Nseir S **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.83

World J Crit Care Med 2016 February 4; 5(1): 83-88
ISSN 2220-3141 (online)

MINIREVIEWS

Critical care of obese patients during and after spine surgery

Hossein Elgafy, Ryan Hamilton, Nicholas Peters, Daniel Paull, Ali Hassan

Hossein Elgafy, Ryan Hamilton, Nicholas Peters, Daniel Paull, Departments of Orthopedic, University of Toledo Medical Center, Toledo, OH 43614-5807, United States

Ali Hassan, Departments of Anesthesia, University of Toledo Medical Center, Toledo, OH 43614-5807, United States

Author contributions: All the authors contributed in outlining the manuscript, gathering the data, and writing the manuscript.

Conflict-of-interest statement: None of the authors have any financial and other conflicts of interest that may bias the current study.

Correspondence to: Hossein Elgafy, MD, MCH, FRCSED, FRCSC, Department of Orthopaedics, University of Toledo Medical Centre, 3065 Arlington Avenue, Toledo, OH 43614-5807, United States. hkelgafy@aol.com
Telephone: +1-419-3833515
Fax: +1-419-3833526

Received: July 30, 2015
Peer-review started: July 31, 2015
First decision: October 8, 2015
Revised: December 4, 2015
Accepted: December 18, 2015
Article in press: December 21, 2015
Published online: February 4, 2016

Abstract

Obesity is one of the most prevalent health problems facing the United States today, with a recent JAMA article published in 2014 estimating the prevalence of one third of all adults in the United States being obese. Also, due to technological advancements, the incidence of spine surgeries is growing. Considering these overall increases in both obesity and the performance of spinal surgeries, it can be inferred that more spinal surgery candidates will be obese. Due to this, certain factors must be taken into consideration when dealing with spine surgeries in the obese. Obesity is closely correlated with additional medical comorbidities, including hypertension, coronary artery disease, congestive heart failure, and diabetes mellitus. The pre-operative evaluation may be more difficult, as a more extensive medical evaluation may be needed. Also, adequate radiographic images can be difficult to obtain due to patient size and equipment limitations. Administering anesthesia becomes more difficult, as does proper patient positioning. Post-operatively, the obese patient is at greater risk for reintubation, difficulty with pain control, wound infection and deep vein thrombosis. However, despite these concerns, appropriate clinical outcomes can still be achieved in the obese spine surgical candidate. Obesity, therefore, is not a contraindication to spine surgery, and appropriate patient selection remains the key to obtaining favorable clinical outcomes.

Key words: Obesity; Spine sugary; Critical care

Core tip: Obesity is one of the most prevalent health problems facing the United States today. Due to technological advancements, the incidence of spine surgeries is also growing. This is particularly true for spinal fusion procedures, as rates were noted to triple from 1990 to 2000. There are potential increased complication risks during and after spine surgery due to associated comorbidities. Spine surgery can be performed safely in obese patients with appropriate management of comorbidities and proper patient selection.

Elgafy H, Hamilton R, Peters N, Paull D, Hassan A. Critical care of obese patients during and after spine surgery. *World J Crit Care Med* 2016; 5(1): 83-88 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/83.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.83

INTRODUCTION

Obesity is one of the most prevalent health problems facing the United States today. Recent studies indicate that 32.2% of adult men and 35.5% of adult women in the United States are considered obese[1,2]. The prevalence of obesity has also increased, notably among adolescents and adult men[3]. Additionally, due to technological advancements, the incidence of spine surgeries is also growing. This is particularly true for spinal fusion procedures, as rates were noted to triple from 1990 to 2000[4]. Spinal fusion was the 19th most common inpatient procedure performed in 2003, rising from 41st in 1997[5]. The purpose of this article is to review the effects that obesity has on spinal surgery patients both during and after surgery and highlight the factors that must be taken into consideration when dealing with these surgeries in the obese.

OBESITY AND ASSOCIATED CO-MORBIDITIES

Most clinicians today define obesity according to a standardized formula known as the body mass index (BMI). This formula was created by Belgian statistician Adolphe Quetelet in 1832 and had been mostly abandoned[6]. It was then thrust to the front of obesity research in 1972 by Keys *et al*[7], who evaluated the methods available at the time for describing the relative weight of patients or populations. He chose the easiest and most reproducible method, which he renamed the BMI. This simple formula requires no special tools or data, as it is simply the patient's weight (kg) divided by the square of their height (m^2). From this information there have been guidelines set to classify patients as underweight, normal weight, overweight, obese, or morbidly obese (Table 1)[8].

Obesity has been shown to be closely correlated to multiple medical comorbidities such as increased rates of diabetes mellitus, hypertension, coronary artery disease, obstructive sleep apnea, and overall mortality[3,9-11]. This has specifically been shown in the surgical spine patient, as Vaidya *et al*[12] found averages of 5.1 and 8.1 comorbidities in obese and morbidly obese patients, respectively, that underwent posterior decompression and fusion with instrumentation. Thus not only does the presence of obesity play a role in the incidence of medical comorbidities, but the degree of obesity is also important. The increased rates of diabetes in these populations must also be carefully considered, as diabetic patients have been noted to have an increase in wound complications[13,14].

OBESITY AND THE PRE-OPERATIVE EVALUATION

The presence of obesity can also affect the diagnostic assessment of a patient being evaluated for spine surgery. Patients that undergo spinal surgery typically have multiple pre-operative imaging studies. These usually include plain radiographs, computed tomography (CT) scan and magnetic resonance imaging (MRI), which offer better detail of bone and soft tissue structures, respectively. All of these methods contribute to accurate diagnosis and appropriate pre-operative planning. Obtaining proper images, however, may be difficult in the obese patient. Plain radiographs are available in most clinics and are relatively easy for the patient to obtain. However, the presence of obesity may result in higher radiation doses and poorer image quality due to decreased tissue penetration. Digital imaging and good technicians can help minimize these issues.

Cross-sectional imaging modalities have special concerns related to patient size and weight. The tables required in these machines are finely calibrated and larger patients may "tweak" the table, resulting in decreased image quality. Additionally, a tube must be entered in order to obtain these images. CT scanners have traditionally been roomier, with apertures approximately 70 cm in diameter. MRI scanners, due to their magnets, are smaller, with standard machine diameters averaging around 60 cm. Obese patients may not fit into these confined spaces or may also have issues with claustrophobia. Due to these concerns standing, or "open", MRI has been developed. These machine diameters average about 70 cm, but also have reduced magnet sizes that may limit image quality. There are also some newer, traditional style MRI machines with table limits at or above 550 pounds with 70 cm diameter tubes. Unfortunately, availability of these machines may be limited[15].

Obesity and its commonly associated comorbidities alter the pre-operative medical evaluation necessary for surgical clearance. For instance, hypertension is a commonly present comorbidity which has been shown to lead to left ventricular hypertrophy. This may contribute to the development of ischemic cardiomyopathy and subsequent ventricular dysfunction. Furthermore, obesity increases the risk of arrhythmias likely through fatty and ischemic changes of the myocardium. Respiratory function may be altered as obese patients exhibit decreased chest wall compliance secondary to adiposity of the chest wall and abdomen. This results into a higher workload of breathing and a decreased functional residual capacity. Obese patients also have a high rate of obstructive sleep apnea. Other considerations include an increase in gastroesophageal reflux disease, fatty changes to the liver, endocrine and metabolic disturbances, including hypercholesterolemia and diabetes, and potential coagulopathies.

Table 1 Patient weight classification according to body mass index

Body mass index (kg/m^2)	Degree of obesity
Below 18.5	Underweight
18.5-24.9	Normal
25.0-29.9	Overweight
30.0-39.9	Obese
40.0 and above	Morbidly obese

Due to these factors the pre-operative evaluation require blood work that includes hemoglobin, electrolyte panel, liver function test, blood glucose level, and a clotting profile. A chest radiograph, pulmonary function tests, and electrocardiogram (ECG) are also recommended. If abnormalities are noted on the ECG further evaluation is likely needed, including an echocardiogram, cardiac stress test, and consultation with a cardiologist[16,17].

ANESTHESIA CONSIDERATIONS FOR SPINAL SURGERY IN OBESE AND MORBIDLY OBESE PATIENTS

Establishing intravenous access may be more difficult in an obese individual. Initial difficulties may be encountered with the administration of anesthesia. The decreased functional residual capacity of obese patients has important considerations for anesthesia. Patients with severely reduced functional residual capacity can develop premature airway closure and ventilation-perfusion mismatches, with resultant hypoxemia. During induction of anesthesia, these results into a shortened duration of nonhypoxic apnea, the period of time between paralysis and intubation before hypoxia occurs. Furthermore, large tongues and narrow airways, commonly seen in patients with obstructive sleep apnea, may make securing an airway more difficult, and fiber-optic intubation techniques may be necessary. Rapid induction of anesthesia is imperative in obese patients because of the high risk of aspiration. Esophageal reflux is common; 75% of obese patients have a high-volume, low-pH gastric residue that places them at risk for pneumonia. In severely obese patients, use of positive airway pressure during preoxygenation and induction may minimize hypoxia associated with the apneic phase of standard intubation. The increased adiposity provides a larger distribution area for certain anesthetic agents, which may make appropriate dosing more difficult[18].

CRITICAL CARE OF OBESE PATIENTS IN THE OPERATING ROOM

Due to higher rates of wound sepsis preoperative antibiotics is strongly recommended in obese patients. The current recommendations for the use of prophylactic antibiotics in spine surgery are: Cephalosporin (cefazolin 1-2 g; 2 g for patient weighing > 86 kg) and if B-lactam allergy, use clindamycin or vancomycin (dosing based on patient weight). It is recommended to start up to 60 min before incision, completed at the time of incision and re-dose antimicrobial intraoperatively every 4 h for prolonged procedure or significant blood loss. When using postoperative doses, discontinue within 24 h after wound closure as continuing of antibiotic prophylaxis longer than 24 h after wound closure has not proved to be beneficial; indeed, it may contribute to the development of antimicrobial resistance[19,20].

Patient positioning is more difficult, as many spine surgeries are performed prone. The degree of obesity plays a role, study showed that morbidly obese patients have longer surgical set up times[12]. Placement on the appropriate operative table is also crucial. Use of a closed frame table, such as a Wilson frame, may contribute to an increase in intra-abdominal pressures. This may cause elevation of the diaphragm, resulting in an increased intra-thoracic pressure, leading to a decrease in venous return[21]. This in turn can cause venous congestion, particularly along the epidural veins, and result in an increase blood loss. Due to these concerns it is often recommended to allow the abdomen to hang free using an open-frame table. Jackson spinal table (MIZUHO OSI, Union City, CA)® commonly used in spine surgery has a patient weight capacity of 500 lb (227 kg). A large abdominal pannus requires further modifications to allow for free passage of intra-operative fluoroscopy machines. Bariatric security straps are available that provide a comfortable hold of the pannus and accommodates up to 1000 lb (454 kg) patient (Figure 1)[22,23].

Peripheral nerve palsies have been noted in this population most likely secondary to increased pressure on contact points and difficulty with positioning[24]. Stretch injuries to the brachial plexus may occur with shoulder abduction more than 90°. Arm boards should be positioned to keep shoulder abduction less than 90° and this should be frequently checked by the anesthesia team during the surgical procedure. All bony prominence should all be carefully padded to avoid any pressure points.

Higher doses of radiation are also needed for adequate tissue penetration, thus exposing both the patient and the operative personnel to higher levels of radiation[25]. Larger patients require longer incisions, more extensive soft tissue dissection, and may present certain technical difficulties, such as obtaining the appropriate angles for pedicle screw placement[26]. Peng *et al*[27], evaluated different factors in obese and non-obese patients undergoing anterior lumbar surgery, concluding that obese patients required a longer duration of both exposure time and total surgical time. They also had longer incision lengths, as well as deeper skin to fascia and fascia to spine depths. Estimated blood loss, however, was not significantly different[27]. Rosen *et al*[28] noted no difference in the operative outcome between obese and non-obese patients that underwent minimally invasive spine surgery for lumbar fusion. This may be due to the tubular retraction system utilized in these procedures, which allows similar sized skin incisions in all patients[28]. Reducing operative times in spinal surgery is important, as longer times increase infection risk and the risk of blindness when the patient is prone,

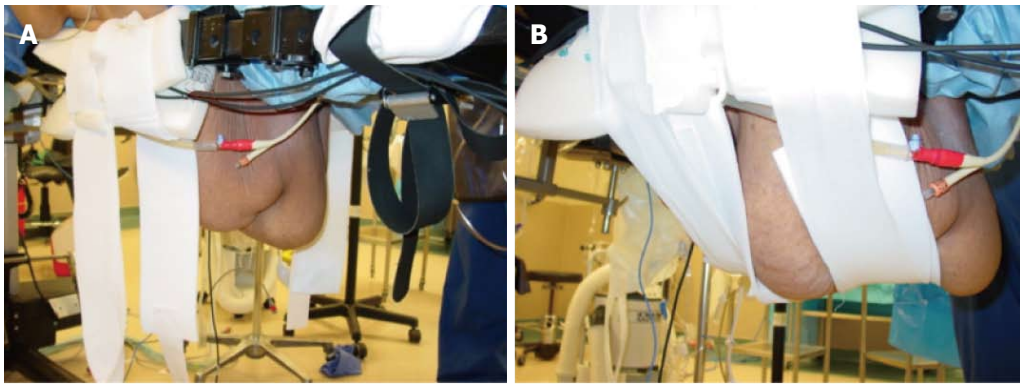


Figure 1 Patient in prone position on the Jackson spinal table. A: A large abdominal pannus will interfere with free passage of intra-operative fluoroscopy; B: Bariatric security straps are used to provide a comfortable hold of the pannus to the table. Foam is used to cover the metal edges of the table and protect the skin from pressure sores.

as this complication has been observed in long lasting surgeries[29,30].

OBESITY AND POST-OPERATIVE CARE AND COMPLICATIONS

The post-operative effects of obesity on surgical patients have remained controversial. Studies in general surgery patients indicated an increase in wound infections with open procedures, but no other differences[31]. Obese cardiac surgery patients were found to have an increased rate of superficial sternal and leg infections, as well as atrial dysrhythmias, but not in overall mortality[32]. Total hip and knee replacement patients have been found to have no difference in complications and post-operative course[33].

Post-operative pain and anesthesia will induce respiratory modifications which include atelectasis to due a restrictive syndrome and diaphragm dysfunction. This in turn can lead to hypoxemia and decreased pulmonary capacity. Jaber *et al*[34], stressed the importance of post-operative oxygenation using non-invasive ventilation in an effort to prevent acute respiratory failure. Several studies have shown that there is an increased mortality related to the complications of postoperative reintubation. Risk factors for such complication include COPD, age older than 60, ASA class of Ⅱ or greater, and obesity[34]. Therefore, post extubation it is of vital importance for adequate ventilation in the obese patients for optimizing surgical outcomes. A prospective study performed by Jaber *et al*[35] in 2005 showed that the use of non-invasive ventilation in patients with acute respiratory failure following extubation lowered the incidence of reintubation by 67%. Two methods of to avoid development of acute respiratory failure using non-invasive ventilation are positive end expiratory pressure and pressure support ventilation.

Post-operative pain control in obese patients also has its own specific challenges with a goal of decreasing the requirement for opioids to improve early rehabilitation and reduce the adverse effects of narcotics. With increased body fat, total body water, and plasma volume the pharmacokinetics of analgesics differs from that of those with ideal body weight diluting concentrations and therefore lowering the efficacy. Moreover, a study by Miscio *et al*[36] explored sensitivity to various noxious stimuli in obese subjects and compared those results to those with normal BMI of similar age. They discovered that obese non-diabetic subjects with a had a lower sensitivity to vibration, mechanical, and heat signals suggesting that obesity may affect the pain pathway and further complicate optimizing pain control[36]. Difficulty arises in the post-operative pain management due to the associated comorbidity of obstructive sleep apnea in obese patients and risk of respiratory depression with narcotics.

The development of deep venous thrombosis (DVT) is of particular concern in the post-operative period in this population, as both obesity and recent surgery are independent risk factors for DVT[37,38]. The post-operative spine patient, however, requires special consideration, as use of chemical prophylaxis in the acute post-operative period brings an increased risk of epidural hematoma and subsequent neurologic compression and deficits[39]. Due to this mechanical prophylaxis, such as compression stockings and sequential compression devices, is of the utmost importance. This should be started intra-operatively and continued throughout the post-operative hospital course. Proper fitting of such devices, however, may be difficult with an obese body habitus. Early ambulation is also important, with patients beginning to walk no later than post-operative day one.

The most frequently encountered complication in the obese spine patient is wound infection[40-42]. Other complications, however, have been noted more frequently in the obese. Patel *et al*[24] did find a correlation between BMI and a higher risk of major complications following elective thoracic and lumbar fusion procedures. Patients with a BMI of 25 were found to have a complication rate of 14%, while ones with a BMI of 30 were at 20%, and a BMI of 40 associated with a 36% rate[24]. Shamji *et al*[26] noted an increased transfusion requirement in thoracic and lumbar fusion patients, as well as an increase in the likelihood of discharge to an assisted living facility.

However, no differences were noted in length of stay, infection rates, or overall mortality[26]. Other studies have noted no difference in complication rates between obese and non-obese spine patients[43,44].

CONCLUSION

Obesity does not appear to be a contraindication for spinal surgery however it does pose a unique set of challenges in the perioperative time frame. It is important for the operative surgeon and anesthesia team to be aware of any special considerations that must be undertaken in preoperative evaluation, intraoperative and postoperative management. The potential for increased operative times, difficulties with anesthesia, operative positioning, higher blood loss, post-extubation complications, post-operative pain management, and increase in wound complications must be realized. However, it appears that with appropriate management of comorbidities and proper patient selection that spine surgery can be performed safely in obese patients.

REFERENCES

1 **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; **311**: 806-814 [PMID: 24570244 DOI: 10.1001/jama.2014.732]

2 **Flegal KM**, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA* 2010; **303**: 235-241 [PMID: 20071471 DOI: 10.1001/jama.2009.2014]

3 **Ogden CL**, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 2006; **295**: 1549-1555 [PMID: 16595758 DOI: 10.1001/jama.295.13.1549]

4 **Deyo RA**, Mirza SK. Trends and variations in the use of spine surgery. *Clin Orthop Relat Res* 2006; **443**: 139-146 [PMID: 16462438 DOI: 10.1097/01.blo.0000198726.62514.75]

5 **Cowan JA**, Dimick JB, Wainess R, Upchurch GR, Chandler WF, La Marca F. Changes in the utilization of spinal fusion in the United States. *Neurosurgery* 2006; **59**: 15-20 [PMID: 16823295 DOI: 10.1227/01.NEU.0000219836.54861.CD]

6 **Eknoyan G**. Adolphe Quetelet (1796-1874)--the average man and indices of obesity. *Nephrol Dial Transplant* 2008; **23**: 47-51 [PMID: 17890752 DOI: 10.1093/ndt/gfm517]

7 **Keys A**, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. *J Chronic Dis* 1972; **25**: 329-343 [PMID: 4650929 DOI: 10.1016/0021-9681(72)90027-6]

8 Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998; **6** Suppl 2: 51S-209S [PMID: 9813653]

9 **Hensrud DD**, Klein S. Extreme obesity: a new medical crisis in the United States. *Mayo Clin Proc* 2006; **81**: S5-S10 [PMID: 17036573 DOI: 10.1016/S0025-6196(11)61175-0]

10 **Pender JR**, Pories WJ. Epidemiology of obesity in the United States. *Gastroenterol Clin North Am* 2005; **34**: 1-7 [PMID: 15823434 DOI: 10.1016/j.gtc.2004.12.010]

11 **Flegal KM**. Epidemiologic aspects of overweight and obesity in the United States. *Physiol Behav* 2005; **86**: 599-602 [PMID: 16242735 DOI: 10.1016/j.physbeh.2005.08.050]

12 **Vaidya R**, Carp J, Bartol S, Ouellette N, Lee S, Sethi A. Lumbar spine fusion in obese and morbidly obese patients. *Spine* (Phila Pa 1976) 2009; **34**: 495-500 [PMID: 19212274 DOI: 10.1097/BRS.0b013e318198c5f2]

13 **Bendo JA**, Spivak J, Moskovich R, Neuwirth M. Instrumented posterior arthrodesis of the lumbar spine in patients with diabetes mellitus. *Am J Orthop* (Belle Mead NJ) 2000; **29**: 617-620 [PMID: 10955466]

14 **Kawaguchi Y**, Matsui H, Ishihara H, Gejo R, Yasuda T. Surgical outcome of cervical expansive laminoplasty in patients with diabetes mellitus. *Spine* (Phila Pa 1976) 2000; **25**: 551-555 [PMID: 10749630 DOI: 10.1097/00007632-200003010-00004]

15 **Ginde AA**, Foianini A, Renner DM, Valley M, Camargo CA. The challenge of CT and MRI imaging of obese individuals who present to the emergency department: a national survey. *Obesity* (Silver Spring) 2008; **16**: 2549-2551 [PMID: 18787528 DOI: 10.1038/oby.2008.410]

16 **Bortenschlager L**, Zaloga GP. Obesity in the Critically Ill Patient. In: Grenvik A, Ayres SM, Holbrook PR, Shoemaker WC editors. Textbook of Critical Care. Philadelphia: WB Saunders Company, 2000: 950-960

17 **Morgan GE**, Mikhail MS, Murray MJ, Larson C. Clinical Anesthesiology. Vol 1. 4th ed. New York: Lange Medical Books/McGraw-Hill Medical Publishing Division, 2002: 748-749

18 **Casati A**, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. *J Clin Anesth* 2005; **17**: 134-145 [PMID: 15809132 DOI: 10.1016/j.jclinane.2004.01.009]

19 **Bratzler DW**, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004; **38**: 1706-1715 [PMID: 15227616 DOI: 10.1086/421095]

20 **Prokuski L**. Prophylactic antibiotics in orthopaedic surgery. *J Am Acad Orthop Surg* 2008; **16**: 283-293 [PMID: 18460689]

21 **Bloomfield GL**, Ridings PC, Blocher CR, Marmarou A, Sugerman HJ. A proposed relationship between increased intra-abdominal, intrathoracic, and intracranial pressure. *Crit Care Med* 1997; **25**: 496-503 [PMID: 9118668 DOI: 10.1097/00003246-199703000-00020]

22 **Böstman O**, Hyrkäs J, Hirvensalo E, Kallio E. Blood loss, operating time, and positioning of the patient in lumbar disc surgery. *Spine* (Phila Pa 1976) 1990; **15**: 360-363 [PMID: 2363066 DOI: 10.1097/00007632-199005000-00004]

23 **Lee TC**, Yang LC, Chen HJ. Effect of patient position and hypotensive anesthesia on inferior vena caval pressure. *Spine* (Phila Pa 1976) 1998; **23**: 941-947 [PMID: 9580963 DOI: 10.1097/00007632-199804150-00019]

24 **Patel N**, Bagan B, Vadera S, Maltenfort MG, Deutsch H, Vaccaro AR, Harrop J, Sharan A, Ratliff JK. Obesity and spine surgery: relation to perioperative complications. *J Neurosurg Spine* 2007; **6**: 291-297 [PMID: 17436915 DOI: 10.3171/spi.2007.6.4.1]

25 **Weiss DJ**, Pipinos II, Longo GM, Lynch TG, Rutar FJ, Johanning JM. Direct and indirect measurement of patient radiation exposure during endovascular aortic aneurysm repair. *Ann Vasc Surg* 2008; **22**: 723-729 [PMID: 18992664 DOI: 10.1016/j.avsg.2008.06.008]

26 **Shamji MF**, Parker S, Cook C, Pietrobon R, Brown C, Isaacs RE. Impact of body habitus on perioperative morbidity associated with fusion of the thoracolumbar and lumbar spine. *Neurosurgery* 2009; **65**: 490-498; discussion 498 [PMID: 19687694 DOI: 10.1227/01.NEU.0000350863.69524.8E]

27 **Peng CW**, Bendo JA, Goldstein JA, Nalbandian MM. Perioperative outcomes of anterior lumbar surgery in obese versus non-obese patients. *Spine J* 2009; **9**: 715-720 [PMID: 19525153 DOI: 10.1016/j.spinee.2009.04.023]

28 **Rosen DS**, Ferguson SD, Ogden AT, Huo D, Fessler RG. Obesity and self-reported outcome after minimally invasive lumbar spinal fusion surgery. *Neurosurgery* 2008; **63**: 956-960; discussion 960 [PMID: 19005386 DOI: 10.1227/01.NEU.0000313626.23194.3F]

29 **Veeravagu A**, Patil CG, Lad SP, Boakye M. Risk factors for postoperative spinal wound infections after spinal decompression and fusion surgeries. *Spine* (Phila Pa 1976) 2009; **34**: 1869-1872 [PMID: 19644339 DOI: 10.1097/BRS.0b013e3181adc989]

30 **Chang SH**, Miller NR. The incidence of vision loss due to perioperative ischemic optic neuropathy associated with spine surgery: the Johns Hopkins Hospital Experience. *Spine* (Phila Pa 1976) 2005; **30**: 1299-1302 [PMID: 15928556 DOI: 10.1097/01.

brs.0000163884.11476.25]
31 **Dindo D**, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet* 2003; **361**: 2032-2035 [PMID: 12814714 DOI: 10.1016/S0140-6736(03)13640-9]
32 **Moulton MJ**, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Obesity is not a risk factor for significant adverse outcomes after cardiac surgery. *Circulation* 1996; **94**: II87-II92 [PMID: 8901725]
33 **Jiganti JJ**, Goldstein WM, Williams CS. A comparison of the perioperative morbidity in total joint arthroplasty in the obese and nonobese patient. *Clin Orthop Relat Res* 1993; **(289)**: 175-179 [PMID: 8472410 DOI: 10.1097/00132586-199312000-00030]
34 **Jaber S**, De Jong A, Castagnoli A, Futier E, Chanques G. Non-invasive ventilation after surgery. *Ann Fr Anesth Reanim* 2014; **33**: 487-491 [PMID: 25168304 DOI: 10.1016/j.annfar.2014.07.742]
35 **Jaber S**, Delay JM, Chanques G, Sebbane M, Jacquet E, Souche B, Perrigault PF, Eledjam JJ. Outcomes of patients with acute respiratory failure after abdominal surgery treated with noninvasive positive pressure ventilation. *Chest* 2005; **128**: 2688-2695 [PMID: 16236943 DOI: 10.1378/chest.128.4.2688]
36 **Miscio G**, Guastamacchia G, Brunani A, Priano L, Baudo S, Mauro A. Obesity and peripheral neuropathy risk: a dangerous liaison. *J Peripher Nerv Syst* 2005; **10**: 354-358 [PMID: 16279984 DOI: 10.1111/j.1085-9489.2005.00047.x]
37 **Stein PD**, Beemath A, Olson RE. Obesity as a risk factor in venous thromboembolism. *Am J Med* 2005; **118**: 978-980 [PMID: 16164883 DOI: 10.1016/j.amjmed.2005.03.012]
38 **Cushman M**. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007; **44**: 62-69 [PMID: 17433897 DOI: 10.1053/j.seminhematol.2007.02.004]
39 **Sansone JM**, del Rio AM, Anderson PA. The prevalence of and specific risk factors for venous thromboembolic disease following elective spine surgery. *J Bone Joint Surg Am* 2010; **92**: 304-313 [PMID: 20124056 DOI: 10.2106/JBJS.H.01815]
40 **Olsen MA**, Mayfield J, Lauryssen C, Polish LB, Jones M, Vest J, Fraser VJ. Risk factors for surgical site infection in spinal surgery. *J Neurosurg* 2003; **98**: 149-155 [PMID: 12650399]
41 **Telfeian AE**, Reiter GT, Durham SR, Marcotte P. Spine surgery in morbidly obese patients. *J Neurosurg* 2002; **97**: 20-24 [PMID: 12120647 DOI: 10.3171/spi.2002.97.1.0020]
42 **Djurasovic M**, Bratcher KR, Glassman SD, Dimar JR, Carreon LY. The effect of obesity on clinical outcomes after lumbar fusion. *Spine* (Phila Pa 1976) 2008; **33**: 1789-1792 [PMID: 18628712 DOI: 10.1097/BRS.0b013e31817b8f6f]
43 **Andreshak TG**, An HS, Hall J, Stein B. Lumbar spine surgery in the obese patient. *J Spinal Disord* 1997; **10**: 376-379 [PMID: 9355052 DOI: 10.1097/00002517-199710000-00003]
44 **Hanigan WC**, Elwood PW, Henderson JP, Lister JR. Surgical results in obese patients with sciatica. *Neurosurgery* 1987; **20**: 896-899 [PMID: 3614568 DOI: 10.1097/00006123-198706000-00012]

P- Reviewer: Boucek C, Kodaz H **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.89

World J Crit Care Med 2016 February 4; 5(1): 89-95
ISSN 2220-3141 (online)

MINIREVIEWS

Corticosteroids for severe influenza pneumonia: A critical appraisal

Wagner Luis Nedel, David Garcia Nora, Jorge Ibrain Figueira Salluh, Thiago Lisboa, Pedro Póvoa

Wagner Luis Nedel, Intensive Care Unit, Hospital Nossa Senhora da Conceição, Porto Alegre, RS 91350-200, Brazil

David Garcia Nora, Intensive Care Unit, Vila Franca de Xira Hospital, 2600-009 Vila Franca de Xira, Portugal

Jorge Ibrain Figueira Salluh, D'or Institute for Research and Education, Rio de Janeiro, RJ 22281-100, Brazil

Thiago Lisboa, Critical Care Department, Hospital de Clinicas de Porto Alegre, Post-Graduation Program (PPG) Pneumology, Universidade Federal do Rio Grande do Sul, Porto Alegre 90035-903, Brazil

Pedro Póvoa, Polyvalent Intensive Care Unit, São Francisco Xavier Hospital, Centro Hospitalar de Lisboa Ocidental, 1169-056 Lisbon, Portugal

Pedro Póvoa, Nova Medical School, CEDOC, New University of Lisbon, 1169-056 Lisbon, Portugal

Author contributions: All authors reviewed, edited and approved the final manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Correspondence to: Jorge Ibrain Figueira Salluh, MD, PhD, D'or Institute for Research and Education, Rua Diniz Cordeiro, 30-3o andar, Botafogo, Rio de Janeiro 22281-100, Brazil. jorgesalluh@gmail.com
Telephone: +55-21-25383541

Received: September 28, 2015
Peer-review started: October 2, 2015
First decision: October 27, 2015
Revised: November 30, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016
Published online: February 4, 2016

Abstract

Influenza pneumonia is associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions with high mortality. Systemic steroids are proposed as a valid therapeutic option even though its effects are still controversial. Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Thus its current use in severe influenza pneumonia should be restricted to very selected cases and in the setting of clinical trials.

Key words: Influenza; Mechanical ventilation; Pneumonia; Corticosteroids; Respiratory failure

Core tip: This review article presents a critical appraisal

to the use of corticosteroids in severe influenza infections covering the most relevant clinical studies, underlying mechanisms (pathophysiologic and pharmacologic aspects) and providing a scenario to help clinicians at bedside facing this challenging situation.

Nedel WL, Nora DG, Salluh JIF, Lisboa T, Póvoa P. Corticosteroids for severe influenza pneumonia: A critical appraisal. *World J Crit Care Med* 2016; 5(1): 89-95 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/89.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.89

INTRODUCTION

According to the World Health Organization, lower respiratory tract infections account for approximately 7% of deaths per year worldwide and viruses are a common cause of community-acquired pneumonia[1]. Among this wide group of species, influenza virus are of utmost importance and numerous interventions have been proposed for its management[2], especially after pandemic H1N1 influenza virus outbreak, which was associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions and resulted in ICU mortality rates ranging from 14% to 46%[3].

Systemic steroids are proposed as a valid therapeutic option due to their potential role in controlling host inflammatory response, inhibiting cytokine production and restoring the inappropriately low endogenous cortisol levels, compensating critical illness-related corticosteroid insufficiency[4]. Although widely used in H1N1 pandemics, the effect of corticosteroids is still controversial. The purpose of this review is to provide an overview of published data about steroid use and outcomes in severe influenza infection.

Influenza infection

Influenza viruses are enveloped negative-sense RNA viruses with segmented genomes that belong to the family *Orthomyoviridae*[5]. There are three antigenically distinct subtypes, A, B and C, which circulate among humans worldwide[6].

Three influenza pandemics occurred in the 20th century[5,7]: 1918 (Spanish influenza), 1957 (Asian influenza) and 1968 (Hong Kong influenza). Different antigenic subtypes of influenza A caused them, each resulting in more than a million deaths. In 2009, a pandemic H1N1 virus developed by reassortment among several influenza A strains. Over 18000 deaths were laboratory confirmed cases but experts agree that more than 250000 deaths may have resulted from H1N1 infection[8].

The 2009 H1N1 influenza pandemic originated a surge of research investigating the mechanisms of lung injury that develop in severe cases of influenza infection, complementing the work started six years before, after the SARS (Severe Acute Respiratory Syndrome) global outbreak.

Seasonal influenza is an acute respiratory disease that presents with sudden onset of high fevers, upper respiratory tract symptoms, chills, myalgia and gastrointestinal tract symptoms. Infection rarely induces symptoms of lower respiratory tract infections or severe lung injury. Pandemic H1N1 infected patients presented with fever, cough and sore throat and the most severe case rapidly developed bilateral pneumonia, severe ARDS, multiple organ failure and death[9,10]. It affected young individuals disproportionately and several epidemiological studies suggested that pregnant women and obese patients were more susceptible to severe infection[5].

Although molecular mechanisms underpinning these associations are not completely understood, it is known that adipocytes and macrophages from obese patients release higher quantities of interleukin (IL)-6 and tumor necrosis factor (TNF)-α when compared to non-obese patients[11]. Hypercytokinemia and a proinflammatory state are related to disease severity in influenza infections. Furthermore, the proinflammatory properties of lectin and anti-inflammatory properties of adiponectin may increase the risk of developing hypoxemic respiratory failure[11]. Biomarkers of endothelial injury (surfactant protein D and von Willebrand factor) were found to be elevated in obese patients with hypoxemic respiratory failure[12]. The likelihood of a combined influenza induced epithelial and endothelial injury is corroborated by pathology reports of pandemic H1N1 patients' lung specimens which showed extensive diffuse alveolar damage, variable degrees of pulmonary hemorrhage (with evidence of perivasculitis and microthrombi) and necrotizing bronchiolitis[13]. Persistence of viral shedding has recently been associated with poorer outcome and longer hospital stay both as a predisposing factor and as a complication of influenza infection[14].

Corticosteroid pharmacology

Corticosteroids are cyclic organic compounds physiologically secreted by zona fasciculata cells of the adrenal cortex. Under physiological circumstances, its synthesis and secretion are tightly regulated by the central nervous system, through the pituitary release of corticotropin (ACTH), which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids[15]. Cortisol, the main human corticosteroid, has a half-life of 60 to 90 min which can be significantly increased with large steroid loads. The volume of distribution (Vd) also increases with higher steroid doses and both parameters are agent-specific[16]. Corticosteroids are metabolized through complexly regulated enzymatic transformations in the liver [through A-ring reductases (5β-reductase and 5α-reductase)] and kidney [through 11-β hydroxysteroid dehydrogenase type 2 (11β-HSD2)][17,18] that diminish their physiologic activity and increase water solubility to enhance their

urinary excretion[15]. Most of the known effects of the corticosteroids are mediated by nuclear receptors.

Corticosteroids in critical illness

Interest in the role of corticosteroids in the pathophysiology of critical illness has existed since the early decades of the 20th century[19] Every acute physical stress or noxious stimuli results in a coordinated systemic response classically referred to as stress response or general adaption syndrome. Among the physiological responses to stress, hypercortisolemia is proportionate to the severity of illness[20]. Such response has traditionally been attributed to activation of the hypothalamic-pituitary-adrenal (HPA) axis[21] with increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone which stimulates the production of ACTH by the anterior pituitary gland, causing a sustained increase in cortisol secretion. This increased corticotropin-driven cortisol production originates multiple effects (metabolic, cardiovascular and immune) aimed at restoring homeostasis during stress[17].

Since the late 90's a paradoxical dissociation between cortisol and corticotropin (slightly elevated or even normal to low levels of corticotropin with permanently high cortisol levels) has been observed during critical illness[22,23]. As a consequence, explanations for hypercortisolemia other than increased cortisol production due to HPA axis activation have been pursued. Proinflammatory cytokines (TNF-α and IL-6), neuropeptides and cathecolamines correlate positively with cortisol production and are independent of HPA axis[24]. The possibility of an increased sensitivity to corticotropin was formulated but considered unlikely because cortisol plasmatic levels were not consistently elevated after exogenous corticotropin stimulation[17,25]. The reduction of cortisol metabolism during critical illness emerged as an alternative or additional mechanism with recent data showing suppression of activity of cortisol metabolizing enzymes in critical care patients. Boonen *et al*[18] found evidence of impaired 11β-HSD2 function and reduction of A-ring reductases activity that may be mediated by bile acids, known competitive inhibitors and transcriptional suppressors of cortisol-metabolizing enzymes.

The possibility that reduced cortisol breakdown is a main contributor to hypercortisolemia during critical illness may changes our conceptual understanding of the stress response. It could mean that low cortisol metabolism with hypercortisolemia would have induced a negative feedback on the HPA-axis resulting in lower corticotropin levels and adrenocortical atrophy. Such effect implies the downregulation or functional inactivation of corticotropin receptors on adrenocortical cells, which would explain the low cortisol response to corticotropin stimulation. Moreover, reduced cortisol inactivation may also potentiate cortisol activity within the vital tissues that express inactivating enzymes[18], what suggests that corticosteroids stress doses in critically ill patients are at least three times too high. These facts imply that the concept of critical illness associated adrenal failure may not be real and question the pathophysiological principles of corticosteroids stress doses in acute injuries.

Observational studies

According to observational data, approximately one third of 2009 H1N1 pandemia cases reported were treated with corticosteroids[26] both as a primary therapy or as a rescue therapy for patients with severe ARDS[27,28]. Despite this, a standard steroid and dose regimen are not well established and its efficacy and safety are not entirely clear.

In general, therapy with steroids in severe infections has shown to be beneficial in a pair of clinical situations: bacterial meningitis in immunocompetent hosts[29] and Pneumocystis jiroveci pneumonia in HIV patients[30]. In other conditions, like severe CAP and ARDS (due to pneumonia or not), no positive impact on mortality has been shown, still being an unresolved matter that deserves further investigation[4].

A common pulmonary presentation of patients affected by pandemic (H1N1) influenza A infection is rapidly progressive pneumonia with bilateral alveolar infiltrates on chest radiography and ARDS, that might be linked to an abnormal immune response[31]. The role of steroids as adjunctive therapy in influenza is very attractive theoretical approach to try to modulate hypercytokinemia associated with the most severe presentation[4]. However, a balance must occur between this phenomenon and the possibility of prolonged viral replication, resulting in more direct cytopathic effect on the infected lungs[32].

The main observational studies on corticosteroid treatment in influenza infected patients are listed in Table 1. All but one[33] evaluate steroids use in H1N1 infections. Xi *et al*[34] retrospectively evaluated data from 155 adults with confirmed H1N1 infection in China, one-third (33.5%) were treated with steroids. In a multivariate analysis, the use of steroids was associated with a trend towards increased hospital mortality (OR = 3.6; 95%CI: 0.98-13.6; P = 0.052). Nevertheless, patients using steroids were often more severely ill.

Martin-Loeches *et al*[31], in an international registry of the European Society of Intensive Care Medicine included 220 patients with suspected or confirmed H1N1, 77.7% on mechanical ventilation and 57.3% with steroid use at ICU admission. A higher incidence of hospital-acquired pneumonia was noted in patients receiving early steroid therapy. These patients also had a higher ICU mortality, but after adjusting for disease severity and other confounding variables, this effect was no longer present.

Kim *et al*[35] in a retrospective analysis of the data from 28 hospitals in South Korea identified 245 critically ill patients with H1N1 infection, 136 of them met criteria for ARDS. The crude 90-d mortality for the 107 (43.6%) patients who received steroids was higher than in the patients who did not received steroids, which was confirmed by propensity adjusted analysis. Patients on steroids also had longer duration of mechanical ventilation

Table 1 Main observational studies evaluating steroid use in influenza infection

Ref.	Study design	Population	Steroid regimen	Outcomes
Bourdreault *et al*[33]	Retrospective cohort	143 hematopoietic cell transplant patients with seasonal influenza	Prednisone < 1 mg/kg per day (low dose) or prednisone > 1 mg/kg per day (high dose)	Steroid use not associated with lower respiratory disease, hypoxemia, need for MV or death
Brun-Buisson *et al*[36]	Retrospective cohort	208 patients with ARDS due to H1N1 pneumonia, 83 receiving steroids	Hydrocortisone 270 mg/d (median) for 11 d (median)	Steroid was associated with mortality in crude analysis (33% *vs* 18%, HR = 2.4; 95%CI: 1.3-4.3; P = 0.004) and after propensity score-adjusted analysis (HR = 2.82; 95%CI: 1.5-5.4; P = 0.002) Early therapy (≤ 3 d of MV) associated with increased mortality Steroid associated with bacterial pneumonia and prolonged MV
Confalonieri *et al*[44]	Case report	One patient with ARDS due to H1N1 infection, not responding to antiviral therapy	Methylprednisolone 1 mg/kg per day	Clinical improvement
Cornejo *et al*[40]	Case report	Two patients with H1N1 that developed organizing pneumonia	Methylprednisolone 500 mg/d for 3 d	Clinical improvement
Diaz *et al*[37]	Multicenter, prospective cohort	372 patients with primary H1H1 pandemic pneumonia, 136 receiving steroids	Not reported	Corticosteroid therapy was not significantly associated with mortality (HR = 1.06; 95%CI: 0.626-1.801; P = 0.825) after a regression analysis adjusted for severity and potential confounding factors
Han *et al*[45]	Multicenter, retrospective cohort	83 patients with H1N1 pneumonia with hospitalar admission, 17 with early glucocorticoid treatment	Median dose of methylprednisolone equivalent of 50 mg/d (use for fever reduction) to 61 mg/d (use for pneumonia)	Early steroid treatment (< 72 h) was associated with development of critical disease compared with who received late (> 72 h) or no steroid treatment: 71% vs 39% (HR = 1.8; 95%CI: 1.2-2.8), after adjustment for confounding variables
Kim *et al*[35]	Multicenter, retrospective cohort and case-control study	245 patients with H1N1 infection, 107 with steroid treatment	Median dose of prednisolone equivalent of 75 mg/d	90-d mortality rate higher in steroids group (OR = 2.2; 95%CI: 1.03-4.71), after propensity score Higher mortality both in cohort (58% *vs* 27%; P < 0.001) and case-control study (54% *vs* 31%; P = 0.004) Steroid group more likely to have secondary bacterial pneumonia, invasive fungal infection and prolonged intensive care unit stay
Luyt *et al*[46]	Multicenter, prospective cohort study	37 survivors of ARDS due to H1N1 infection, 20 with steroid treatment	Not reported	No relationship between steroid use and muscle weakness at 1-yr post-ICU discharge
Martin-Loeches *et al*[31]	Multicenter, prospective cohort study	220 patients with H1N1 infection, 126 with steroid treatment at ICU admission	Minimal equivalent dose of 24 mg/d (methylprednisolone) or 30 mg/d (prednisone)	Early use of steroids was not significantly associated with mortality by Cox regression analysis adjusted for severity and confounding factors: HR = 1.3; 95%CI: 0.7-2.4; P = 0.4 Early steroid use associated with an increased rate of HAP (OR = 2.2; 95%CI: 1.0-4.8; P < 0.05) by Cox regression analysis Similar results observed when only patiens with ARDS were analyzed Patients who received early steroid therapy were sicker than who did not receive them according to SAPS 3 (55.9 ± 16.8 *vs* 49.0 ± 14.5; P = 0.001)
Quispe-Laime *et al*[47]	Case series	13 patients with suspected H1N1 pneumonia and ALI-ARDS diagnosis	Methylprednisolone 1 mg/kg per day (severe ARDS) or hydrocortisone 300 mg/d. Duration of 21.2 ± 6.1 d	Twelve patients improved lung function, were extubated and discharged alive from the ICU By day 7 of treatment patients experienced a significant improvement in lung injury and multiple organ dysfunction scores (P < 0.001)

ALI: Acute lung injury; ARDS: Acute distress respiratory syndrome; HAP: Hospital-acquired pneumonia; HR: Hazard ratio; ICU: Intensive care unit; MV: Mechanical ventilation; OR: Odds ratio; SAPS: Simplified acute physiology score.

and ICU stay, and more bacterial pneumonia or invasive fungal infections.

Brun-Buisson *et al*[36] evaluated 208 patients with severe H1N1 infections and ARDS in a multicenter study in France. Steroids were administered to 39.9% and, after use of several analytical techniques to adjust for differences in steroid-treated *vs* non-steroid-treated patients to compare clinical outcomes, the association between steroid therapy and death remained significant, a fact that was more pronounced in patients receiving early steroid therapy.

Diaz *et al*[37], in a multicenter cohort composed by 372-patients with primary viral pneumonia due to H1N1, with 136 patients (36.6%) received corticosteroids, did not found any association between steroid therapy and mortality.

A systematic review and meta-analysis[3] composed by nine cohort studies (n = 1405) and 14 case-control studies (n = 4700) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection (cohort studies RR = 1.85; 95%CI: 1.46-2.33; $P < 0.00001$; case-control studies OR = 4.22; 95%CI: 3.10-5.76; $P < 0.00001$). Subgroup and sensitive analysis were consistent with each other, suggesting that steroid treatment is associated with higher mortality. Nonetheless, corticosteroid tends to be used in the sickest case-patients.

None of these studies provided data on mechanical ventilation parameters. Lung protective ventilation is the standard of care for ARDS patients[38], and lack of data regarding this issue implies a dose of uncertainty about a major factor in determining which determines clinical outcomes[39]. The timing and dose of corticosteroid therapy were also not controlled in the study, and no specific drug regimen has been suggested in this context. Actually, several administration regimens, dosage and therapy duration are described in different studies, resulting in high heterogeneous strategies, adding complexity to systematic analysis. Observational - in particular retrospective - studies are potentially susceptible to bias, due to a lack of control of confounder variables, heterogeneity due to clinical diversity, and the fact that severe patients are more likely to receive corticosteroids than mild cases. Currently a conclusive trial on corticosteroids in severe H1N1 infection would be difficult or even not possible to perform. As a result it is reasonable to conclude from the available evidence that corticosteroids failed to demonstrate any clinical impact in severe influenza infection and, in addition, the data points to potential harm.

Case reports suggested beneficial use in specific contexts, such as organizing pneumonia[40], post-viral inflammatory pneumonitis[41] and H1N1 pneumonia in a pregnant woman[42].

Interventional studies

There is only one clinical trial addressing corticosteroid use in H1N1 influenza virus treatment. Wang *et al*[43] enrolled 38 patients with H1N1 pneumonia undergoing mechanical ventilation to be randomized to receive adjuvant treatment of corticosteroid either with sirolimus or without sirolimus for 14 d. In the sirolimus group, there was a shorter time spent on mechanical ventilation (7 d *vs* 15 d; P = 0.03), greater PaO_2-FiO_2 values on days 3 and 7 compared to the non-sirolimus group and improved SOFA score on day 3 and day 7. Sirolimus, as a mTOR inhibitor, could potentiate corticosteroid effect by limiting inflammatory cytokine production. The corticosteroid effect per se was not addressed in this small open-label randomized controlled trial as every patient enrolled received corticosteroids. As a consequence, no harmful or beneficial effect of steroids in H1N1 pneumonia can be inferred.

Critical analysis

Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Recent insights on a decrease in cortisol breakdown during critical illness questions the classic concept of adrenal failure with low cortisol production and constitutes a molecular argument against the use of corticosteroids as standard of care for patients with critical illness: The increased cortisol circulating levels and tissue activity make an additional synthetic corticosteroid dose either redundant or excessive and not devoid of deleterious effects.

Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Thus its current use in Severe Influenza pneumonia should be restricted to selected cases and in the setting of clinical trials.

REFERENCES

1 **Ramsey CD**, Kumar A. Influenza and endemic viral pneumonia. *Crit Care Clin* 2013; **29**: 1069-1086 [PMID: 24094391 DOI: 10.1016/j.ccc.2013.06.003]

2 **Dunning J**, Openshaw P. Severe Influenza: Clinical Features and Treatment Options. *Curr Resp Med Rev* 2012; **1**: 208-217 [DOI: 10.2174/157339812800493223]

3 **Zhang Y**, Sun W, Svendsen ER, Tang S, MacIntyre RC, Yang P, Zhang D, Wang Q. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. *Crit Care* 2015; **19**: 46 [PMID: 25888424 DOI: 10.1186/s13054-015-0764-5]

4 **Póvoa P**, Salluh JI. What is the role of steroids in pneumonia therapy? *Curr Opin Infect Dis* 2012; **25**: 199-204 [PMID: 22156902 DOI: 10.1097/QCO.0b013e32834f44c7]

5 **Hendrickson CM**, Matthay MA. Viral Pathogens and Acute Lung Injury: Investigations Inspired by the SARS Epidemic and the 2009 H1N1 Influenza Pandemic. *Semin Respir Crit Care Med* 2013; **34**:

475-486 [PMID: 23934716 DOI: 10.1055/s-0033-1351122]
6 **Hilleman MR**. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. *Vaccine* 2002; **20**: 3068-3087 [PMID: 12163258 DOI: 10.1016/S0264-410X(02)00254-2]
7 **Potter CW**. A history of influenza. *J Appl Microbiol* 2001; **91**: 572-579 [PMID: 11576290 DOI: 10.1046/j.1365-2672.2001.01492.x]
8 **Dawood FS**, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, Bandaranayake D, Breiman RF, Brooks WA, Buchy P, Feikin DR, Fowler KB, Gordon A, Hien NT, Horby P, Huang QS, Katz MA, Krishnan A, Lal R, Montgomery JM, Mølbak K, Pebody R, Presanis AM, Razuri H, Steens A, Tinoco YO, Wallinga J, Yu H, Vong S, Bresee J, Widdowson MA. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis* 2012; **12**: 687-695 [PMID: 22738893 DOI: 10.1016/S1473-3099(12)70121-4]
9 **Webb SA**, Pettilä V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, Cretikos M, Davies AR, Finfer S, Harrigan PW, Hart GK, Howe B, Iredell JR, McArthur C, Mitchell I, Morrison S, Nichol AD, Paterson DL, Peake S, Richards B, Stephens D, Turner A, Yung M. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009; **361**: 1925-1934 [PMID: 19815860 DOI: 10.1056/NEJMoa0908481]
10 **Jain S**, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, Sugerman DE, Druckenmiller JK, Ritger KA, Chugh R, Jasuja S, Deutscher M, Chen S, Walker JD, Duchin JS, Lett S, Soliva S, Wells EV, Swerdlow D, Uyeki TM, Fiore AE, Olsen SJ, Fry AM, Bridges CB, Finelli L. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009; **361**: 1935-1944 [PMID: 19815859 DOI: 10.1056/NEJMoa0906695]
11 **Konter J**, Baez E, Summer RS. Obesity: "priming" the lung for injury. *Pulm Pharmacol Ther* 2013; **26**: 427-429 [PMID: 22449512 DOI: 10.1016/j.pupt.2012.03.003]
12 **Stapleton RD**, Dixon AE, Parsons PE, Ware LB, Suratt BT. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest* 2010; **138**: 568-577 [PMID: 20435656 DOI: 10.1378/chest.10-0014]
13 **Mauad T**, Hajjar LA, Callegari GD, da Silva LF, Schout D, Galas FR, Alves VA, Malheiros DM, Auler JO, Ferreira AF, Borsato MR, Bezerra SM, Gutierrez PS, Caldini ET, Pasqualucci CA, Dolhnikoff M, Saldiva PH. Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* 2010; **181**: 72-79 [PMID: 19875682 DOI: 10.1164/rccm.200909-1420OC]
14 **Giannella M**, Alonso M, Garcia de Viedma D, Lopez Roa P, Catalán P, Padilla B, Muñoz P, Bouza E. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect* 2011; **17**: 1160-1165 [PMID: 20946412 DOI: 10.1111/j.1469-0691.2010.03399]
15 **Katzung, BG**, Masters, SB, Trevor AJ. Adrenocorticosteroids & Adrenocortical Antagonists. Basic & clinical pharmacology. New York: McGraw-Hil, 2012: 697-713
16 **Mckay LI**, Cidlowski JA. Pharmacokinetics of Corticosteroids. In: Kufe DW, Pollock RE WR, editors. Holland-Frei Cancer Medicine 6th edition. 6th ed. Hamilton (ON): BC Decker; 2003
17 **Marik PE**. Critical illness-related corticosteroid insufficiency. *Chest* 2009; **135**: 181-193 [PMID: 19136406 DOI: 10.1378/chest.08-1149]
18 **Boonen E**, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ, Vander Perre S, Langouche L, Vanhorebeek I, Walker BR, Van den Berghe G. Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013; **368**: 1477-1488 [PMID: 23506003 DOI: 10.1056/NEJMoa1214969]
19 **Selye H**. A syndrome produced by diverse nocuous agents. 1936. *J Neuropsychiatry Clin Neurosci* 1998; **10**: 230-231 [PMID: 9722327]
20 **Widmer IE**, Puder JJ, König C, Pargger H, Zerkowski HR, Girard J, Müller B. Cortisol response in relation to the severity of stress and illness. *J Clin Endocrinol Metab* 2005; **90**: 4579-4586 [PMID: 15886236 DOI: 10.1210/jc.2005-0354]
21 **Carrasco GA**, Van de Kar LD. Neuroendocrine pharmacology of stress. *Eur J Pharmacol* 2003; **463**: 235-272 [PMID: 12600714 DOI: 10.1016/j.bbr.2011.01.038]
22 **Bornstein SR**, Engeland WC, Ehrhart-Bornstein M, Herman JP. Dissociation of ACTH and glucocorticoids. *Trends Endocrinol Metab* 2008; **19**: 175-180 [PMID: 18394919 DOI: 10.1016/j.tem.2008.01.009]
23 **Vermes I**, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab* 1995; **80**: 1238-1242 [PMID: 7714094 DOI: 10.1210/jcem.80.4.7714094]
24 **Bornstein SR**, Chrousos GP. Clinical review 104: Adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: neural and immune inputs. *J Clin Endocrinol Metab* 1999; **84**: 1729-1736 [PMID: 10323408 DOI: 10.1210/jcem.84.5.5631]
25 **Neary N**, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 217-223 [PMID: 20375886 DOI: 10.1097/MED.0b013e328338f608]
26 **Falagas ME**, Vouloumanou EK, Baskouta E, Rafailidis PI, Polyzos K, Rello J. Treatment options for 2009 H1N1 influenza: evaluation of the published evidence. *Int J Antimicrob Agents* 2010; **35**: 421-430 [PMID: 20185273 DOI: 10.1016/j.ijantimicag.2010.01.006]
27 **Kumar A**, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K, Lamontagne F, Turgeon AF, Lapinsky S, Ahern SP, Smith O, Siddiqui F, Jouvet P, Khwaja K, McIntyre L, Menon K, Hutchison J, Hornstein D, Joffe A, Lauzier F, Singh J, Karachi T, Wiebe K, Olafson K, Ramsey C, Sharma S, Dodek P, Meade M, Hall R, Fowler RA. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009; **302**: 1872-1879 [PMID: 19822627 DOI: 10.1001/jama.2009.1496]
28 **Domínguez-Cherit G**, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, Poblano-Morales M, Baltazar-Torres JA, Bautista E, Martinez A, Martinez MA, Rivero E, Valdez R, Ruiz-Palacios G, Hernández M, Stewart TE, Fowler RA. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009; **302**: 1880-1887 [PMID: 19822626 DOI: 10.1001/jama.2009.1536]
29 **Brouwer MC**, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2015; **9**: CD004405 [PMID: 26362566]
30 **Ewald H**, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection. *Cochrane Database Syst Rev* 2015; **4**: CD006150 [PMID: 25835432 DOI: 10.1002/14651858.CD006150.pub2]
31 **Martin-Loeches I**, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. *Intensive Care Med* 2011; **37**: 272-283 [PMID: 21107529 DOI: 10.1007/s00134-010-2078-z]
32 **Ison MG**. Adjuvant immunosuppression in the management of severe influenza: friend or foe? *Crit Care Med* 2014; **42**: 457-459 [PMID: 24434448 DOI: 10.1097/CCM.0b013e3182a63779]
33 **Boudreault AA**, Xie H, Leisenring W, Englund J, Corey L, Boeckh M. Impact of corticosteroid treatment and antiviral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. *Biol Blood Marrow Transplant* 2011; **17**: 979-986 [PMID: 20870025 DOI: 10.1016/j.bbmt.2010.09.014]
34 **Xi X**, Xu Y, Jiang L, Li A, Duan J, Du B. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect Dis* 2010; **10**: 256 [PMID: 20799934 DOI: 10.1186/1471-2334-10-256]
35 **Kim SH**, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB,

Lim CM, Koh Y. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am J Respir Crit Care Med* 2011; **183**: 1207-1214 [PMID: 21471084 DOI: 10.1164/rccm.201101-0110OC]

36 **Brun-Buisson C**, Richard JC, Mercat A, Thiébaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2011; **183**: 1200-1206 [PMID: 21471082 DOI: 10.1164/rccm.201101-0135OC]

37 **Diaz E**, Martin-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, Estella A, Gil Rueda B, Guerrero JE, Valverdú-Vidal M, Vergara JC, López-Pueyo MJ, Magret M, Recio T, López D, Rello J, Rodriguez A. Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect* 2012; **64**: 311-318 [PMID: 22240033 DOI: 10.1016/j.jinf.2011.12.010]

38 **Slutsky AS**, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2014; **370**: 980 [PMID: 24597883 DOI: 10.1056/NEJMc1400293]

39 **Matthay MA**, Liu KD. Con: corticosteroids are not indicated for treatment of acute lung injury from H1N1 viral pneumonia. *Am J Respir Crit Care Med* 2011; **183**: 1127-1128 [PMID: 21531953 DOI: 10.1164/rccm.201103-0395ED]

40 **Cornejo R**, Llanos O, Fernández C, Carlos Díaz J, Cardemil G, Salguero J, Luengo C, Tobar E, Romero C, Gálvez LR. Organizing pneumonia in patients with severe respiratory failure due to novel A (H1N1) influenza. *BMJ Case Rep* 2010; **2010**: [PMID: 22767562 DOI: 10.1136/bcr.02.2010.2708]

41 **Roberts C**, Nirmalan M, O'Shea S. Steroid-sensitive post-viral inflammatory pneumonitis (PVIP). *Am J Respir Crit Care Med* 2010; **182**: 1089-1090 [PMID: 20947911]

42 **Djibré M**, Berkane N, Salengro A, Ferrand E, Denis M, Chalumeau-Lemoine L, Parrot A, Mayaud C, Fartoukh M. Non-invasive management of acute respiratory distress syndrome related to Influenza A (H1N1) virus pneumonia in a pregnant woman. *Intensive Care Med* 2010; **36**: 373-374 [PMID: 19820915 DOI: 10.1007/s00134-009-1684-0]

43 **Wang CH**, Chung FT, Lin SM, Huang SY, Chou CL, Lee KY, Lin TY, Kuo HP. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. *Crit Care Med* 2014; **42**: 313-321 [PMID: 24105455 DOI: 10.1097/CCM.0b013e3182a2727d]

44 **Confalonieri M**, D'Agaro P, Campello C. Corticosteroids do not cause harmful increase of viral load in severe H1N1 virus infection. *Intensive Care Med* 2010; **36**: 1780-1781 [PMID: 20631982 DOI: 10.1007/s00134-010-1964-8]

45 **Han K**, Ma H, An X, Su Y, Chen J, Lian Z, Zhao J, Zhu BP, Fontaine RE, Feng Z, Zeng G. Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. *Clin Infect Dis* 2011; **53**: 326-333 [PMID: 21810744 DOI: 10.1093/cid/cir398]

46 **Luyt CE**, Combes A, Becquemin MH, Beigelman-Aubry C, Hatem S, Brun AL, Zraik N, Carrat F, Grenier PA, Richard JC, Mercat A, Brochard L, Brun-Buisson C, Chastre J. Long-term outcomes of pandemic 2009 influenza A(H1N1)-associated severe ARDS. *Chest* 2012; **142**: 583-592 [PMID: 22948576 DOI: 10.1378/chest.12-0917]

47 **Quispe-Laime AM**, Bracco JD, Barberio PA, Campagne CG, Rolfo VE, Umberger R, Meduri GU. H1N1 influenza A virus-associated acute lung injury: response to combination oseltamivir and prolonged corticosteroid treatment. *Intensive Care Med* 2010; **36**: 33-41 [PMID: 19924393 DOI: 10.1007/s00134-009-1727-6]

P- Reviewer: Chastre J, Loke YK **S- Editor**: Qiu S **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.96

World J Crit Care Med 2016 February 4; 5(1): 96-102
ISSN 2220-3141 (online)

MINIREVIEWS

Mild to moderate intra-abdominal hypertension: Does it matter?

Liivi Maddison, Joel Starkopf, Annika Reintam Blaser

Liivi Maddison, Joel Starkopf, Annika Reintam Blaser, Department of Anaesthesiology and Intensive Care, University of Tartu, 51014 Tartu, Estonia

Liivi Maddison, Joel Starkopf, Department of Anaesthesiology and Intensive Care, Tartu University Hospital, 51014 Tartu, Estonia

Annika Reintam Blaser, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Lucerne Cantonal Hospital, 6000 Lucerne, Switzerland

Author contributions: All authors contributed to the concept of the manuscript; Maddison L drafted the manuscript; Starkopf J and Reintam Blaser A made critical revisions related to important intellectual content of the manuscript; all authors approved the final version of the manuscript.

Supported by the Ministry of Education and Research of Estonia (IUT34-24).

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Correspondence to: Annika Reintam Blaser, MD, PhD, Department of Anaesthesiology and Intensive Care, University of Tartu, Puusepa 8, 51014 Tartu, Estonia. annika.reintam.blaser@ut.ee
Telephone: +37-25-142281
Fax: +37-25-142281

Received: August 29, 2015
Peer-review started: September 6, 2015
First decision: October 27, 2015
Revised: November 18, 2015
Accepted: December 3, 2015

Article in press: December 4, 2015
Published online: February 4, 2016

Abstract

This review summarizes the epidemiology, pathophysiological consequences and impact on outcome of mild to moderate (Grade Ⅰ to Ⅱ) intra-abdominal hypertension (IAH), points out possible pitfalls in available treatment recommendations and focuses on tasks for future research in the field. IAH occurs in about 40% of ICU patients. Whereas the prevalence of abdominal compartment syndrome seems to be decreasing, the prevalence of IAH does not. More than half of IAH patients present with IAH grade Ⅰ and approximately a quarter with IAH grade Ⅱ. However, most of the studies have addressed IAH as a yes-or-no variable, with little or no attention to different severity grades. Even mild IAH can have a negative impact on tissue perfusion and microcirculation and be associated with an increased length of stay and duration of mechanical ventilation. However, the impact of IAH and its different grades on mortality is controversial. The influence of intra-abdominal pressure (IAP) on outcome most likely depends on patient and disease characteristics and the concomitant macro- and microcirculation. Therefore, management might differ significantly. Today, clear triggers for interventions in different patient groups with mild to moderate IAH are not defined. Further studies are needed to clarify the clinical importance of mild to moderate IAH identifying clear triggers for interventions to lower the IAP.

Key words: Intra-abdominal pressure; Intra-abdominal hypertension; Pathophysiology; Epidemiology; Severity; Treatment

Core tip: This review summarizes the epidemiology,

pathophysiological consequences and impact on outcome of mild to moderate intra-abdominal hypertension (IAH) and focuses on tasks for future research in the field. More than half of IAH patients present with IAH Grade Ⅰ and approximately a quarter with IAH grade Ⅱ. Even mild IAH can have a negative impact on tissue perfusion and be associated with impaired clinical outcomes. However, the impact of IAH and its different grades on mortality is controversial. Clear triggers for interventions in different patient groups with mild to moderate IAH are not defined.

Maddison L, Starkopf J, Reintam Blaser A. Mild to moderate intra-abdominal hypertension: Does it matter? *World J Crit Care Med* 2016; 5(1): 96-102 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/96.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.96

INTRODUCTION

Intra-abdominal hypertension (IAH) occurs in 20%-40% of intensive care patients and has a significant impact on outcome[1-3]. IAH is defined as intra-abdominal pressure (IAP) of 12 mmHg or above, whereas normal IAP is in the range of 0 to 11 mmHg[4]. The cut-off point of 12 mmHg for IAH was initially selected empirically[5,6], but is now supported by several epidemiological studies[1,5,7-11]. Based on severity, IAH is graded into four levels. Grade Ⅰ refers to IAP from 12 to 15 mmHg, grade Ⅱ 16 to 20 mmHg, grade Ⅲ 21 to 25 mmHg, and grade Ⅳ above 25 mmHg, respectively. The most severe form is abdominal compartment syndrome (ACS), defined as sustained IAP ⩾ 20 mmHg (with or without an abdominal perfusion pressure (APP) of ⩽ 60 mmHg) in association with the new onset or worsening of existing organ failure[4]. This is a life-threatening syndrome[6], which, however, seldom occurs in clinical practice[2,3,12]. In these cases, the deterioration of cardiac, respiratory and renal performance is usually clearly evident and determines the immediate need for life-saving treatment. The management of IAP below 20 mmHg is much more controversial[2,13] as there is no clear trigger for when and to what extent to initiate the treatment of IAH.

This review was undertaken to differentiate IAH grade Ⅰ and Ⅱ from higher grades of IAH regarding the pathophysiological changes and impact on outcome, and to discuss possible differences in management based on the severity of IAH.

EPIDEMIOLOGY AND OUTCOME OF IAH AND ITS DIFFERENT SEVERITY GRADES

There are several recent studies describing the epidemiology of IAH and investigating its impact on outcome[10,14,15].

Kim *et al*[15] included 100 consecutive patients in a prospective observational single-center study on a mixed intensive care unit (ICU) population. The overall incidence of IAH was 42%, while IAH grade Ⅰ occurred in 23%, grade Ⅱ in 14%, grade Ⅲ in 3% and grade Ⅳ in 2% of IAH patients (Figure 1). Patients with IAH had higher APACHE Ⅱ and Ⅲ scores, body mass index (BMI) and more sepsis on admission. However, there was no difference in the length of ICU stay or hospital mortality in patients with IAH (irrespective of the grade) *vs* patients without IAH.

Iyer *et al*[14] included 403 consecutive patients to investigate the incidence of IAH/ACS and to develop a screening tool for the early identification of patients requiring IAP monitoring. The incidence of IAH was 39% and of ACS, 2%. IAH grade Ⅰ occurred in 27%, grade Ⅱ in 9%, grade Ⅲ in 2% and grade Ⅳ in 1% (Figure 1). Regarding outcomes, patients with IAH had significantly longer duration of mechanical ventilation and, length of stay in the ICU and in the hospital. No difference in mortality was detected between the patients with or without IAH; however, patients with IAH of higher grades (Ⅱ-Ⅳ) had higher ICU mortality (13% *vs* 3.4%, P = 0.003)[14].

A recent systematic review and individual patient data meta-analysis reported distribution of IAP values among 1669 critically ill patients upon admission to ICU[10]. The mean IAP was 9.9 mmHg; whereas 27.7% of patients had IAH and 2.7% ACS on admission. Although the exact data on different IAH grades were not given, the IAP distribution histogram supports the studies discussed above (Kim *et al*[15] and Iyer *et al*[14]). Concerning the outcomes, the ICU length of stay, the ICU and the hospital mortality were significantly increased in the IAH group.

It is somewhat surprising that outcomes differ significantly when the data from Reintam *et al*[2], Malbrain *et al*[10] and Blaser *et al*[16] and our own earlier studies are compared to the results of Kim *et al*[15] or Iyer *et al*[14]. One possible explanation might be that the meta-analysis is based on studies published predominantly between 1995 and 2008. Almost two decades of research has very likely improved our understanding and management of IAH/ACS[12,17], and this may explain the decrease in morbidity and mortality. Moreover, most of the earlier studies (including the ones in the meta-analysis by Malbrain *et al*[10]) enrolled only selected patients (*e.g.,* patients with pancreatitis, trauma, mechanically ventilated or presenting other risk factors for IAH). Therefore, the patient groups are not entirely comparable. Furthermore, assigning patients with IAP of 12 to 15 mmHg to the same group as ACS most likely confuses the results in all the above-mentioned studies. As the incidence of ACS is decreasing and the outcome simultaneously improving[12,16,17], its impact to the overall group of IAH patients is diminishing.

Considering these factors, the clinical importance of IAH is much dependent on the severity (grade) of IAH, but these associations have been poorly studied.

EFFECT OF MODERATE IAH IN DIFFERENT PATIENT GROUPS

Next to the severity of IAH, the nature and course of

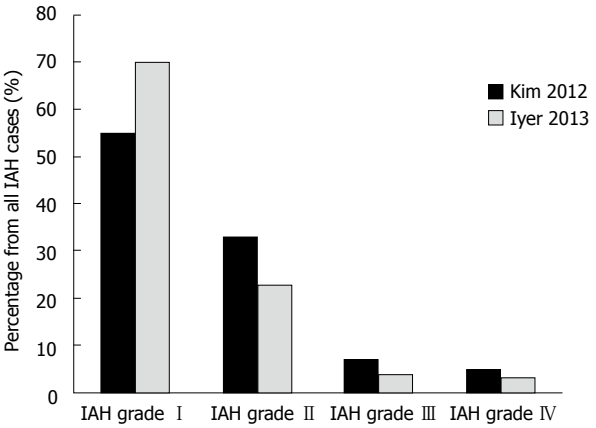


Figure 1 Prevalence of different grades of intra-abdominal hypertension in clinical studies performed in consecutive intensive care unit patients. IAH: Intra-abdominal hypertension.

underlying pathology needs to be taken into account. Higher grades of IAH may be less deleterious if the disease is cured (*e.g.,* after abdominal surgery), whereas moderate IAH may have additional aggravating effect on the patients with uncontrolled primary pathology (*e.g.,* shock with continuing need for fluid resuscitation).

In patients with pancreatitis or intra-abdominal infections already the mild IAH deserves close attention as a sign of increased oedema formation. In these patients development of IAH/ACS is primarily caused by the inflammatory process inside the abdominal cavity and may be further exacerbated by aggressive fluid therapy[18,19].

Intraperitoneal bleeding should be recognized promptly and therefore in trauma patients any increase of IAP, even at the low grades, deserves particular attention.

During pregnancy IAP increases physiologically, but the effect of the IAH has been poorly studied in this specific patient group. Recently, it has been postulated that the inability to adapt to the increasing intra-abdominal volume, reflected as sustained increase of IAP above 12 mmHg may be involved in the etiopathogenesis of pre-eclampsia[20].

Children, not specifically addressed in this review, require different approach. Organ dysfunction in paediatric patients has been reported to occur at the IAP 10 to 15 mmHg, and the ACS may develop already at the IAP of 16 mmHg[19,21,22].

In contrary, after elective abdominal hernia repair transient increase of IAP up to 18 mmHg may be well tolerated[23].

EFFECT OF IAH ON SPLANCHNIC BLOOD FLOW, MICROCIRCULATION AND METABOLISM

An experimental study on pigs demonstrated that a pneumoperitoneum-caused IAP of 12 mmHg combined with positive end-expiratory pressure of 10 cmH_2O decreases blood flow in the hepatic and mesenteric arteries and portal vein, impairs the hepatic and intestinal mucosal microcirculation, attenuates the hepatic pO_2 and intestinal mucosal pH, this all indicating to seriously disturbed splanchnic blood flow[24]. Olofsson *et al*[25] showed in pigs that increased IAP correlates with decreased gastrointestinal microcirculation measured by laser Doppler flowmetry, whereas microcirculation in mucosal layer was significantly less affected than in serosa. Cheng *et al*[26] demonstrated that, in rabbits, microvascular blood flow is decreased by 40% during IAP 15 mmHg for 2 h, and by 81% when the IAP was 25 mmHg for 6 h, while markers of intestinal injury increased significantly, in proportion to IAP and exposure time. After prolonged exposure to increased IAP, erosions and necrosis of the jejunal villi, mitochondrial swelling and discontinuity of intracellular tight junctions were microscopically observed[26]. These findings are clearly contrasted by recent study on mechanically ventilated sheep without sepsis, which demonstrated decreased renal blood flow and diuresis but preserved blood flow in superior mesenteric artery at IAP of 20 mmHg and no changes in microcirculatory variables. However, sheep with IAH received large amounts of fluids compared to sham and still developed relevant lactic acidosis. As shown by Dubin *et al*[27] in septic sheep, resuscitation was able to normalize mean arterial blood pressure, cardiac output, superior mesenteric artery blood flow and sublingual and serosal intestinal microvascular flow indexes, but not to restore percentage of perfused ileal villi, which could explain elevation of lactate. These different findings may be explained by several aspects: the level, mechanism and duration of the elevated IAP, presence or absence of sepsis, resuscitation strategy as well as the methodology of assessment of microcirculation all may play an important role.

In humans, the effect of IAP on gut perfusion is not well studied, but significant reduction of splanchnic blood flow has been demonstrated after the IAP increases from 7 to 14 mmHg[28]. As the splanchnic area is difficult to access in clinical setting, the monitoring of sublingual microcirculation might be considered for indirect evaluation of splanchnic microcirculation[29], although it is not clear whether this is well applicable in case of IAH where splanchnic bed is directly affected through the extravascular pressure.

So far, the associations between IAP and sublingual microcirculation have been evaluated in two studies[30,31]. No significant alterations in sublingual microcirculation were demonstrated at IAH grades Ⅰ and Ⅱ, neither in elective surgery nor in critically ill patients. In elective laparoscopic surgery the microcirculatory perfusion indices were relatively low at the baseline and did not improve during the study period[30].

In heterogeneous group of critically ill patients, the moderate but prolonged increase of IAP (median 14.5 mmHg) for up to 24 h exhibits a negligible influence on the sublingual microcirculation[31]. Ten out of 15 of these patients were in circulatory shock, and it is somewhat

surprising that no significant alterations in the sublingual microcirculation were detected[31]. Observed positive correlations between microvascular flow index, MAP and APP, however, may support the importance of APP in clinical management of this situation[31].

Relevant alterations in microcirculation should result in the increased anaerobic metabolism and this hypothesis has led to studies investigating influence of IAP on tissue metabolism[30-35]. The findings suggest that the deterioration of tissue metabolism in the abdominal area may occur well before IAH-related organ dysfunction become evident[30-35].

In animal experiments, tissue microdialysis has been increasingly used to evaluate metabolic status in different vascular beds and in different conditions. By this method, Meier *et al*[35] were able to demonstrate the accumulation of metabolites of anaerobic glycolysis in the rectus abdominis muscle (RAM) of rats subjected to IAH. The RAM is surrounded by a tight sheet of fascia, which makes the muscle-fascia compartment relatively non-compliant. The pressure in the intra-abdominal cavity directly influences the muscle tissue and its perfusion. This muscle is easily accessible and makes the RAM microdialysis minimally invasive; therefore the RAM serves as a good model of intra-abdominal organ[32].

We performed RAM microdialysis in elective laparoscopic surgery (median IAP 12.5 mmHg) and in critically ill patients (median IAP 14.5 mmHg)[32,33]. In both groups the RAM tissue metabolism was seriously disturbed when compared to the baseline before surgery or to the references from other studies[36]. Elevated lactate, lactate-to-pyruvate ratio, and glutamate levels indicated anaerobic metabolism during moderately raised IAP. The correlation analysis revealed a negative correlation of APP, pyruvate and glycerol, supporting the relevance of APP as a resuscitation end-point when setting the targets for MAP and vasopressor therapy[33].

Considering these factors, some experimental studies indicate that increased IAP results in impaired splanchnic microcirculation and metabolism. Limited data suggests that similar changes may occur also in humans although direct assessment of the splanchnic area would be desirable to confirm these findings. Setting the APP or any other macrocirculatory variable as a resuscitation endpoint in patients with IAH remains controversial.

PITFALLS IN MANAGEMENT RECOMMENDATIONS

The Abdominal Compartment Society management algorithm suggests initiating medical treatment at IAP of 12 mmHg or higher and tailoring treatment to keep IAP below 15 mmHg[4]. Several mechanisms may lead to IAH: increased baseline IAP (*e.g.,* obesity), increased intra-abdominal volume (*e.g.,* ascites or oedema), and decreased abdominal wall compliance (*e.g.,* tight abdominal closure after hernia repair)[6,37]. It is clear that these different mechanisms require different therapeutic approaches. However, the severity of IAH (grade of IAH) should also guide the selection of the best management option in these different situations. It is not clear whether in some cases lower grade IAH could merely be observed, whereas in others it should be aggressively treated with, *e.g.*, sedatives and muscle relaxants. Current IAH/ACS guidelines suggest stepwise IAH treatment: From medical and minimally invasive techniques to aggressive surgical decompression[4]. A stepwise approach in general is definitely wise. However, different grades of IAH and different patient groups are not considered. As most of the options for IAP reduction are not without risks (*e.g.*, drainages) and side effects (*e.g.,* sedation, muscle relaxation), it is important not to apply these strategies without clear indication. It is possible that not treating moderate IAH could impair the outcome in one patient, whereas aggressive treatment (*e.g.,* muscle relaxation) could be harmful in the other.

Future studies should form the basis for more detailed recommendations, whereas currently these decisions should be made during careful bedside evaluation, and require deep knowledge and experience.

FUTURE STUDIES

Based on existing evidence, it is likely that lower grades of IAH are relevant in terms of both pathophysiology and clinical consequences. However, the relationships are most likely complex, and the influence of IAP depends on patient characteristics (*e.g.,* obese *vs* non-obese; ventilated *vs* spontaneously breathing, critically ill *vs* ward patients), concomitant macro- (dependent on MAP) and microcirculation and disease characteristics (*e.g.,* pancreatitis *vs* pneumonia). As IAH has been often assessed as a yes-or-no variable, these issues are not yet clarified. Accordingly, there are several issues that should be studied more closely in future studies.

IMPORTANCE OF IAH GRADES IN DIFFERENT PATIENT GROUPS

Normal IAP in critically ill patients is thought to be between 5-7 mmHg[4], but there is not enough data to identify normal values in spontaneously breathing patients. Moreover, "normal" or expected IAP levels in patients with abdominal pathology, *e.g.,* after elective major abdominal surgery, are unknown.

Signs of organ dysfunction, duration of mechanical ventilation, ICU length of stay and ICU mortality seem to increase in patients with elevated IAH, whereas in most cases, IAP ranges between 12-16 mmHg. Dalfino *et al*[11] showed that elevated IAP and low APP are associated with the development of acute renal failure (ARF) in critically ill patients after shock and identified a cut-off IAP of 12 mmHg for increasing the risk of ARF. A cut-off value of 12 mmHg for IAH is also supported by several other studies[1,5,7-10]. However, it is not clear whether the current IAH grading system can be

translated to gradually increasing mortality or worsening organ function.

Spontaneously breathing patients

None of the studies has specifically addressed IAH in spontaneously breathing patients. Therefore, it is not known, whether 12 mmHg is also applicable to this subset of patients. Moreover, the likelihood of more unstable measurement conditions in spontaneously breathing patients may lead to wide variations, and muscle tonus may play an important role.

Patients with chronically elevated IAP

Obesity and pregnancy are chronic states of low-graded IAH to which the patient has adapted[6,38]. Both conditions develop relatively slowly, and the human organism adapts to these (patho) physiological changes, but there is still an issue if such patients need to be admitted to an ICU. IAP levels that trigger specific treatment should be most likely higher, but how much so, remains unclear.

Patients after abdominal surgery

Post-operative complications after abdominal surgery are frequent and are associated with increased morbidity and mortality[39-42]. Intra-abdominal hypertension and its pathophysiological consequences may contribute to the development of postoperative complications[43,44], but no specific data are available thus far. Therefore, a cut-off that triggers interventions directed to lower IAP and/or to increase APP in such patients is warranted.

CONCOMITANT CHANGES IN MACRO- AND MICROCIRCULATION DURING IAH

Ideally, the management of hemodynamics should ensure normal microcirculation and organ function in different vascular beds. We currently lack reliable tool(s) to assess microcirculation at the bedside, and the clinical signs (diuresis, mottled skin) and macrohemodynamic variables (MAP, cardiac output) rather than microcirculatory changes direct the patient management in clinical practise. However, in the case of increased abdominal pressure, "normal" MAP and cardiac output might be insufficient to assure the adequate perfusion of abdominal and retroperitoneal organs. Moreover, due to heterogeneous aspects of microcirculatory perfusion, effect of classical hemodynamic interventions on microcirculation will most likely be limited[45]. Whether microcirculatory measurements may be supportive for hemodynamic management during IAH remains to be elucidated.

The identification of patient groups where even mild IAH leads to microcirculatory dysfunction with anaerobic metabolism would be desirable for the more precise adjustment of management suggestions.

MANAGEMENT OF IAH

Higher grades of IAH are infrequent; most patients with IAH qualify as grade Ⅰ of IAH. Therefore, further studies should focus on mild to moderate IAH to clarify, which patients should be treated aggressively and which patients can simply be observed. Studies are needed to allow revision of the algorithm based on evidence. More specific recommendations including treatment triggers in spontaneously breathing patients, obese patients, patients after abdominal surgery and other specific groups, are warranted.

CONCLUSION

IAH occurs in about 40% of the ICU population. More than half of these patients present with IAH grade Ⅰ and approximately a quarter with IAH grade Ⅱ. Patients with IAH have a significantly longer duration of mechanical ventilation and, longer length of stay in the ICU and in the hospital. The impact of IAH and its different grades on mortality is controversial.

Preliminary data suggest that grades Ⅰ and Ⅱ IAH has a negative impact on tissue perfusion and microcirculation. Further studies are needed to clarify whether and in which particular sub-group of patients the occurrence of mild to moderate IAH should trigger immediate interventions directed at lowering the IAP.

REFERENCES

1 **Malbrain ML**, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, Del Turco M, Wilmer A, Brienza N, Malcangi V, Cohen J, Japiassu A, De Keulenaer BL, Daelemans R, Jacquet L, Laterre PF, Frank G, de Souza P, Cesana B, Gattinoni L. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med* 2005; **33**: 315-322 [PMID: 15699833 DOI: 10.1097/01.CCM.0000153408.09806.1B]

2 **Reintam A**, Parm P, Kitus R, Kern H, Starkopf J. Primary and secondary intra-abdominal hypertension--different impact on ICU outcome. *Intensive Care Med* 2008; **34**: 1624-1631 [PMID: 18446319 DOI: 10.1007/s00134-008-1134-4]

3 **Reintam Blaser A**, Parm P, Kitus R, Starkopf J. Risk factors for intra-abdominal hypertension in mechanically ventilated patients. *Acta Anaesthesiol Scand* 2011; **55**: 607-614 [PMID: 21418151 DOI: 10.1111/j.1399-6576.2011.02415.x]

4 **Kirkpatrick AW**, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190-1206 [PMID: 23673399 DOI: 10.1007/s00134-013-2906-z]

5 **Malbrain ML**, Chiumello D, Pelosi P, Wilmer A, Brienza N, Malcangi V, Bihari D, Innes R, Cohen J, Singer P, Japiassu A, Kurtop E, De Keulenaer BL, Daelemans R, Del Turco M, Cosimini P, Ranieri M, Jacquet L, Laterre PF, Gattinoni L. Prevalence of intra-abdominal hypertension in critically ill patients: a multicentre epidemiological study. *Intensive Care Med* 2004; **30**: 822-829 [PMID: 14758472 DOI: 10.1007/s00134-004-2169-9]

6 **Malbrain ML**, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppäniemi A, Olvera C, Ivatury R, D'Amours S, Wendon J, Hillman K, Johansson K, Kolkman K, Wilmer A. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment

Syndrome. I. Definitions. *Intensive Care Med* 2006; **32**: 1722-1732 [PMID: 16967294 DOI: 10.1007/s00134-006-0349-5]
7 **Regueira T**, Bruhn A, Hasbun P, Aguirre M, Romero C, Llanos O, Castro R, Bugedo G, Hernandez G. Intra-abdominal hypertension: incidence and association with organ dysfunction during early septic shock. *J Crit Care* 2008; **23**: 461-467 [PMID: 19056007 DOI: 10.1016/j.jcrc.2007.12.013]
8 **Vidal MG**, Ruiz Weisser J, Gonzalez F, Toro MA, Loudet C, Balasini C, Canales H, Reina R, Estenssoro E. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med* 2008; **36**: 1823-1831 [PMID: 18520642 DOI: 10.1097/CCM.0b013e31817c7a4d]
9 **Santa-Teresa P**, Muñoz J, Montero I, Zurita M, Tomey M, Alvarez-Sala L, García P. Incidence and prognosis of intra-abdominal hypertension in critically ill medical patients: a prospective epidemiological study. *Ann Intensive Care* 2012; **2** Suppl 1: S3 [PMID: 22873419 DOI: 10.1186/2110-5820-2-S1-S3]
10 **Malbrain ML**, Chiumello D, Cesana BM, Reintam Blaser A, Starkopf J, Sugrue M, Pelosi P, Severgnini P, Hernandez G, Brienza N, Kirkpatrick AW, Schachtrupp A, Kempchen J, Estenssoro E, Vidal MG, De Laet I, De Keulenaer BL. A systematic review and individual patient data meta-analysis on intra-abdominal hypertension in critically ill patients: the wake-up project. World initiative on Abdominal Hypertension Epidemiology, a Unifying Project (WAKE-Up!). *Minerva Anestesiol* 2014; **80**: 293-306 [PMID: 24603146]
11 **Dalfino L**, Tullo L, Donadio I, Malcangi V, Brienza N. Intra-abdominal hypertension and acute renal failure in critically ill patients. *Intensive Care Med* 2008; **34**: 707-713 [PMID: 18157662 DOI: 10.1007/s00134-007-0969-4]
12 **Carr JA**. Abdominal compartment syndrome: a decade of progress. *J Am Coll Surg* 2013; **216**: 135-146 [PMID: 23062520 DOI: 10.1016/j.jamcollsurg.2012.09.004]
13 **Reintam A**, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal failure score in critically ill patients: a prospective observational study. *Crit Care* 2008; **12**: R90 [PMID: 18625051 DOI: 10.1186/cc6958]
14 **Iyer D**, Rastogi P, Åneman A, D'Amours S. Early screening to identify patients at risk of developing intra-abdominal hypertension and abdominal compartment syndrome. *Acta Anaesthesiol Scand* 2014; **58**: 1267-1275 [PMID: 25307712 DOI: 10.1111/aas.12409]
15 **Kim IB**, Prowle J, Baldwin I, Bellomo R. Incidence, risk factors and outcome associations of intra-abdominal hypertension in critically ill patients. *Anaesth Intensive Care* 2012; **40**: 79-89 [PMID: 22313065]
16 **Blaser AR**, Sarapuu S, Tamme K, Starkopf J. Expanded measurements of intra-abdominal pressure do not increase the detection rate of intra-abdominal hypertension: a single-center observational study. *Crit Care Med* 2014; **42**: 378-386 [PMID: 24145841 DOI: 10.1097/CCM.0b013e3182a6459b]
17 **Balogh ZJ**, Lumsdaine W, Moore EE, Moore FA. Postinjury abdominal compartment syndrome: from recognition to prevention. *Lancet* 2014; **384**: 1466-1475 [PMID: 25390328 DOI: 10.1016/S0140-6736(14)61689-5]
18 **De Waele JJ**, Leppäniemi AK. Intra-abdominal hypertension in acute pancreatitis. *World J Surg* 2009; **33**: 1128-1133 [PMID: 19350318 DOI: 10.1007/s00268-009-9994-5]
19 **De Waele JJ**, Ejike JC, Leppäniemi A, De Keulenaer BL, De Laet I, Kirkpatrick AW, Roberts DJ, Kimball E, Ivatury R, Malbrain ML. Intra-abdominal hypertension and abdominal compartment syndrome in pancreatitis, paediatrics, and trauma. *Anaesthesiol Intensive Ther* 2015; **47**: 219-227 [PMID: 25973660 DOI: 10.5603/AIT.a2015.0027]
20 **Sawchuck DJ**, Wittmann BK. Pre-eclampsia renamed and reframed: Intra-abdominal hypertension in pregnancy. *Med Hypotheses* 2014; **83**: 619-632 [PMID: 25189485 DOI: 10.1016/j.mehy.2014.08.001]
21 **Beck R**, Halberthal M, Zonis Z, Shoshani G, Hayari L, Bar-Joseph G. Abdominal compartment syndrome in children. *Pediatr Crit Care Med* 2001; **2**: 51-56 [PMID: 12797889]
22 **Ertel W**, Oberholzer A, Platz A, Stocker R, Trentz O. Incidence and clinical pattern of the abdominal compartment syndrome after "damage-control" laparotomy in 311 patients with severe abdominal and/or pelvic trauma. *Crit Care Med* 2000; **28**: 1747-1753 [PMID: 10890613]
23 **Petro CC**, Raigani S, Fayezizadeh M, Rowbottom JR, Klick JC, Prabhu AS, Novitsky YW, Rosen MJ. Permissible Intraabdominal Hypertension following Complex Abdominal Wall Reconstruction. *Plast Reconstr Surg* 2015; **136**: 868-881 [PMID: 26090761 DOI: 10.1097/PRS.0000000000001621]
24 **Kotzampassi K**, Paramythiotis D, Eleftheriadis E. Deterioration of visceral perfusion caused by intra-abdominal hypertension in pigs ventilated with positive end-expiratory pressure. *Surg Today* 2000; **30**: 987-992 [PMID: 11110392]
25 **Olofsson PH**, Berg S, Ahn HC, Brudin LH, Vikström T, Johansson KJ. Gastrointestinal microcirculation and cardiopulmonary function during experimentally increased intra-abdominal pressure. *Crit Care Med* 2009; **37**: 230-239 [PMID: 19050608 DOI: 10.1097/CCM.0b013e318192ff51]
26 **Cheng J**, Wei Z, Liu X, Li X, Yuan Z, Zheng J, Chen X, Xiao G, Li X. The role of intestinal mucosa injury induced by intra-abdominal hypertension in the development of abdominal compartment syndrome and multiple organ dysfunction syndrome. *Crit Care* 2013; **17**: R283 [PMID: 24321230 DOI: 10.1186/cc13146]
27 **Dubin A**, Edul VS, Pozo MO, Murias G, Canullán CM, Martins EF, Ferrara G, Canales HS, Laporte M, Estenssoro E, Ince C. Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. *Crit Care Med* 2008; **36**: 535-542 [PMID: 18216603 DOI: 10.1097/01.CCM.0000300083.74726.43]
28 **Windberger UB**, Auer R, Keplinger F, Längle F, Heinze G, Schindl M, Losert UM. The role of intra-abdominal pressure on splanchnic and pulmonary hemodynamic and metabolic changes during carbon dioxide pneumoperitoneum. *Gastrointest Endosc* 1999; **49**: 84-91 [PMID: 9869728]
29 **Verdant CL**, De Backer D, Bruhn A, Clausi CM, Su F, Wang Z, Rodriguez H, Pries AR, Vincent JL. Evaluation of sublingual and gut mucosal microcirculation in sepsis: a quantitative analysis. *Crit Care Med* 2009; **37**: 2875-2881 [PMID: 19770750 DOI: 10.1097/CCM.0b013e3181b029c1]
30 **Maddison L**, Riigor KM, Karjagin J, Starkopf J. Sublingual microcirculatory changes during transient intra-abdominal hypertension--a prospective observational study in laparoscopic surgery patients. *Clin Hemorheol Microcirc* 2014; **57**: 367-374 [PMID: 24081312 DOI: 10.3233/CH-131791]
31 **Maddison L**, Karjagin J, Buldakov M, Mäll M, Kruusat R, Lillemäe K, Kirsimägi U, Starkopf J. Sublingual microcirculation in patients with intra-abdominal hypertension: a pilot study in 15 critically ill patients. *J Crit Care* 2014; **29**: 183.e1-183.e6 [PMID: 24125769 DOI: 10.1016/j.jcrc.2013.08.018]
32 **Maddison L,** Karjagin J, Tenhunen J, Starkopf J. Moderate intra-abdominal hypertension is associated with an increased lactate-pyruvate ratio in the rectus abdominis muscle tissue: a pilot study during laparoscopic surgery. *Ann Intensive Care* 2012; **2** Suppl 1: S14 [PMID: 22873415 DOI: 10.1186/2110-5820-2-S1-S14]
33 **Maddison L,** Karjagin J, Tenhunen J, Kirsimägi U, Starkopf J. Moderate intra-abdominal hypertension leads to anaerobic metabolism in the rectus abdominis muscle tissue of critically ill patients: a prospective observational study. *Biomed Res Int* 2014; **2014**: 857492 [PMID: 24745026 DOI:10.1155/2014/857492]
34 **Benninger E**, Laschke MW, Cardell M, Holstein JH, Lustenberger T, Keel M, Trentz O, Menger MD, Meier C. Early detection of subclinical organ dysfunction by microdialysis of the rectus abdominis muscle in a porcine model of critical intra-abdominal hypertension. *Shock* 2012; **38**: 420-428 [PMID: 22683730 DOI: 10.1097/SHK.0b013e31825ef7e7]
35 **Meier C**, Contaldo C, Schramm R, Holstein JH, Hamacher J, Amon M, Wanner GA, Trentz O, Menger MD. Microdialysis of the rectus abdominis muscle for early detection of impending abdominal compartment syndrome. *Intensive Care Med* 2007; **33**: 1434-1443 [PMID: 17576536 DOI: 10.1007/s00134-007-0725-9]

36 **Hörer TM**, Skoog P, Norgren L, Magnuson A, Berggren L, Jansson K, Larzon T. Intra-peritoneal microdialysis and intra-abdominal pressure after endovascular repair of ruptured aortic aneurysms. *Eur J Vasc Endovasc Surg* 2013; **45**: 596-606 [PMID: 23540804 DOI: 10.1016/j.ejvs.2013.03.002]

37 **Blaser AR**, Björck M, De Keulenaer B, Regli A. Abdominal compliance: A bench-to-bedside review. *J Trauma Acute Care Surg* 2015; **78**: 1044-1053 [PMID: 25909429 DOI: 10.1097/TA.0000000000000616]

38 **Chun R**, Baghirzada L, Tiruta C, Kirkpatrick AW. Measurement of intra-abdominal pressure in term pregnancy: a pilot study. *Int J Obstet Anesth* 2012; **21**: 135-139 [PMID: 22326198 DOI: 10.1016/j.ijoa.2011.10.010]

39 **Straatman J**, Cuesta MA, de Lange-de Klerk ES, van der Peet DL. Hospital cost-analysis of complications after major abdominal surgery. *Dig Surg* 2015; **32**: 150-156 [PMID: 25791798 DOI: 10.1159/000371861]

40 **McCoy CC**, Englum BR, Keenan JE, Vaslef SN, Shapiro ML, Scarborough JE. Impact of specific postoperative complications on the outcomes of emergency general surgery patients. *J Trauma Acute Care Surg* 2015; **78**: 912-918[PMID: 25909409 DOI: 10.1097/TA.0000000000000611]

41 **Yang CK**, Teng A, Lee DY, Rose K. Pulmonary complications after major abdominal surgery: National Surgical Quality Improvement Program analysis. *J Surg Res* 2015; **198**: 441-449 [PMID: 25930169 DOI: 10.1016/j.jss.2015.03.028]

42 **Albisinni S**, Oderda M, Fossion L, Varca V, Rassweiler J, Cathelineau X, Chlosta P, De la Taille A, Gaboardi F, Piechaud T, Rimington P, Salomon L, Sanchez-Salas R, Stolzenburg JU, Teber D, Van Velthoven R. The morbidity of laparoscopic radical cystectomy: analysis of postoperative complications in a multicenter cohort by the European Association of Urology (EAU)-Section of Uro-Technology. *World J Urol* 2015; Epub ahead of print [PMID: 26135307 DOI: 10.1007/s00345-015-1633-1]

43 **Jhanji S**, Lee C, Watson D, Hinds C, Pearse RM. Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications. *Intensive Care Med* 2009; **35**: 671-677 [PMID: 18936911 DOI: 10.1007/s00134-008-1325-z]

44 **Jhanji S**, Vivian-Smith A, Lucena-Amaro S, Watson D, Hinds CJ, Pearse RM. Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. *Crit Care* 2010; **14**: R151 [PMID: 20698956 DOI: 10.1186/cc9220]

45 **De Backer D**, Donadello K, Taccone FS, Ospina-Tascon G, Salgado D, Vincent JL. Microcirculatory alterations: potential mechanisms and implications for therapy. *Ann Intensive Care* 2011; **1**: 27 [PMID: 21906380 DOI: 10.1186/2110-5820-1-27]

P- Reviewer: Qiu HB **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Lu YJ

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i1.103

World J Crit Care Med 2016 February 4; 5(1): 103-110
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest

Kushaharan Sathianathan, Ravindranath Tiruvoipati, Sanjiv Vij

Kushaharan Sathianathan, Critical Care Unit, Latrobe Regional Hospital, Traralgon, VIC 3844, Australia

Ravindranath Tiruvoipati, Department of Intensive Care Medicine, Frankston Hospital, Frankston, VIC 3199, Australia

Ravindranath Tiruvoipati, School of Public Health, Faculty of Medicine, Nursing and Health Sciences, Monash University, Mildura, VIC 3800, Australia

Sanjiv Vij, Intensive Care Unit, Dandenong Hospital, Dandenong, VIC 3175, Australia

Sanjiv Vij, Intensive Care Unit, Royal Melbourne Hospital, Parkville, VIC 3050, Australia

Author contributions: Sathianathan K and Tiruvoipati R were responsible for conception and design of this study; Sathianathan K was responsible for acquisition of data; Tiruvoipati R and Sathianathan K were responsible for data analysis; Sathianathan K, Tiruvoipati R and Vij S were responsible for interpretation of the data; all authors were responsible for drafting the manuscript or revising it critically for important intellectual content, and have given final approval of the manuscript for final submission.

Institutional review board statement: This study was deemed by the Human Research Ethics Committee (HREC) of Monash Health to be a quality assurance exercise, and thus did not require submission to the Monash Health HREC (Research Project Application No. 13290Q).

Informed consent statement: The Human Research Ethics Committee or Monash Health waived the requirement for consent from individual patients as the study was seen as a retrospective audit of data routinely collected for patient care and not experimental research.

Conflict-of-interest statement: The authors have no financial or personal relationships with other people or organisations that could inappropriately influence this study.

Data sharing statement: Data presented in this manuscript is anonymised and the risk of identifying any individual patient is very low. No additional data available for this study beyond that stated in the manuscript.

Correspondence to: Ravindranath Tiruvoipati, Associate Professor, Department of Intensive Care Medicine, Frankston Hospital, 2 Hastings Road, Frankston, VIC 3199, Australia. travindranath@hotmail.com
Telephone: +61-431-279347

Received: August 22, 2015
Peer-review started: August 23, 2015
First decision: October 8, 2015
Revised: December 8, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016
Published online: February 4, 2016

Abstract

AIM: To identify patient, cardiac arrest and management factors associated with hospital survival in comatose survivors of cardiac arrest.

METHODS: A retrospective, single centre study of comatose patients admitted to our intensive care unit (ICU) following cardiac arrest during the twenty year period between 1993 and 2012. This study was deemed by the Human Research Ethics Committee (HREC) of Monash Health to be a quality assurance exercise, and thus did not require submission to the Monash Health HREC (Research Project Application, No. 13290Q). The study population included all patients admitted to our

ICU between 1993 and 2012, with a discharge diagnosis including "cardiac arrest". Patients were excluded if they did not have a cardiac arrest prior to ICU admission (*i.e.*, if their primary arrest was during their admission to ICU), or were not comatose on arrival to ICU. Our primary outcome measure was survival to hospital discharge. Secondary outcome measures were ICU and hospital length of stay (LOS), and factors associated with survival to hospital discharge.

RESULTS: Five hundred and eighty-two comatose patients were admitted to our ICU following cardiac arrest, with 35% surviving to hospital discharge. The median ICU and hospital LOS was 3 and 5 d respectively. There was no survival difference between in-hospital and out-of-hospital cardiac arrests. Males made up 62% of our cardiac arrest population, were more likely to have a shockable rhythm (56% *vs* 37%, $P < 0.001$), and were more likely to survive to hospital discharge (40% *vs* 28%, $P = 0.006$). On univariate analysis, therapeutic hypothermia, regardless of method used (*e.g.*, rapid infusion of ice cold fluids, topical ice, "Arctic Sun", passive rewarming, "Bair Hugger") and location initiated (*e.g.*, pre-hospital, emergency department, intensive care) was associated with increased survival. There was however no difference in survival associated with target temperature, time at target temperature, location of initial cooling, method of initiating cooling, method of maintaining cooling or method of rewarming. Patients that survived were more likely to have a shockable rhythm ($P < 0.001$), shorter time to return of spontaneous circulation ($P < 0.001$), receive therapeutic hypothermia ($P = 0.03$), be of male gender ($P = 0.006$) and have a lower APACHE Ⅱ score ($P < 0.001$). After multivariate analysis, only a shockable initial rhythm (OR = 6.4, 95%CI: 3.95-10.4; $P < 0.01$) and a shorter time to return of spontaneous circulation (OR = 0.95, 95%CI: 0.93-0.97; $P < 0.01$) was found to be independently associated with survival to hospital discharge.

CONCLUSION: In comatose survivors of cardiac arrest, shockable rhythm and shorter time to return of spontaneous circulation were independently associated with increased survival to hospital discharge.

Key words: Cardiac arrest; Hypothermia; Hyperthermia; Arrhythmia; Resuscitation

Core tip: Admission to intensive care after cardiac arrest is increasing. With the improvements in intensive care practice the survival to hospital discharge is being reported in up to 50% of patients. This study, one of the largest series published so far, was aimed to identify any association between patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies with survival to hospital discharge. The results of this study confirm that of all the factors studied, shockable rhythm and shorter time to return of spontaneous circulation were independently associated with increased survival to hospital discharge.

Sathianathan K, Tiruvoipati R, Vij S. Prognostic factors associated with hospital survival in comatose survivors of cardiac arrest. *World J Crit Care Med* 2016; 5(1): 103-110 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/103.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.103

INTRODUCTION

Cardiovascular disease accounts for 37% of deaths in Australia, the majority being due to cardiac arrest, with an incidence of 148 per 100000[1]. Unconscious survivors of primary cardiac arrest are at high risk of death and neurological injury[2,3]. Hospital survival rates of up to 50% have been described[4,5].

Recent focus on the hospital management of patients following cardiac arrest has been on therapeutic hypothermia, or targeted temperature management (TTM). Therapeutic hypothermia has been described in human survivors of cardiac arrest as early as the 1950's[6]. Animal studies were undertaken in the early 1990's[7], followed by feasibility studies on humans[8-10]. Two landmark trials published in 2002[3,11] demonstrated therapeutic hypothermia improved survival and neurological recovery in comatose survivors of out-of-hospital VF arrest. In 2011, two systematic reviews[12,13] showed no benefit of therapeutic hypothermia over normothermia, and in 2013, the "TTM" trial[4] showed no benefit (or harm) between a targeted temperature of 33 ℃ and a targeted temperature of 36 ℃. All TTM trial subjects were also maintained below 37.5 ℃ for the first 72 h following cardiac arrest, even after rewarming, however this was not the standard practice for our hospital. A higher temperature prior to cooling has already been associated with greater survival[5], however we chose to use the time frame described in the TTM trial (see "MAX-TEMP" below).

A range of different cooling regimes have been described, including "moderate" hypothermia (33 ℃ for 12 h), 33 ℃ for 24 h, and "mild" hypothermia (32-34 ℃ for 24 h)[3,9-11]. Multiple methods have been described for inducing cooling, maintaining cooling and rewarming[3,9,11,14-16]. The optimal approach to inducing and maintaining a targeted temperature remains uncertain[5].

Dandenong Hospital has over twenty years' experience in the management of comatose survivors of cardiac arrest, providing a large pool of patient data to allow for identification of any association between patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies with survival to hospital discharge.

MATERIALS AND METHODS

We undertook a single centre retrospective study at the intensive care unit (ICU) of Dandenong Hospital (DDH).

DDH is a 530 bed metropolitan teaching hospital affiliated with Monash University. The emergency department sees 58000 patients per annum, and the hospital has 48000 acute admissions per annum. The ICU is a 14 bed level 2 general ICU with 1100 annual admissions and 8.6% mortality.

This study was deemed by the Human Research Ethics Committee (HREC) of Monash Health to be a quality assurance exercise, and thus did not require submission to the Monash Health HREC (Research Project Application No. 13290Q). The study population included all patients admitted to our ICU between 1993 and 2012, with a discharge diagnosis including "cardiac arrest". Patients were excluded if they did not have a cardiac arrest prior to ICU admission (*i.e.*, if their primary arrest was during their admission to ICU), or were not comatose on arrival to ICU.

Patients were identified using the ICU database. Acute physiology and chronic health evaluation (APACHE) data (APACHE Ⅱ and Ⅲ) were obtained from the ICU database. APACHE data were only available for patients admitted from July 1999. Further patient information was extracted from the hospital medical records. The baseline characteristics collected were age, gender, admission diagnosis, location of cardiac arrest (*i.e.*, in-patient *vs* out-of-hospital), initial rhythm, time to return of spontaneous circulation, hospital admission source and ICU admission source. Information collected describing management were documentation of therapeutic hypothermia plan, decision to institute cooling, location of initial cooling, method of initiating cooling, method of maintaining cooling, targeted temperature, time taken to achieve target temperature, time at target temperature (both planned and actual), method of rewarming and the maximum temperature reached in the first 72 h following cardiac arrest (MAX-TEMP). The "MAX-TEMP" variable was created to investigate any association between hospital survival and hyperthermia within the first 72 h following cardiac arrest, using the same 37.5 ℃ cut-off used in the TTM trial.

Primary outcome measure was survival to hospital discharge. Secondary outcome measures were ICU length of stay (LOS), hospital LOS and the patient, cardiac arrest and management factors associated with survival to hospital discharge.

IBM SPSS Statistics (release 22.0.0.0, IBM Corp., Armonk, NY, United States) was used to analyse our data. Continuous data were presented as mean [standard deviation (SD)] and compared using student *t*-test. Parametric data were presented as median [interquartile range (IQR)] and compared using Mann-Whitney test. Nominal data were analysed using Chi-squared test. Binary logistic regression analysis was used to identify independent associations with hospital survival. *P*-values less than 0.05 were considered significant.

RESULTS

The ICU database search identified 728 patients admitted to our ICU between 1993 and 2012 with a discharge diagnosis including "cardiac arrest" (Figure 1). 109 patients were excluded for not having a cardiac arrest prior to ICU admission and a further 37 patients for not being comatose on arrival to ICU, leaving a total of 582 patients. There were no APACHE data available for patients admitted prior to July 1999 (n = 155, 26.6%). These patients were excluded from further analysis involving APACHE data, but were still included for all other analyses.

Overall survival to hospital discharge was 35%, with median ICU and hospital length of stays (LOS) of 3 and 5 d respectively (Table 1). Table 2 separates our patients into survivors and non-survivors, identifying statistically significant differences in initial rhythm, time to return of spontaneous circulation, APACHE Ⅱ score, gender and the institution of therapeutic hypothermia. There was no survival difference between in-hospital and out-of-hospital cardiac arrests. Males made up 62% of our cardiac arrest population (Table 1), were more likely to have a shockable rhythm (56% *vs* 37%, $P < 0.001$) (data not presented), and were more likely to survive to hospital discharge (40% *vs* 28%, $P = 0.006$) (Table 2).

On univariate analysis, therapeutic hypothermia, regardless of method used (*e.g.*, rapid infusion of ice cold fluids, topical ice, "Arctic Sun", passive rewarming, "Bair Hugger") and location initiated (*e.g.*, pre-hospital, emergency department, intensive care) was associated with increased survival (Table 2). There was however no additional difference in survival associated with target temperature, time at target temperature, location of initial cooling, method of initiating cooling, method of maintaining cooling or method of rewarming (data not presented). There was greater survival associated with MAX-TEMP higher than 37.5 ℃ (41% *vs* 27%, $P < 0.001$) (data not presented).

Comparing patients that presented before and after 2002 (Table 3), the second decade had statistically significant increases in non-shockable rhythms, time to return of spontaneous circulation, out-of-hospital cardiac arrests, prescription of therapeutic hypothermia and APACHE Ⅱ scores. Patients in this group took longer to cool and were cooled for a longer period of time. There was a statistically significant decrease in mean age and a non-significant decrease in survival in the second period. There was a statistically significant increase in ICU LOS, but a non-significant decrease in the hospital LOS in the second period. There was also a statistically significant increase in the implementation of therapeutic hypothermia over the course of the study period (Figure 2).

Binary logistic regression analysis identified only a shockable initial rhythm (OR = 6.4, 95%CI: 3.95-10.4; $P < 0.01$) and a shorter time to return of spontaneous circulation (OR = 0.95, 95%CI: 0.93-0.97; $P < 0.01$) to be independently associated with survival to hospital discharge (Table 4).

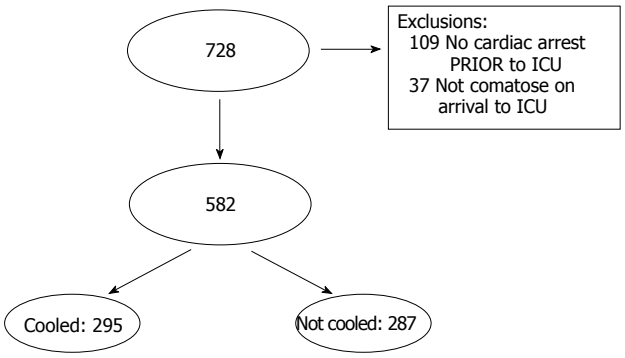


Figure 1 Flow diagram of all patients.

Table 1 Demographics, cardiac arrest details and management of included patients

Variable	All patients *n* = 582
Patient	
Age (yr) - mean (SD) (*n* = 581)	63 (16)
Gender (male) - *n* (%) (*n* = 579)	361 (62)
Cardiac arrest	
Time to ROSC (min) - mean (SD) (*n* = 571)	23 (15)
Presenting rhythm (shockable) - *n* (%) (*n* = 582)	286 (49)
Location of arrest (OHCA) - *n* (%) (*n* = 582)	408 (70)
Apache 2 score - mean (SD) (*n* = 427)	28 (8.4)
Apache 3 score - mean (SD) (*n* = 427)	78 (37.8)
Management	
Cooled - *n* (%) (*n* = 582)	295 (51)
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)
Time to temp[1] (h) - mean (SD) (*n* = 288)	2.1 (3.0)
Time at temp[2] (h) - median (IQR) (*n* = 290)	24 (12-24)
Outcome	
Survived to hospital discharge - *n* (%) (*n* = 582)	206 (35)
ICU LOS (d) - median (IQR) (*n* = 582)	3 (1-5)
Hospital LOS (d) - median (IQR) (*n* = 581)	5 (2-14)

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

DISCUSSION

This twenty year retrospective study identified multiple patient factors, cardiac arrest characteristics and post-cardiac arrest management strategies that were associated with increased survival to hospital discharge in comatose survivors of cardiac arrest.

A shockable rhythm, and a shorter time to return of spontaneous circulation were both associated with increased survival (Table 2). The Victorian Ambulance Cardiac Arrest Register (VACAR)[17] showed there was a higher chance of survival in patients found with a shockable rhythm. In addition, patients found with a shockable rhythm were more likely to have an earlier return of spontaneous circulation and survive to hospital admission[18,19]. These variables were the only two factors identified in our study to be independently associated with survival to hospital discharge following multivariate analysis.

Table 2 Comparison of survivors and non-survivors

Variable	Died *n* = 376 (65%)	Survived *n* = 206 (35%)	*P* value
Patient			
Age (yr) - mean (SD) (*n* = 581)	64 (17)	63 (15)	0.28
Gender (male) - *n* (%) (*n* = 579)	218 (58)	143 (70)	0.006
Cardiac arrest			
Time to ROSC (min) - mean (SD) (*n* = 571)	26 (14.5)	18 (14.3)	< 0.001
Presenting rhythm (shockable) - *n* (%) (*n* = 582)	134 (36)	152 (72)	< 0.001
Location of arrest (OHCA) - *n* (%) (*n* = 582)	269 (72)	139 (67)	0.3
Apache 2 score - mean (SD) (*n* = 427)	30 (7.6)	24 (8.5)	< 0.001
Apache 3 score - mean (SD) (*n* = 427)	79 (37.9)	77 (37.8)	0.5
Management			
Cooled - *n* (%) (*n* = 582)	178 (47)	117 (57)	0.03
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)	33 (33-33)	0.44
Time to temp[1] (h) - mean (SD) (*n* = 288)	1.8 (2.9)	2.5 (3.1)	0.04
Time at temp[2] (h) - median (IQR) (*n* = 290)	24 (12-24)	24 (12-24)	0.84
Outcome			
ICU LOS (d) - median (IQR) (*n* = 582)	2 (1- 4)	4 (2-7)	< 0.001
Hospital LOS (d) - median (IQR) (*n* = 581)	3 (1-6)	15 (8-27)	< 0.001

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

The association between male gender and increased survival to hospital discharge (Table 2) was expected, as men are more likely to have an out-of-hospital cardiac arrest[20], are more likely to survive to hospital admission[21] and are more likely to survive to hospital discharge[19,20]. Men are also more likely to have coronary artery disease and to have a shockable rhythm, both resulting in better survival following cardiac arrest[20,22].

There was a statistically significant association between lower APACHE Ⅱ scores and increased survival, but not with APACHE Ⅲ. The original APACHE score included 34 physiological variables[23], which was reduced to 12 with APACHE Ⅱ, along with inclusions of age, chronic health and surgical procedures[24]. APACHE Ⅲ was later introduced with 17 physiological variables, increased chronic health categories, less weighting for chronic health and a section for ICU admission source[25]. APACHE Ⅳ has subsequently been released, however due to its complexity, APACHE Ⅱ and APACHE Ⅲ are still used in mainstream practice[26]. Of the above, only APACHE Ⅱ measured at 24 h has been shown to correlate with mortality in patients following cardiac arrest[27]. The alteration in the chronic health section and the different weighting given to it, may explain the lack of correlation between the APACHE Ⅱ and APACHE Ⅲ scoring systems in our study population.

In addition to the TTM trial[4], there have been many other trials from Scandinavia looking at the management of patients following cardiac arrest[28-31]. Initially, because patients were selected for cooling based on "hypothermia after cardiac arrest" (HACA) inclusion criteria[3], only

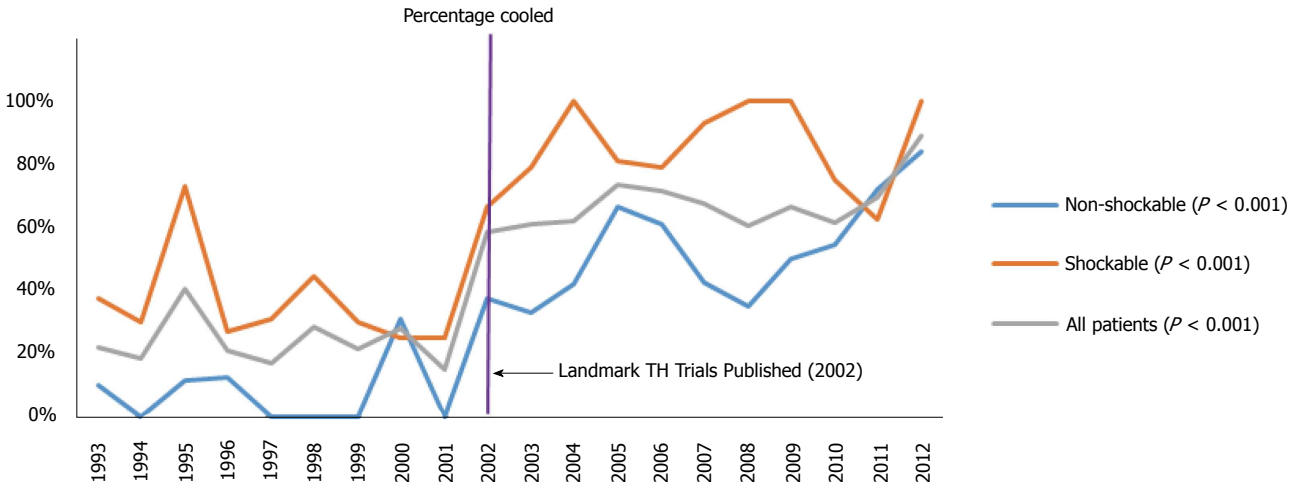


Figure 2 Percentage of patients cooled over time.

Table 3 Comparison of patients before and after 2002

Variable	1993-2002 *n* = 257 (44%)	2003-2012 *n* = 325 (56%)	*P* value
Patient			
Age (yr) - mean (SD) (*n* = 581)	65 (15)	62 (16)	0.04
Gender (male) - *n* (%) (*n* = 579)	161 (63)	200 (62)	0.73
Cardiac arrest			
Time to ROSC (min) - mean (SD) (*n* = 571)	21 (14)	24 (15)	0.02
Presenting rhythm (shockable) - n (%) (*n* = 582)	151 (59)	135 (42)	< 0.001
Location of arrest (OHCA) - *n* (%) (*n* = 582)	165 (64)	243 (75)	0.006
Apache 2 score - mean (SD) (*n* = 427)	26 (8.3)	29 (8.3)	0.007
Apache 3 score - mean (SD) (*n* = 427)	75 (35.9)	79 (38.2)	0.23
Management			
Cooled - *n* (%) (*n* = 582)	73 (28)	222 (68)	< 0.001
Target temperature (℃) - median (IQR) (*n* = 290)	33 (33-33)	33 (33-33)	0.62
Time to temp[1] (h) - mean (SD) (*n* = 288)	1.3 (2.2)	2.4 (3.2)	0.04
Time at temp[2] (h) - median (IQR) (*n* = 290)	12 (12-24)	24 (12-24)	0.56
Outcome			
Survived to hospital discharge - *n* (%) (*n* = 582)	99 (38)	107 (33)	0.16
ICU LOS (d) - median (IQR) (*n* = 582)	2 (1-4)	3 (1-6)	0.008
Hospital LOS (d) - median (IQR) (*n* = 581)	6 (2-15)	4 (2-13)	0.18

[1]Time to temp = time taken to reach target temperature (hours); [2]Time at temp = time at target temperature (hours). LOS: Length of stay (days); ROSC: Return of spontaneous circulation (minutes); OHCA: Out of hospital cardiac arrest; IQR: Interquartile range.

28% received therapeutic hypothermia[28]. However, as with our study, the percentage of patients receiving therapeutic hypothermia increased over time (28% in 2007[28], 44% in 2012[29], and 61.7% in 2013[30]) (Figure 2).

Our study identified no association between survival and the location of cooling, method of initiating cooling, method of maintaining cooling or method of rewarming. This may have been confounded by our lack of information on the efficacy of the different cooling strategies implemented. The RICH trial previously documented that pre-hospital cooling added no survival benefit over in-hospital cooling[16]. Other studies have documented the ability of various devices to achieve and maintain a specified temperature[14,15], however it is unclear whether improved efficacy directly translates to improved survival. Despite advances in cooling technology, patients that presented in the second half of the study took longer to achieve target temperature compared to those in the first half (Table 3).

The time of publication of the two practice-changing therapeutic hypothermia trials[3,11] evenly divided our study period into two ten year intervals. Looking at these two periods, there was no statistically significant difference in survival to hospital discharge (Table 3). In fact, there was a non-significant trend to worsening survival (38% *vs* 33%, *P* = 0.16), despite a higher percentage of patients being cooled and a younger group of patients. There are a number of explanations for this. To begin with, the latter group had sicker patients, as indicated by a higher mean APACHE Ⅱ score, which has previously been associated with worse outcomes following cardiac arrest[27]. There was also an increase in non-shockable rhythms and a higher mean time to return of spontaneous circulation, both of which have been associated with worse hospital survival[18,19]. This non-significant decrease in survival also came with the cost of a statistically significant increase in ICU length of stay.

The finding that survival was associated with a higher maximum temperature in the first 72 h (MAX-TEMP) following cardiac arrest (37.4 ℃ *vs* 37.9 ℃, *P* = 0.003) was unexpected. Fever is present in 42%-52% of patients post cardiac arrest[32,33], and has previously been associated with a poor outcome[34,35]. A multicentered observational cohort study from Canada,

Table 4 Final model of logistic regression analysis

Variables	B	SE	Wald	df	Sig.	OR	95%CI	
							Lower	Upper
ROSC	-0.048	0.009	27.588	1	0.000	0.953	0.937	0.971
Shockable rhythm	1.860	0.248	56.222	1	0.000	6.422	3.949	10.441
APACHE II	-0.001	0.003	0.156	1	0.693	0.999	0.993	1.005
Therapeutic hypothermia	0.088	0.248	0.126	1	0.722	1.092	0.672	1.775
Gender	-0.456	0.247	3.388	1	0.066	0.634	0.390	1.030
Constant	-0.210	0.410	0.263	1	0.608	0.810		

ROSC: Time to return of spontaneous circulation.

however, identified that a higher temperature prior to cooling was associated with greater survival (35.6 ℃ *vs* 36.1 ℃, $P < 0.0001$)[5]. We are uncertain whether a difference of only 0.5 ℃ in mean temperatures prior to cooling, or maximum temperatures following cardiac arrest, are significant enough to justify having an effect on outcome. In our study, a lower MAX-TEMP was associated with a shorter median ICU LOS (1 d *vs* 4 d, $P = 0.016$) implying that many patients in our study may have died while still in the cooling process. In addition, for those regaining consciousness, fever may have been tolerated by the treating team, but we were unable to support this statement with the data available.

Another unexpected finding was the association between a longer time to target temperature and greater survival. We found a difference of 42 min (1.8 h *vs* 2.5 h, $P = 0.04$) between the mean time to target temperature of the survivors and non-survivors. This was also noted in the Canadian study mentioned previously, where the difference in means between survivors and non-survivors was 54 min (3.4 h *vs* 4.3 h, $P = 0.001$)[5]. We are unsure whether a difference of less than an hour to achieve a target temperature is sufficient to influence survival. Our finding may have been confounded by our study period overlapping with the start of the RINSE trial[36], resulting in the introduction of non-selective pre-hospital cooling and increased number of patients presenting to ICU who were already hypothermic.

Our study had a number of limitations. We undertook a study that was retrospectively analysed and only involved a single site, raising concerns regarding causality and generalizability. Our primary endpoint was hospital survival, and did not include data on functional outcome, nor follow-up post discharge. Our data lacked many peri-arrest details, preventing us from using Utstein reporting. We lacked APACHE data for patients admitted prior to July 1999. Even though our twenty years of study data enabled comparison before and after the practice changing papers, there were also many other major changes, not only in the management of patients following cardiac arrest, but also in ICU management overall. In addition, this period overlapped with many therapeutic hypothermia studies[9,11,16,36], resulting in changes to therapeutic hypothermia protocols, including the introduction of pre-hospital cooling.

Over the twenty years during which this study encompassed, there was no appreciable change in survival to hospital discharge for comatose survivors of cardiac arrest admitted to our ICU. Increased survival to hospital discharge was found to be independently associated with a shockable initial rhythm and a shorter time to return of spontaneous circulation.

A similar study will need to be repeated following the translation of the TTM Trial findings into clinical practice.

ACKNOWLEDGMENTS

Dr. Julian Hunt-Smith, Supervisor of Training, Intensive Care Unit, Royal Melbourne Hospital, 300 Grattan St, Parkville, VIC 3050, Australia. Alexandra Gorelik, Senior Statistician, Melbourne EpiCentre, Royal Melbourne Hospital, 300 Grattan St., Parkville, VIC 3050, Australia.

COMMENTS

Background

The intensive care management of patients following cardiac arrest is variable. This is particularly the case with regard to temperature management. Therapeutic hypothermia has been used in patients following cardiac arrest since the 1950's. However, more than 6 decades later, its role in the management of patients following cardiac arrest, and the parameters targeted, still remain up for debate.

Research frontiers

The targeted temperature management (TTM) trial has made us review our original thoughts on the use of therapeutic hypothermia in patients following cardiac arrest, leading to a new era in TTM. These new strategies have now been incorporated into international post-resuscitation guidelines.

Innovations and breakthroughs

This study looks at a twenty-year time period of the treatment of patients following cardiac arrest in a single institution enabling an insight into the practice changes that have occurred.

Applications

The study was conducted using retrospective data, allowing us to make a number of associations. Using out findings, further studies can be designed to not only look at temperature as a means of therapy, but potentially also as potential prognostic indicator for patients following cardiac arrest.

Terminology

"TTM" is a medical therapy where a patient's core body temperature is actively controlled to maintain a desired level; "Therapeutic hypothermia" is a subset

of TTM where the desired core body temperature is set to a target below 35 ℃; "Cardiac arrest" is the failure of the heart to pump blood, resulting in cessation of circulation; "Shockable rhythm" is an electrical cardiac rhythm causing a cardiac arrest that may be responsive to cardiac defibrillation, such as ventricular fibrillation and ventricular tachycardia'; "Non-shockable rhythm" is an electrical cardiac rhythm causing a cardiac arrest that is not responsive to cardiac defibrillation, such as asystole and pulseless electrical activity.

Peer-review

This is an interesting article describing the experience of a single center on the outcomes of cardiac arrest patients admitted to the intensive care unit.

REFERENCES

1 **Jennings PA**, Cameron P, Walker T, Bernard S, Smith K. Out-of-hospital cardiac arrest in Victoria: rural and urban outcomes. *Med J Aust* 2006; **185**: 135-139 [PMID: 16893352]

2 **Bernard S**. Outcome from prehospital cardiac arrest in Melbourne, Australia. *Emerg Med* 1998; **10**: 25-29 [DOI: 10.1111/j.1442-2026.1998.tb00486.x]

3 **Hypothermia after Cardiac Arrest Study Group**. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346**: 549-556 [PMID: 11856793 DOI: 10.1056/NEJMoa012689]

4 **Nielsen N**, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wise MP, Åneman A, Al-Subaie N, Boesgaard S, Bro-Jeppesen J, Brunetti I, Bugge JF, Hingston CD, Juffermans NP, Koopmans M, Køber L, Langørgen J, Lilja G, Møller JE, Rundgren M, Rylander C, Smid O, Werer C, Winkel P, Friberg H. Targeted temperature management at 33°C versus 36° C after cardiac arrest. *N Engl J Med* 2013; **369**: 2197-2206 [PMID: 24237006 DOI: 10.1056/NEJMoa1310519]

5 **Lin S**, Scales DC, Dorian P, Kiss A, Common MR, Brooks SC, Goodman SG, Salciccioli JD, Morrison LJ. Targeted temperature management processes and outcomes after out-of-hospital cardiac arrest: an observational cohort study*. *Crit Care Med* 2014; **42**: 2565-2574 [PMID: 25188550 DOI: 10.1097/CCM.0000000000000551]

6 **Benson DW**, Williams GR, Spencer FC, Yates AJ. The use of hypothermia after cardiac arrest. *Anesth Analg* 1959; **38**: 423-428 [PMID: 13798997 DOI: 10.1213/00000539-195911000-00010]

7 **Sterz F**, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991; **19**: 379-389 [PMID: 1999100 DOI: 10.1097/00003246-199103000-00017]

8 **Zeiner A**, Holzer M, Sterz F, Behringer W, Schörkhuber W, Müllner M, Frass M, Siostrzonek P, Ratheiser K, Kaff A, Laggner AN. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke* 2000; **31**: 86-94 [PMID: 10625721 DOI: 10.1161/01.STR.31.1.86]

9 **Bernard SA**, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med* 1997; **30**: 146-153 [PMID: 9250636 DOI: 10.1016/S0196-0644(97)70133-1]

10 **Felberg RA**, Krieger DW, Chuang R, Persse DE, Burgin WS, Hickenbottom SL, Morgenstern LB, Rosales O, Grotta JC. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. *Circulation* 2001; **104**: 1799-1804 [PMID: 11591617 DOI: 10.1161/hc4001.097037]

11 **Bernard SA**, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557-563 [PMID: 11856794 DOI: 10.1056/NEJMoa003289]

12 **Nielsen N**, Friberg H, Gluud C, Herlitz J, Wetterslev J. Hypothermia after cardiac arrest should be further evaluated--a systematic review of randomised trials with meta-analysis and trial sequential analysis. *Int J Cardiol* 2011; **151**: 333-341 [PMID: 20591514 DOI: 10.1016/j.ijcard.2010.06.008]

13 **Walters JH**, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: a systematic review. *Resuscitation* 2011; **82**: 508-516 [PMID: 21367510 DOI: 10.1016/j.resuscitation.2011.01.021]

14 **Mayer SA**, Kowalski RG, Presciutti M, Ostapkovich ND, McGann E, Fitzsimmons BF, Yavagal DR, Du YE, Naidech AM, Janjua NA, Claassen J, Kreiter KT, Parra A, Commichau C. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. *Crit Care Med* 2004; **32**: 2508-2515 [PMID: 15599159 DOI: 10.1097/01.CCM.0000147441.39670.37]

15 **Kliegel A**, Losert H, Sterz F, Kliegel M, Holzer M, Uray T, Domanovits H. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest--a feasibility study. *Resuscitation* 2005; **64**: 347-351 [PMID: 15733765 DOI: 10.1016/j.resuscitation.2004.09.002]

16 **Bernard SA**, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, Kelly AM, Silvester W. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010; **122**: 737-742 [PMID: 20679551 DOI: 10.1161/CIRCULATIONAHA.109.906859]

17 **Fridman M**, Barnes V, Whyman A, Currell A, Bernard S, Walker T, Smith KL. A model of survival following pre-hospital cardiac arrest based on the Victorian Ambulance Cardiac Arrest Register. *Resuscitation* 2007; **75**: 311-322 [PMID: 17583414 DOI: 10.1016/j.resuscitation.2007.05.005]

18 **Bernard S**. Hypothermia after cardiac arrest: expanding the therapeutic scope. *Crit Care Med* 2009; **37**: S227-S233 [PMID: 19535951 DOI: 10.1097/CCM.0b013e3181aa5d0c]

19 **Herlitz J**, Engdahl J, Svensson L, Angquist KA, Young M, Holmberg S. Factors associated with an increased chance of survival among patients suffering from an out-of-hospital cardiac arrest in a national perspective in Sweden. *Am Heart J* 2005; **149**: 61-66 [PMID: 15660035 DOI: 10.1016/j.ahj.2004.07.014]

20 **Akahane M**, Ogawa T, Koike S, Tanabe S, Horiguchi H, Mizoguchi T, Yasunaga H, Imamura T. The effects of sex on out-of-hospital cardiac arrest outcomes. *Am J Med* 2011; **124**: 325-333 [PMID: 21435423 DOI: 10.1016/j.amjmed.2010.10.020]

21 **Kitamura T**, Kiyohara K, Iwami T. The great east Japan earthquake and out-of-hospital cardiac arrest. *N Engl J Med* 2013; **369**: 2165-2167 [PMID: 24283245 DOI: 10.1056/NEJMc1306058]

22 **Albert CM**, McGovern BA, Newell JB, Ruskin JN. Sex differences in cardiac arrest survivors. *Circulation* 1996; **93**: 1170-1176 [PMID: 8653838 DOI: 10.1161/01.CIR.93.6.1170]

23 **Knaus WA**, Zimmerman JE, Wagner DP, Draper EA, Lawrence DE. APACHE-acute physiology and chronic health evaluation: a physiologically based classification system. *Crit Care Med* 1981; **9**: 591-597 [PMID: 7261642 DOI: 10.1097/00003246-198108000-00008]

24 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249 DOI: 10.1097/00003246-198510000-00009]

25 **Knaus WA**, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619-1636 [PMID: 1959406 DOI: 10.1378/chest.100.6.1619]

26 **Niewiński G**, Starczewska M, Kański A. Prognostic scoring systems for mortality in intensive care units--the APACHE model. *Anaesthesiol Intensive Ther* 2014; **46**: 46-49 [PMID: 24643928]

27 **Donnino MW**, Salciccioli JD, Dejam A, Giberson T, Giberson B, Cristia C, Gautam S, Cocchi MN. APACHE II scoring to predict outcome in post-cardiac arrest. *Resuscitation* 2013; **84**: 651-656 [PMID: 23178739 DOI: 10.1016/j.resuscitation.2012.10.024]

28 **Oksanen T**, Pettilä V, Hynynen M, Varpula T. Therapeutic

hypothermia after cardiac arrest: implementation and outcome in Finnish intensive care units. *Acta Anaesthesiol Scand* 2007; **51**: 866-871 [PMID: 17635393 DOI: 10.1111/j.1399-6576.2007.01365.x]

29 **Reinikainen M**, Oksanen T, Leppänen P, Torppa T, Niskanen M, Kurola J. Mortality in out-of-hospital cardiac arrest patients has decreased in the era of therapeutic hypothermia. *Acta Anaesthesiol Scand* 2012; **56**: 110-115 [PMID: 22091826 DOI: 10.1111/j.1399-6576.2011.02543.x]

30 **Vaahersalo J**, Hiltunen P, Tiainen M, Oksanen T, Kaukonen KM, Kurola J, Ruokonen E, Tenhunen J, Ala-Kokko T, Lund V, Reinikainen M, Kiviniemi O, Silfvast T, Kuisma M, Varpula T, Pettilä V. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. *Intensive Care Med* 2013; **39**: 826-837 [PMID: 23417209 DOI: 10.1007/s00134-013-2868-1]

31 **Lindner TW**, Langørgen J, Sunde K, Larsen AI, Kvaløy JT, Heltne JK, Draegni T, Søreide E. Factors predicting the use of therapeutic hypothermia and survival in unconscious out-of-hospital cardiac arrest patients admitted to the ICU. *Crit Care* 2013; **17**: R147 [PMID: 23880105 DOI: 10.1186/cc12826]

32 **Gebhardt K**, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Prevalence and effect of fever on outcome following resuscitation from cardiac arrest. *Resuscitation* 2013; **84**: 1062-1067 [PMID: 23619740 DOI: 10.1016/j.resuscitation.2013.03.038]

33 **Cocchi MN**, Boone MD, Giberson B, Giberson T, Farrell E, Salciccioli JD, Talmor D, Williams D, Donnino MW. Fever after rewarming: incidence of pyrexia in postcardiac arrest patients who have undergone mild therapeutic hypothermia. *J Intensive Care Med* 2013; **29**: 365-369 [PMID: 23783999]

34 **Bro-Jeppesen J**, Hassager C, Wanscher M, Søholm H, Thomsen JH, Lippert FK, Møller JE, Køber L, Kjaergaard J. Post-hypothermia fever is associated with increased mortality after out-of-hospital cardiac arrest. *Resuscitation* 2013; **84**: 1734-1740 [PMID: 23917079 DOI: 10.1016/j.resuscitation.2013.07.023]

35 **Leary M**, Grossestreuer AV, Iannacone S, Gonzalez M, Shofer FS, Povey C, Wendell G, Archer SE, Gaieski DF, Abella BS. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. *Resuscitation* 2013; **84**: 1056-1061 [PMID: 23153649 DOI: 10.1016/j.resuscitation.2012.11.003]

36 **Deasy C**, Bernard S, Cameron P, Jacobs I, Smith K, Hein C, Grantham H, Finn J. Design of the RINSE trial: the rapid infusion of cold normal saline by paramedics during CPR. *BMC Emerg Med* 2011; **11**: 17 [PMID: 21995804 DOI: 10.1186/1471-227X-11-17]

P- Reviewer: Jayaraman D, Zhang ZH **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2016 May 4; 5(2): 111-170

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

A peer-reviewed, online, open-access journal of critical care medicine

Editorial Board

2016-2019

The *World Journal of Critical Care Medicine* Editorial Board consists of 235 members, representing a team of worldwide experts in critical care medicine. They are from 44 countries, including Argentina (2), Australia (7), Austria (2), Bangladesh (1), Belgium (4), Brazil (4), Canada (6), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (6), Germany (9), Greece (9), Hungary (1), India (10), Iran (2), Israel (6), Italy (13), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (2), Singapore (2), Slovenia (1), South Africa (1), Spain (6), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (7), United States (70), and Uruguay (1).

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 5 Number 2 May 4, 2016

Contents

World Journal of Critical Care Medicine
Volume 5 Number 2 May 4, 2016

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Critical Care Medicine
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
May 4, 2016

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.111

World J Crit Care Med 2016 May 4; 5(2): 111-120
ISSN 2220-3141 (online)

REVIEW

Association between infections caused by multidrug-resistant gram-negative bacteria and mortality in critically ill patients

Elisabeth Paramythiotou, Christina Routsi

Elisabeth Paramythiotou, Second Department of Critical Care, Medical School, University of Athens, Attikon University Hospital, 12462 Athens, Greece

Christina Routsi, First Department of Critical Care, Medical School, University of Athens, Evangelismos Hospital, 10676 Athens, Greece

Author contributions: Both authors designed the review, conducted the literature review, wrote the article, prepared the table and made critical revisions related to the intellectual content.

Conflict-of-interest statement: Authors have no conflict of interest.

Correspondence to: Elisabeth Paramythiotou, MD, PhD, Second Department of Critical Care, Medical School, University of Athens, Attikon University Hospital, Rimini Stree, 12462 Athens, Greece. lparamyth61@hotmail.com
Telephone: +30-210-6003766
Fax: +30-210-5326414

Received: October 3, 2015
Peer-review started: October 15, 2015
First decision: November 30, 2015
Revised: December 30, 2015
Accepted: March 7, 2016
Article in press: March 9, 2016
Published online: May 4, 2016

Abstract

The incidence of gram-negative multidrug-resistant (MDR) bacterial pathogens is increasing in hospitals and particularly in the intensive care unit (ICU) setting. The clinical consequences of infections caused by MDR pathogens remain controversial. The purpose of this review is to summarize the available data concerning the impact of these infections on mortality in ICU patients. Twenty-four studies, conducted exclusively in ICU patients, were identified through PubMed search over the years 2000-2015. Bloodstream infection was the only infection examined in eight studies, respiratory infections in four and variable infections in others. Comparative data on the appropriateness of empirical antibiotic treatment were provided by only seven studies. In ten studies the presence of antimicrobial resistance was not associated with increased mortality; on the contrary, in other studies a significant impact of antibiotic resistance on mortality was found, though, sometimes, mediated by inappropriate antimicrobial treatment. Therefore, a direct association between infections due to gram-negative MDR bacteria and mortality in ICU patients cannot be confirmed. Sample size, presence of multiple confounders and other methodological issues may influence the results. These data support the need for further studies to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

Key words: Critically ill patients; Infections; Multidrug resistance; Gram-negative pathogens; Mortality

Core tip: The incidence of gram-negative multidrug-

resistant (MDR) bacterial pathogens is increasing in hospitals and particularly in the intensive care unit (ICU) setting. The clinical consequences of infections caused by MDR pathogens remain controversial. Until the present time a direct association between infections due to gram-negative MDR bacteria and mortality in ICU patients cannot be confirmed by the studies available. Further studies are needed to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

Paramythiotou E, Routsi C. Association between infections caused by multidrug-resistant gram-negative bacteria and mortality in critically ill patients. *World J Crit Care Med* 2016; 5(2): 111-120 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/111.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.111

INTRODUCTION

Nosocomial-acquired infections are a frequently encountered problem in critically ill patients posing a severe burden on the morbidity and mortality noticed in the intensive care unit (ICU) setting. In the Extended Prevalence of Infection in Intensive Care (EPIC Ⅱ) study carried out in May 2007[1] recruiting 1265 ICUs in 75 countries, 51% of patients were considered infected, a prevalence rate considerably higher than the 20% of the previous EPIC Ⅰ study[2]. Furthermore, ICU and hospital mortality rates of infected patients were more than twice than those of non-infected. Notably, 62% of the isolates were gram-negative bacteria.

An important factor further contributing to the untoward effects of infection is the ever growing resistance of pathogens. Although resistance trends vary among hospitals, there is significant evidence that the prevalence of multidrug-resistance (MDR) is increasing. Particularly in the ICU setting several specific factors contribute to higher percentages of antimicrobial resistance in this particular environment[3,4]. Overuse of antibiotics, prolonged ICU stay, use of indwelling devices, presence of comorbidities, lack of isolation practices, easy spread of resistant pathogens among countries as a result of international travels significantly increase the burden of resistance in the critically ill.

Since 2008 the acronym "ESKAPE" has been given to a group of pathogens [*Enterococus faecium, Staphylococcus aureus, Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii, Pseudomonas aeruginosa* (*P. aeruginosa*) and *Enterobacter* species] that pose a high threat to patients' safety emphasizing the need for new and effective antibiotics[5]. In the critically ill patient the importance of gram-negatives as pathogens in the ICU has been featured by several epidemiologic studies both in Europe[1] and in the United States[6]. In addition, the Centers for Disease Control and Prevention (CDC) identified the increase in antibiotic resistance as one of the most important threats to human health worldwide[7].

Apart from the clinical, the economic consequences of antimicrobial resistance are also a matter of concern[8]. It is almost generally accepted that acquisition of MDR strains is often associated with higher utilization costs, compared to susceptible ones[9,10]. On the contrary, the clinical consequences of infections caused by MDR pathogens have been a matter of debate. Although there is a general agreement about the association of MDR with prolonged hospital stay, the possible association between antimicrobial resistance and mortality remains controversial. In some studies a positive association has been found whereas in other studies no significant excess of mortality has been detected.

Earlier studies regarding the resistance and ICU outcomes have addressed gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Vancomycin-resistant enterococcus*[11-13]. Furthermore, though numerous studies have examined the impact of resistant gram-negative bacilli in hospitalized patients in general, a limited number of them have focused exclusively on ICU patients. The purpose of this review is to summarize the available data concerning the impact of infections caused by MDR gram-negative pathogens upon clinical outcome, laying particular emphasis on mortality of the critically ill. A brief description of the epidemiology and characteristics of the main gram-negative pathogens will precede.

EPIDEMIOLOGY AND MECHANISMS OF RESISTANCE

In the critically ill patients gram-negative pathogens with the greatest burden are the non-fermenting bacteria *Acinetobacter baumannii* and *P. aeruginosa* for which few therapeutic options are available and *Enterobacteriacae* mainly *Kebsiella pneumoniae* equipped with a significant number of resistance mechanisms. The Antimicrobial Availability Task Force formed by the Infectious Diseases Society of America has identified these three gram-negative pathogens as a source of particular importance for difficult to treat infections[5].

K. pneumoniae

K. pneumoniae is an established nosocomial pathogen capable of collecting plasmids which confer resistance to many antimicrobials. An illustrating example of their capacity are plasmids encoding extended-spectrum beta-lactamases rendering them resistant against newer cephalosporins. Later, another main mechanism of resistance for *K. pneumoniae* was added, the acquisition of carbapenemases. The carbapenemases commonly encountered are the *K. pneumoniae* carbapenemase (KPC) variants and the zinc-dependent metallo-beta-lactamases (Mbls).

KPCs are beta-lactamases capable of hydrolyzing penicillins, all cephalosporins, mono-bactams, carbapen-

ems and even β-lactamase inhibitors. They were firstly isolated in 1996 in Northern Carolina, United States, then in New York city hospitals and then in many states[14]. Since then, KPC-producing bacteria have been isolated in most places around the world, including South America, Europe and Asia. In many countries such as Greece, Israel, Poland and Italy[15-17], KPCs have become endemic but in other cases they remain a rare infection cause. Infections caused by KPCs include life-threatening infections such as bacteremia and pneumonia in critically ill patients.

The three families of metallo-beta lactamases (VIM, IMP and NDM) have spread inter-nationally but with significant local differences. VIM-producing *K. pneumoniae* are isolated mainly in Europe where they are epidemic in some countries of Southern Europe. On the contrary, IMPs are isolated in countries of Asia and also in Australia[18,19]. New Delhi metallo-beta-lactamase is the most recently isolated type of metallo-beta-lactamase. Although the epidemic started in India, it has spread to several parts of the world[20].

P. aeruginosa

P. aeruginosa is a common cause of nosocomial infections, often associated with higher mortality when compared to other bacterial pathogens[21,22]. Especially in the ICU setting severe infections are caused by this aerobic gram-negative bacilli, namely bloodstream infections, whether related or not to the use of a central venous catheter and ventilator-associated pneumonia. *P. aeruginosa* is the cause of a high percentage of nosocomial infections in critically ill patients. In the EPIC Ⅱ study *Pseudomonas* species caused 19.9% of infections in the ICU[1] while another multicenter study concerning bloodstream infections coming from 9 countries, showed that *P. aeruginosa* was the cause of bacteremia in 5.3% of cases[23]. Several mechanisms are implicated in the development of resistance in *P. aeruginosa* strains. One of the main mechanisms is the resistance to carbapenems, one of the most important drugs for the treatment of *P. aeruginosa*-associated infections. Resistance is often caused by carbapenemases, mainly Ambler class B metallo-b-lactamases and more recently KPC serine carbapenemases. A combination of resistance mechanisms is usually present[24]. In a recent study Castanheira *et al*[25] examined 529 carbapenem non-susceptible *P. aeruginosa* isolates from 14 European and Mediterranean countries. They noticed an increased prevalence of Mbls and increased resistance to imipenem and meropenem while a percentage of 99.3 of isolates was susceptible to colistin.

Acinetobacter baumannii

Acinetobacters are gram-negative, catalase-positive, oxidase-negative, non-motile, non-fermenting coccobacilli. They have concentrated a wide array of antimicrobial resistance mechanisms which include enzymatic degradation by beta-lactamases (including TEM, SHV, CTX-M, OXA, VIM, IMP and others). Furthermore, several non-enzymatic mechanisms contribute to the emergence of resistance to a variety of antimicrobials including quinolones, aminoglycosides, tetracyclines, glycylcyclines and polymyxins[19]. One of the most important mechanisms is the emergence of resistance to carbapenems, which is encountered in larger percentages than in other gram-negatives[26]. In such cases polymyxins are the only therapeutic solution. Unfortunately, the isolation of colistin-resistant carbapenem-resistant *A. baumannii* is on the rise[27]. A large spectrum of nosocomial infections are caused by *A. baumannii* including bloodstream infections, pneumonia, catheter-associated infections, *etc. A. baumannii* belongs to the group of ESKAPE pathogens and in the EPIC Ⅱ study infections caused by this pathogen covered a percentage of 8.9%[1].

DEFINITIONS

Antimicrobial resistance

A general definition of antimicrobial resistance is the ability of an organism to resist the action of an antimicrobial agent to which it was previously susceptible. One of the major difficulties in the evaluation of relevant studies was the lack of a standard definition for the MDR, extra-drug resistant (XDR) and the pan-drug resistant (PDR) pathogens due to the lack of classification criteria and specific definitions. Various authors have used different methods to characterize organisms as "resistant" based on *in vitro* antimicrobial susceptibility test results. As a result, microbiology data could not be reliably compared across different healthcare settings. The diversity of definitions of MDR and PDR for *A. baumannii* and *P. aeruginosa* has been reviewed by Falagas *et al*[28]. In this paper, an impressive diversity of resistance definitions became apparent highlighting the need for a consensus on that important matter.

In 2012 Magiorakos *et al*[29] international experts established a standardized international terminology through a joint initiative by the European Centre for Disease Prevention and Control and the CDC. In this definition an "antimicrobial category" was constructed for each isolate. Accordingly, MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories; XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and PDR was defined as non-susceptibility to all agents in all antimicrobial categories. Applying the suggested definitions could make data from relevant studies comparable allowing therefore, the extraction of reliable conclusions.

In the present review, since we included studies between 2000 and 2015, the definitions used by different authors of the included studies vary. Some of them define the resistance as resistance only to carbapenems while others to several classes of antimicrobial agents.

Twenty four studies were identified during the predefined period according to the search criteria[9,30-56]. A synopsis of the studies' characteristics such as design, sample size, type of infection, resistance definition, pathogen (s) and clinical outcome data are presented in Table 1. Nine out of the twenty three studies had a retrospective study design, ten were prospective and in two studies the type was not reported. Two studies were part of secondary analysis of large prospective studies.

Several differences regarding definitions, design, control group selection and the sample size were observed. Two studies were conducted in surgical ICUs while others in mixed ICUs. The causative pathogen was only one in thirteen studies (*P. aeruginosa* in 5, *A. baumannii* in 5, and *K. pneumoniae* in 3 studies) whereas two studies dealt with two resistant pathogens. The remaining studies examined the impact of all three important gram-negative pathogens, some of them involving also other *Enterobacteriacae* (such as *E. coli*) or gram-positive bacteria such as *S. aureus*. Four studies have focused exclusively on carbapenem-resistant compared to carbapenem-susceptible strains of *P. aeruginosa* or *A. baumannii*.

The site of infection differed among studies. Eight studies examined bloodstream infections; four studies examined respiratory infections related to mechanical ventilation, one study enrolled patients with pneumonia or bloodstream infection and nine studies enrolled patients affected by infections of any origin. Finally, in two studies colonization with or without infection was examined. One of them is the recent large, two-center prospective cohort study, which quantified the effects of carbapanemase-producing *Enterobacteriaceae* carriage on patient outcome in the ICU (MOSAR study)[30]. Although this study did not explore any association with infection, being focused on colonization, it was included because colonization precedes infection in most instances and, therefore, it represents an indirect marker of a patient being at risk of a possible poorer outcome.

Concerning the control group selection, in nine studies both cases and controls came from the pool of patients presenting an infection due to a MDR pathogen and survivors were compared to non-survivors. In eight studies patients infected with a MDR strain were compared to those with a susceptible one or to those without any infection. Comparative data on the appropriateness of empirical antibiotic treatment were provided by only seven[48,50,51,52,54,55] out of twenty-four studies.

As for the main target of this review, *i.e.,* resistance-associated mortality, a negative association was documented in ten studies. In the remaining studies a positive result was noted, though with different endpoints. Among the latter, the hospital-associated mortality was affected in two studies while in another study both ICU and hospital mortality were influenced. In the large sample size study by Lambert *et al*[47] the results showed that the presence of antimicrobial resistance had a low additional effect (20%) on mortality. In two other studies, the increased mortality was considered as the indirect consequence of the inappropriate therapy. Finally, in the study by Dautzenberg *et al*[30] patients colonized with carbapenemase-producing Enterobacteriaceae had a 1.79 times higher hazard of dying in ICU than no colonized patients, primarily because of an increased length of stay.

Additionally, 3 review articles summarizing the published data on this issue were identified[31-33] as well as another one presenting the clinical consequences of specific MDR pathogen, namely *P. aeruginosa*[34]. In the review by Shorr[33], studies mostly conducted on general hospitalized population were included providing that among the studied patients a more than 39% of cases was hospitalized in the ICU. The collective findings of these studies suggested that gram-negative bacterial resistance increases the burden in the ICU in terms of mortality, length of stay and charges. Of note, associations between gram-negative resistance and mortality or prolonged length of stay sometimes disappeared in multivariate analyses after adjusting for confounding factors.

GENERAL COMMENTS

The clinical consequences of the common MDR gram-negative bacilli on the critically ill patients have been the subject of examination in a number of studies presented in this review. Several studies found a significant impact of antibiotic resistance on mortality whereas others did not show such impact. However, as shown in Table 1, there was a considerable heterogeneity of published studies with respect to study design, definitions and outcomes measured. As a result, some confusion with regard to the actual antibiotic resistance impact on mortality from gram-negative infections is unavoidable.

Assessing the contribution of infections caused by antimicrobial resistant pathogens to an adverse clinical outcome in ICU patients is difficult, given the confounding created by crucial factors such as the illness severity, co-morbidities, infection site, treatment strategy and others[9,57]. Large, well-conducted epidemiological studies, focusing on the association between gram-negative bacterial resistance to antimicrobial agents and mortality in the ICU setting are limited in the currently available literature.

Most of the studies identified suffer from a number of limitations. Firstly, nine studies were retrospective and, therefore, prone to several forms of potential biases. Secondly, diverse definitions of the term "multi-drug resistance" have been used based on different thresholds over the past years in different institutions[28], particularly before the standardized international terminology was available[29]. As a result, according to *in vitro* susceptibilities some patients would have been classified into the opposite category (or vice versa).

Table 1 Studies describing mortality in intensive care unit patients with infections caused by multi-drug resistant bacteria *vs* susceptible

Ref.	Study design	No. of cases	Type of infection	Isolates/resistance definition	Results/comments
Blot *et al*[35]	Retrospective, cohort study	328	BSI	Variable/ceftazidime-resistance	Antibiotic resistance does not affect the outcome
Peres-Bota *et al*[36]	Prospective	186	Variable infections	Variable[2]/at least to ceftazidime, animoglycosides, carbapenems or quinolones	No difference in mortality
Ortega *et al*[37]	Single center prospective study	53	Colonization and infection	*P. aeruginosa*/resistant at least to two classes of antibiotics	No difference in mortality
Combes *et al*[38]	Secondary analysis of a large prospective cohort study	115	VAP	*P. aeruginosa*/resistance to piperacillin	28-d mortality not associated with piperacillin resistance
Kwa *et al*[39]	Retrospective cohort study	129	VAP	Variable MDR bacteria/resistance to all available systemic antibiotics	MDR was associated with a higher likelihood of infection-attributed mortality
Playford *et al*[9]	Retrospective case-control study	197	Variable (including colonization)	*A. baumannii*/susceptible only to amikacin and colisin	Positive association with increased hospital mortality
Daniels *et al*[40]	Retrospective, propensity-matched cohort study	84	Variable infections	*A. baumannii*/resistance to 3 or more classes of antibiotics	No difference in 28-d mortality
Parker *et al*[41]	Secondary analysis of a randomized trial	739	VAP	*P. aeruginosa* or variable MDR bacteria[2]/resistance to 2 or more classes of antibiotics	Higher 28-d ICU and hospital mortality
Pinheiro *et al*[42]	Retrospective case–control study	131	Variable infections	*P. aeruginosa*/multi- or pandrug resistant	No association with mortality
Katsaragakis *et al*[43]	Prospective observational study in a surgical ICU	60	Variable infections	*A. baumannii*/susceptibility only to colistin	Multi- resistance not associated with mortality
Routsi *et al*[44]	Prospective observational study	96	BSI	*A. baumannii*/carbapenem resistance	No association with mortality
Mouloudi *et al*[45]	Double case -control study	59	BSI	*K. pneumoniae*/carbapenem resistance	Positive association between KPC producing *K. pneumoniae* and mortality
Michalopoulos *et al*[46]	Retrospective case-control study	84	Primary BSIs (78% ICU-acquired, 22% ward-acquired)	*K. pneumoniae*, *A. baumanni*, *P. aeruginosa*/resistance to at least 4 out of 7 antibiotic classes	Higher hospital mortality, compared to controls
Lambert *et al*[47]	Multicenter prospective cohort study	119699	Pneumonia,	*E.coli*, *A. baumannii*, *P. aeruginosa*, *S. aureus*/resistance to 3rd generation cephalosporins, ceftazidime, and oxacillin, respectively	The additional effect of the most common antimicrobial resistance patterns on mortality is comparatively low
Tabah *et al*[48]	Prospective multicentre cohort study	1156	BSI BSI	Multiple isolates[2]/according to the ESCMID	Resistance is associated with increased 28-d mortality
Patel *et al*[49]	Prospective cohort matched case-control	298	Variable infections	*A. baumannii*, *K. pneumoniae*, *P. aeruginosa*/susceptible to ≤ 1 antimicrobial agent	Resistance not associated with mortality
Zilberberg *et al*[50]	Single center retrospective cohort study	1076	BSI	Variable gram-negative/*Paeruginosa* resistant to at least 3 antimicrobials, ESBL, CPE	Impact of MDR on inappropriate therapy/indirect effect on increased hospital mortality
Shorr *et al*[51]	Retrospective cohort study	131	BSI	*A. baumannii*/carbapenem resistance	Impact of carbapenem resistance on inappropriate therapy/indirect effect on mortality
Papadimitriou–Olivgeris *et al*[52]	Single center study	273	Variable infections	*K. pneumoniae*/resistance to gentamicin, colistin and/or tigecycline	Positive association with mortality
Dabar *et al*[53]	3-center, prospective cohort study	120	Variable infections	Variable pathogens/MDR *P. aeruginosa*: Resistance to at least 3 of the following: *Pseudomonas* acting beta-lactams, carbapenems, aminoglycosides, and quinolones	MDR *P. aeruginosa* infection was independent risk factor for mortality

Dautzenberg *et al*[30]1	2-center prospective cohort study	132	Colonization	*CPE*	Higher hazard of dying (primarily because of an increased LOS)
Bass *et al*[54]	Prospective case-control study	168	BSI	Gram-negative bacteria/carbapenem resistance	Increased mortality/combination therapy was associated with improve survival rate
Vardakas *et al*[55]	Retrospective Cohort study	140	Variable infections	*K. pneumonia*/carbapenem resistance	No difference in mortality
Martin-Loeches *et al*[56]	Prospective observetional study		VAP and HAP	Variable/according to CDC/ECDC	Patients with MDR bacteria had a higher mortality than those with no-MDR

[1]Colonization only; [2]Gram-positive included. BSI: Blood stream infection; VAP: Ventilator associated pneumonia; MDR: Multidrug-resistant; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; CPE: Carbapenem – producing enterobactaeriacae; ESBL: Extended spectrum beta lactamases; HAP: Hospital acquired pneumonia; ECDC: European Centre for Disease Prevention and Control; CDC: Centers for Disease Control and Prevention.

Thirdly, different outcome definitions could have also influenced the results. For example, some studies assess the overall ICU mortality, while others the in-hospital or the attributable mortality[57]. Of note, whether the deaths in critically ill patients are directly attributable to antibiotic resistant infections cannot be easily evaluated since it is often subjected to the physicians' clinical assessment. Finally, the small sample size of cases in some studies was a restricting factor for the detection of any significant difference.

SPECIFIC METHODOLOGIC ISSUES

Important methodologic issues addressing the choice of reference group might influence the conduct and the results of studies evaluating the relationship between acquisition of antimicrobial-resistant organisms and outcome, as discussed in detail elsewhere[57-59]. Briefly, instead of the standard case-control method, a case-case-control study design has been proposed with two separate case-control analyses to overcome limitations of the conventional studies assessing the effect of hospital or ICU-acquired infections by a particular pathogen. A complete analysis might include two groups of case patients; those infected with resistant pathogens and those with susceptible ones, compared with the control group, *i.e.,* uninfected patients. To our knowledge, only few studies have included double-case patients in similar efforts and none of the studies that have been included in the present review.

SITES OF INFECTION

In several studies all patients infected with antimicrobial resistant gram-negative pathogens are analyzed together. This is due, in part, to the small size of studies; insufficient numbers of the patients included do not allow stratification. However, certain types of infection as pneumonia or peritonitis may carry greater mortality than other infection types[35,60,61]. Indeed, among bacteremic patients, high-risk source of bacteremia (including the lung, abdominal or unknown sources) were more prevalent among nonsurvivors[35,60].

ROLE OF VIRULENCE

Whether the association of antimicrobial resistance with an increased risk of death, found in some studies, is exclusively related to the risk of receiving inappropriate initial empirical antimicrobial treatment, or it is also related to a higher virulence of pathogens exhibiting higher MICs to certain antimicrobials is not clear[62]. Probably, this question cannot be answered by such type of clinical studies where different gram-negative bacteria of nonsimilar virulence are usually examined together[60]. For example, *P. aeruginosa* isolates are known to be extremely virulent; however, as it has been shown, MDR *P. aeruginosa* strains have impaired virulence when compared to susceptible ones[63].

Theoretically, an increased intrinsic virulence of resistant gram-negative strains could explain, at least in part, an adverse clinical outcome. However, to date, no studies have demonstrated such an association; thus, in general, antibiotic resistance is not believed to be itself a virulence factor as compared to similar susceptible species[57]. Nevertheless, in certain situations the antimicrobial resistance may be considered a "virulence like" factor in specific ecological niches which MDR bacteria are able to colonize. This is especially true in the ICU environment where MDR pathogens can cause disease more readily[64].

ROLE OF INITIAL APPROPRIATE ANTIMICROBIAL TREATMENT

Treatment factors may contribute to adverse outcomes in patients infected with a resistant pathogen[57].The importance of an early and appropriate antimicrobial treatment and its favorable impact on the clinical outcome is well known[60,65]. Inappropriate empirical antimicrobial therapy is one of the major confounders in studies aiming to assess the impact of MDR to mortality[32].

This issue was not assessed in sixteen out of the twenty-three studies included in the present review. In most studies which addressed this issue, the presence of MDR pathogens was an important factor for receiving

inappropriate empiric treatment. For example, in a recent study[51], the presence of carbapenem-resistant *A.baumannii* as the infectious pathogen more than doubled the risk of receiving non-initially appropriate antimicrobial treatment, compared to having a carbapenem-susceptible isolate.

Failure to receive appropriate therapy further increases the risk of hospital mortality. In the EUROBACT study[48], even after controlling for adequacy of antimicrobial treatment, antimicrobial resistance, along with the timing to adequate treatment, was an independent predictor of 28-d mortality. However, XDR or PDR resistance levels were not associated with higher 28-d mortality when compared with MDR levels.

To our knowledge, this is the first review that focuses exclusively on studies conducted in the critical care setting. Studies examining the impact of antimicrobial resistance on the outcome of hospitalized patients in general (either in the ICU or in the hospital wards) have also shown diverse results[66]. As a case in point, a prospective observational study, evaluating the impact of VIM production on the outcome of patients with *K. pneumoniae* bloodstream infections, showed that VIM production had no effect on mortality whereas in the subgroup of patients infected with VIM - producing *K. pneumoniae*, carbapenem resistance, advanced age and severity of underlying disease were independent predictors of adverse outcome. However, after adjustment for inappropriate therapy, the effect of carbapenem resistance on outcome was nonsignificant. Therefore, the higher mortality was probably mediated by the failure to provide effective antimicrobial therapy[67].

Finally, it should be noted that there is little data assessing whether being admitted to an ICU with high levels of antimicrobial resistance is associated with a worse outcome than being admitted to an ICU with low rates of resistance. A recent publication using data from the large, international EPIC Ⅱ study on infections in ICUs[1] showed that being hospitalized in an ICU in a region with high levels of antimicrobial resistance is not associated *per se* with a worse outcome[68]. In this study the selection of countries with high levels of antimicrobial resistance rates was made using reported MRSA rates. According to the authors this could be considered as a selection bias because general resistance rates may have been different.

CONCLUSION

Although mortality associated with gram-negative infections is high, data from the available literature do not confirm that there is a direct association between antimicrobial resistance and mortality in ICU patients. Appropriate antimicrobial administration remains of paramount importance. Due to papers' limitations including the sample size and multiple confounders due to individual patient's characteristics and different healthcare systems any conclusion should be carefully considered. These data support the need of further studies to elucidate the real impact of infections caused by resistant bacteria in ICU patients.

REFERENCES

1 **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]

2 **Vincent JL**, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; **274**: 639-644 [PMID: 7637145 DOI: 10.1001/jama.1995.03530080055041]

3 **Cantón R**, Akóva M, Carmeli Y, Giske CG, Glupczynski Y, Gniadkowski M, Livermore DM, Miriagou V, Naas T, Rossolini GM, Samuelsen Ø, Seifert H, Woodford N, Nordmann P. Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; **18**: 413-431 [PMID: 22507109 DOI: 10.1111/j.1469-0691.2012.03821.x]

4 **Petty NK**, Ben Zakour NL, Stanton-Cook M, Skippington E, Totsika M, Forde BM, Phan MD, Gomes Moriel D, Peters KM, Davies M, Rogers BA, Dougan G, Rodriguez-Baño J, Pascual A, Pitout JD, Upton M, Paterson DL, Walsh TR, Schembri MA, Beatson SA. Global dissemination of a multidrug resistant Escherichia coli clone. *Proc Natl Acad Sci USA* 2014; **111**: 5694-5699 [PMID: 24706808 DOI: 10.1073/pnas.1322678111]

5 **Boucher HW**, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 1-12 [PMID: 19035777 DOI: 10.1086/595011]

6 **Wisplinghoff H**, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; **39**: 309-317 [PMID: 15306996 DOI: 10.1086/421946]

7 **Centers for Disease Control and Prevention**. The threat of antibiotic resistance in the United States. [accessed 2015 Jul 10]. Available from: URL: http//www.cdc.gov

8 **Maragakis LL**, Perencevich EN, Cosgrove SE. Clinical and economic burden of antimicrobial resistance. *Expert Rev Anti Infect Ther* 2008; **6**: 751-763 [PMID: 18847410 DOI: 10.1586/14787210.6.5.751]

9 **Playford EG**, Craig JC, Iredell JR. Carbapenem-resistant Acinetobacter baumannii in intensive care unit patients: risk factors for acquisition, infection and their consequences. *J Hosp Infect* 2007; **65**: 204-211 [PMID: 17254667 DOI: 10.1016/j.jhin.2006.11.010]

10 **Tansarli GS**, Karageorgopoulos DE, Kapaskelis A, Falagas ME. Impact of antimicrobial multidrug resistance on inpatient care cost: an evaluation of the evidence. *Expert Rev Anti Infect Ther* 2013; **11**: 321-331 [PMID: 23458771 DOI: 10.1586/eri.13.4]

11 **Lautenbach E**, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. *Infect Control Hosp Epidemiol* 1999; **20**: 318-323 [PMID: 10349947]

12 **González C**, Rubio M, Romero-Vivas J, González M, Picazo JJ. Bacteremic pneumonia due to Staphylococcus aureus: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis* 1999; **29**: 1171-1177 [PMID: 10524959 DOI: 10.1086/313440]

13 **Stroud L**, Edwards J, Danzing L, Culver D, Gaynes R. Risk factors for mortality associated with enterococcal bloodstream infections. *Infect Control Hosp Epidemiol* 1996; **17**: 576-580 [PMID: 8880229]

14 **Munoz-Price LS**, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Gniadkowski M, Hayden MK, Kumarasamy K, Livermore DM, Maya JJ, Nordmann P, Patel JB,

Paterson DL, Pitout J, Villegas MV, Wang H, Woodford N, Quinn JP. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. *Lancet Infect Dis* 2013; **13**: 785-796 [PMID: 23969216 DOI: 10.1016/S1473-3099(13)70190-7]

15 **Baraniak A**, Izdebski R, Herda M, Fiett J, Hryniewicz W, Gniadkowski M, Kern-Zdanowicz I, Filczak K, Łopaciuk U. Emergence of Klebsiella pneumoniae ST258 with KPC-2 in Poland. *Antimicrob Agents Chemother* 2009; **53**: 4565-4567 [PMID: 19620323 DOI: 10.1128/AAC.00436-09]

16 **Giani T**, D'Andrea MM, Pecile P, Borgianni L, Nicoletti P, Tonelli F, Bartoloni A, Rossolini GM. Emergence in Italy of Klebsiella pneumoniae sequence type 258 producing KPC-3 Carbapenemase. *J Clin Microbiol* 2009; **47**: 3793-3794 [PMID: 19759220 DOI: 10.1128/JCM.01773-09]

17 **Souli M**, Galani I, Antoniadou A, Papadomichelakis E, Poulakou G, Panagea T, Vourli S, Zerva L, Armaganidis A, Kanellakopoulou K, Giamarellou H. An outbreak of infection due to beta-Lactamase Klebsiella pneumoniae Carbapenemase 2-producing K. pneumoniae in a Greek University Hospital: molecular characterization, epidemiology, and outcomes. *Clin Infect Dis* 2010; **50**: 364-373 [PMID: 20041768 DOI: 10.1086/649865]

18 **Mendes RE**, Bell JM, Turnidge JD, Yang Q, Yu Y, Sun Z, Jones RN. Carbapenem-resistant isolates of Klebsiella pneumoniae in China and detection of a conjugative plasmid (blaKPC-2 plus qnrB4) and a blaIMP-4 gene. *Antimicrob Agents Chemother* 2008; **52**: 798-799 [PMID: 18086850 DOI: 10.1128/AAC.01185-07]

19 **Peleg AY**, Franklin C, Bell JM, Spelman DW. Dissemination of the metallo-beta-lactamase gene blaIMP-4 among gram-negative pathogens in a clinical setting in Australia. *Clin Infect Dis* 2005; **41**: 1549-1556 [PMID: 16267725 DOI: 10.1086/497831]

20 **Nordmann P**, Poirel L, Toleman MA, Walsh TR. Does broad-spectrum beta-lactam resistance due to NDM-1 herald the end of the antibiotic era for treatment of infections caused by Gram-negative bacteria? *J Antimicrob Chemother* 2011; **66**: 689-692 [PMID: 21393184 DOI: 10.1093/jac/dkq520]

21 **Osmon S**, Ward S, Fraser VJ, Kollef MH. Hospital mortality for patients with bacteremia due to Staphylococcus aureus or Pseudomonas aeruginosa. *Chest* 2004; **125**: 607-616 [PMID: 14769745 DOI: 10.1378/chest.125.2.607]

22 **Harbarth S**, Ferrière K, Hugonnet S, Ricou B, Suter P, Pittet D. Epidemiology and prognostic determinants of bloodstream infections in surgical intensive care. *Arch Surg* 2002; **137**: 1353-1359; discussion 1359 [PMID: 12470098 DOI: 10.1001/archsurg.137.12.1353]

23 **Ammerlaan HS**, Harbarth S, Buiting AG, Crook DW, Fitzpatrick F, Hanberger H, Herwaldt LA, van Keulen PH, Kluytmans JA, Kola A, Kuchenbecker RS, Lingaas E, Meessen N, Morris-Downes MM, Pottinger JM, Rohner P, dos Santos RP, Seifert H, Wisplinghoff H, Ziesing S, Walker AS, Bonten MJ. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. *Clin Infect Dis* 2013; **56**: 798-805 [PMID: 23223600 DOI: 10.1093/cid/cis1006]

24 **Villegas MV**, Kattan JN, Correa A, Lolans K, Guzman AM, Woodford N, Livermore D, Quinn JP. Dissemination of Acinetobacter baumannii clones with OXA-23 Carbapenemase in Colombian hospitals. *Antimicrob Agents Chemother* 2007; **51**: 2001-2004 [PMID: 17403994 DOI: 10.1128/AAC.00226-07]

25 **Castanheira M**, Deshpande LM, Costello A, Davies TA, Jones RN. Epidemiology and carbapenem resistance mechanisms of carbapenem-non-susceptible Pseudomonas aeruginosa collected during 2009-11 in 14 European and Mediterranean countries. *J Antimicrob Chemother* 2014; **69**: 1804-1814 [PMID: 24603963 DOI: 10.1093/jac/dku048]

26 **Sievert DM**, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. *Infect Control Hosp Epidemiol* 2013; **34**: 1-14 [PMID: 23221186 DOI: 10.1086/668770]

27 **Qureshi ZA**, Hittle LE, O'Hara JA, Rivera JI, Syed A, Shields RK, Pasculle AW, Ernst RK, Doi Y. Colistin-resistant Acinetobacter baumannii: beyond carbapenem resistance. *Clin Infect Dis* 2015; **60**: 1295-1303 [PMID: 25632010 DOI: 10.1093/cid/civ048]

28 **Falagas ME**, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) Acinetobacter baumannii and Pseudomonas aeruginosa. *J Med Microbiol* 2006; **55**: 1619-1629 [PMID: 17108263 DOI: 10.1099/jmm.0.46747-0]

29 **Magiorakos AP**, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**: 268-281 [PMID: 21793988 DOI: 10.1111/j.1469-0691.2011.03570]

30 **Dautzenberg MJ**, Wekesa AN, Gniadkowski M, Antoniadou A, Giamarellou H, Petrikkos GL, Skiada A, Brun-Buisson C, Bonten MJ, Derde LP. The association between colonization with carbapenemase-producing enterobacteriaceae and overall ICU mortality: an observational cohort study. *Crit Care Med* 2015; **43**: 1170-1177 [PMID: 25882764 DOI: 10.1007/s00259-015-3041-6]

31 **Vardakas KZ**, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? *J Infect* 2013; **66**: 401-414 [PMID: 23142195 DOI: 10.1016/j.jinf.2012.10.028]

32 **Blot S**, Depuydt P, Vandewoude K, De Bacquer D. Measuring the impact of multidrug resistance in nosocomial infection. *Curr Opin Infect Dis* 2007; **20**: 391-396 [PMID: 17609598 DOI: 10.1097/QCO.0b013e32818be6f7]

33 **Shorr AF**. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Crit Care Med* 2009; **37**: 1463-1469 [PMID: 19242341 DOI: 10.1097/CCM.0b013e31819ced02]

34 **Nathwani D**, Raman G, Sulham K, Gavaghan M, Menon V. Clinical and economic consequences of hospital-acquired resistant and multidrug-resistant Pseudomonas aeruginosa infections: a systematic review and meta-analysis. *Antimicrob Resist Infect Control* 2014; **3**: 32 [PMID: 25371812 DOI: 10.1186/2047-2994-3-32]

35 **Blot S**, Vandewoude K, De Bacquer D, Colardyn F. Nosocomial bacteremia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. *Clin Infect Dis* 2002; **34**: 1600-1606 [PMID: 12032895 DOI: 10.1086/340616]

36 **Peres-Bota D**, Rodriguez H, Dimopoulos G, DaRos A, Mélot C, Struelens MJ, Vincent JL. Are infections due to resistant pathogens associated with a worse outcome in critically ill patients? *J Infect* 2003; **47**: 307-316 [PMID: 14556755 DOI: 10.1016/S0163-4453(03)00100-2]

37 **Ortega B**, Groeneveld AB, Schultsz C. Endemic multidrug-resistant Pseudomonas aeruginosa in critically ill patients. *Infect Control Hosp Epidemiol* 2004; **25**: 825-831 [PMID: 15518023 DOI: 10.1086/502303]

38 **Combes A**, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J. Impact of piperacillin resistance on the outcome of Pseudomonas ventilator-associated pneumonia. *Intensive Care Med* 2006; **32**: 1970-1978 [PMID: 16957901]

39 **Kwa AL**, Low JG, Lee E, Kurup A, Chee HL, Tam VH. The impact of multidrug resistance on the outcomes of critically ill patients with Gram-negative bacterial pneumonia. *Diagn Microbiol Infect Dis* 2007; **58**: 99-104 [PMID: 17300905 DOI: 10.1016/j.diagmicrobio.2006.11.014]

40 **Daniels TL**, Deppen S, Arbogast PG, Griffin MR, Schaffner W, Talbot TR. Mortality rates associated with multidrug-resistant Acinetobacter baumannii infection in surgical intensive care units. *Infect Control Hosp Epidemiol* 2008; **29**: 1080-1083 [PMID: 18837670 DOI: 10.1086/591456]

41 **Parker CM**, Kutsogiannis J, Muscedere J, Cook D, Dodek P, Day AG, Heyland DK. Ventilator-associated pneumonia caused by multidrug-resistant organisms or Pseudomonas aeruginosa:

prevalence, incidence, risk factors, and outcomes. *J Crit Care* 2008; **23**: 18-26 [PMID: 18359417 DOI: 10.1016/j.jcrc.2008.02.00]

42 **Pinheiro MR**, Lacerda HR, Melo RG, Maciel MA. Pseudomonas aeruginosa infections: factors relating to mortality with emphasis on resistance pattern and antimicrobial treatment. *Braz J Infect Dis* 2008; **12**: 509-515 [PMID: 19287840 DOI: 10.1590/S1413-86702008000600013]

43 **Katsaragakis S**, Markogiannakis H, Samara E, Pachylaki N, Theodoraki EM, Xanthaki A, Toutouza M, Toutouzas KG, Theodorou D. Predictors of mortality of Acinetobacter baumannii infections: A 2-year prospective study in a Greek surgical intensive care unit. *Am J Infect Control* 2010; **38**: 631-635 [PMID: 20471716 DOI: 10.1016/j.ajic.2010.01.009]

44 **Routsi C**, Pratikaki M, Platsouka E, Sotiropoulou C, Nanas S, Markaki V, Vrettou C, Paniara O, Giamarellou H, Roussos C. Carbapenem-resistant versus carbapenem-susceptible Acinetobacter baumannii bacteremia in a Greek intensive care unit: risk factors, clinical features and outcomes. *Infection* 2010; **38**: 173-180 [PMID: 20224962 DOI: 10.1007/s15010-010-0008-1]

45 **Mouloudi E**, Protonotariou E, Zagorianou A, Iosifidis E, Karapanagiotou A, Giasnetsova T, Tsioka A, Roilides E, Sofianou D, Gritsi-Gerogianni N. Bloodstream infections caused by metallo-β-lactamase/Klebsiella pneumoniae carbapenemase-producing K. pneumoniae among intensive care unit patients in Greece: risk factors for infection and impact of type of resistance on outcomes. *Infect Control Hosp Epidemiol* 2010; **31**: 1250-1256 [PMID: 20973725 DOI: 10.1086/657135]

46 **Michalopoulos A**, Falagas ME, Karatza DC, Alexandropoulou P, Papadakis E, Gregorakos L, Chalevelakis G, Pappas G. Epidemiologic, clinical characteristics, and risk factors for adverse outcome in multiresistant gram-negative primary bacteremia of critically ill patients. *Am J Infect Control* 2011; **39**: 396-400 [PMID: 21035919 DOI: 10.1016/j.ajic.2010.06.017]

47 **Lambert ML**, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis* 2011; **11**: 30-38 [PMID: 21126917 DOI: 10.1016/S1473-3099(10)70258-9]

48 **Tabah A**, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, Paiva JA, Cakar N, Ma X, Eggimann P, Antonelli M, Bonten MJ, Csomos A, Krueger WA, Mikstacki A, Lipman J, Depuydt P, Vesin A, Garrouste-Orgeas M, Zahar JR, Blot S, Carlet J, Brun-Buisson C, Martin C, Rello J, Dimopoulos G, Timsit JF. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. *Intensive Care Med* 2012; **38**: 1930-1945 [PMID: 23011531 DOI: 10.1007/s00134-012-2695-9]

49 **Patel SJ**, Oliveira AP, Zhou JJ, Alba L, Furuya EY, Weisenberg SA, Jia H, Clock SA, Kubin CJ, Jenkins SG, Schuetz AN, Behta M, Della-Latta P, Whittier S, Rhee K, Saiman L. Risk factors and outcomes of infections caused by extremely drug-resistant gram-negative bacilli in patients hospitalized in intensive care units. *Am J Infect Control* 2014; **42**: 626-631 [PMID: 24725516 DOI: 10.1016/j.ajic.2014.01.027]

50 **Zilberberg MD**, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care* 2014; **18**: 596 [PMID: 25412897 DOI: 10.1186/s13054-014-0596-8]

51 **Shorr AF**, Zilberberg MD, Micek ST, Kollef MH. Predictors of hospital mortality among septic ICU patients with Acinetobacter spp. bacteremia: a cohort study. *BMC Infect Dis* 2014; **14**: 572 [PMID: 25358621 DOI: 10.1186/s12879-014-0572-6]

52 **Papadimitriou-Olivgeris M**, Marangos M, Christofidou M, Fligou F, Bartzavali C, Panteli ES, Vamvakopoulou S, Filos KS, Anastassiou ED. Risk factors for infection and predictors of mortality among patients with KPC-producing Klebsiella pneumoniae bloodstream infections in the intensive care unit. *Scand J Infect Dis* 2014; **46**: 642-648 [PMID: 25017796 DOI: 10.3109/00365548.2014.923106]

53 **Dabar G**, Harmouche C, Salameh P, Jaber BL, Jamaleddine G, Waked M, Yazbeck P. Community- and healthcare-associated infections in critically ill patients: a multicenter cohort study. *Int J Infect Dis* 2015; **37**: 80-85 [PMID: 26051976 DOI: 10.1016/j.ijid.2015.05.024]

54 **Bass SN**, Bauer SR, Neuner EA, Lam SW. Impact of combination antimicrobial therapy on mortality risk for critically ill patients with carbapenem-resistant bacteremia. *Antimicrob Agents Chemother* 2015; **59**: 3748-3753 [PMID: 25845872 DOI: 10.1128/AAC.00091-15]

55 **Vardakas KZ**, Matthaiou DK, Falagas ME, Antypa E, Koteli A, Antoniadou E. Characteristics, risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in the intensive care unit. *J Infect* 2015; **70**: 592-599 [PMID: 25447713 DOI: 10.1016/j.jinf.2014.11.003]

56 **Martin-Loeches I**, Torres A, Rinaudo M, Terraneo S, de Rosa F, Ramirez P, Diaz E, Fernández-Barat L, Li Bassi GL, Ferrer M. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organisms. *J Infect* 2015; **70**: 213-222 [PMID: 25445887 DOI: 10.1016/j.jinf.2014.10.004]

57 **Cosgrove SE**. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006; **42** Suppl 2: S82-S89 [PMID: 16355321 DOI: 10.1086/499406]

58 **Schwaber MJ**, Carmeli Y. Antimicrobial resistance and patient outcomes: the hazards of adjustment. *Crit Care* 2006; **10**: 164 [PMID: 16982010 DOI: 10.1186/cc5019]

59 **Kaye KS**, Engemann JJ, Mozaffari E, Carmeli Y. Reference group choice and antibiotic resistance outcomes. *Emerg Infect Dis* 2004; **10**: 1125-1128 [PMID: 15207068 DOI: 10.3201/eid1006.020665]

60 **Kang CI**, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW. Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. *Antimicrob Agents Chemother* 2005; **49**: 760-766 [PMID: 15673761 DOI: 10.1128/AAC.49.2.760-766.2005]

61 **Raymond DP**, Pelletier SJ, Crabtree TD, Evans HL, Pruett TL, Sawyer RG. Impact of antibiotic-resistant Gram-negative bacilli infections on outcome in hospitalized patients. *Crit Care Med* 2003; **31**: 1035-1041 [PMID: 12682469 DOI: 10.1097/01.CCM.0000060015.77443.31]

62 **Holmes NE**, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, Anderson TL, Roberts SA, Gao W, Christiansen KJ, Coombs GW, Johnson PD, Howden BP. Antibiotic choice may not explain poorer outcomes in patients with Staphylococcus aureus bacteremia and high vancomycin minimum inhibitory concentrations. *J Infect Dis* 2011; **204**: 340-347 [PMID: 21742831 DOI: 10.1093/infdis/jir270]

63 **Deptuła A**, Gospodarek E. Reduced expression of virulence factors in multidrug-resistant Pseudomonas aeruginosa strains. *Arch Microbiol* 2010; **192**: 79-84 [PMID: 19960337 DOI: 10.1007/s00203-009-0528-1]

64 **Beceiro A**, Tomás M, Bou G. Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? *Clin Microbiol Rev* 2013; **26**: 185-230 [PMID: 23554414 DOI: 10.1128/CMR.00059-12]

65 **Kollef MH**. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 2000; **31** Suppl 4: S131-S138 [PMID: 11017862 DOI: 10.1086/314079]

66 **Giske CG**, Monnet DL, Cars O, Carmeli Y. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. *Antimicrob Agents Chemother* 2008; **52**: 813-821 [PMID: 18070961 DOI: 10.1128/AAC.01169-07]

67 **Daikos GL**, Petrikkos P, Psichogiou M, Kosmidis C, Vryonis E, Skoutelis A, Georgousi K, Tzouvelekis LS, Tassios PT, Bamia C, Petrikkos G. Prospective observational study of the impact of

VIM-1 metallo-beta-lactamase on the outcome of patients with Klebsiella pneumoniae bloodstream infections. *Antimicrob Agents Chemother* 2009; **53**: 1868-1873 [PMID: 19223638 DOI: 10.1128/AAC.00782-08]

68 **Hanberger H**, Antonelli M, Holmbom M, Lipman J, Pickkers P, Leone M, Rello J, Sakr Y, Walther SM, Vanhems P, Vincent JL. Infections, antibiotic treatment and mortality in patients admitted to ICUs in countries considered to have high levels of antibiotic resistance compared to those with low levels. *BMC Infect Dis* 2014; **14**: 513 [PMID: 25245620 DOI: 10.1186/1471-2334-14-513]

P- Reviewer: Inchauspe AA, Merino G, Wang J, Xu ZQ
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.121

World J Crit Care Med 2016 May 4; 5(2): 121-136
ISSN 2220-3141 (online)

REVIEW

Efficacy of prone position in acute respiratory distress syndrome patients: A pathophysiology-based review

Vasilios Koulouras, Georgios Papathanakos, Athanasios Papathanasiou, Georgios Nakos

Vasilios Koulouras, Georgios Papathanakos, Athanasios Papathanasiou, Georgios Nakos, Intensive Care Unit, University Hospital of Ioannina, 45500 Ioannina, Greece

Author contributions: All authors equally contributed to this paper with literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Correspondence to: Vasilios Koulouras, Associate Professor in Intensive Care Medicine, Intensive Care Unit, University Hospital of Ioannina, Stavros Niarchos Avenue, 45500 Ioannina, Greece. vpkoulouras@yahoo.gr
Telephone: +30-26-51099353
Fax: +30-26-51099343

Received: November 28, 2015
Peer-review started: November 30, 2015
First decision: December 28, 2015
Revised: January 11, 2016
Accepted: March 7, 2016
Article in press: March 9, 2016
Published online: May 4, 2016

Abstract

Acute respiratory distress syndrome (ARDS) is a syndrome with heterogeneous underlying pathological processes. It represents a common clinical problem in intensive care unit patients and it is characterized by high mortality. The mainstay of treatment for ARDS is lung protective ventilation with low tidal volumes and positive end-expiratory pressure sufficient for alveolar recruitment. Prone positioning is a supplementary strategy available in managing patients with ARDS. It was first described 40 years ago and it proves to be in alignment with two major ARDS pathophysiological lung models; the "sponge lung" - and the "shape matching" -model. Current evidence strongly supports that prone positioning has beneficial effects on gas exchange, respiratory mechanics, lung protection and hemodynamics as it redistributes transpulmonary pressure, stress and strain throughout the lung and unloads the right ventricle. The factors that individually influence the time course of alveolar recruitment and the improvement in oxygenation during prone positioning have not been well characterized. Although patients' response to prone positioning is quite variable and hard to predict, large randomized trials and recent meta-analyses show that prone position in conjunction with a lung-protective strategy, when performed early and in sufficient duration, may improve survival in patients with ARDS. This pathophysiology-based review and recent clinical evidence strongly support the use of prone positioning in the early management of severe ARDS systematically and not as a rescue maneuver or a last-ditch effort.

Key words: Prone position; Acute respiratory distress syndrome; Mechanical ventilation; Ventilator-induced lung injury; Pathophysiology

Core tip: Lung protective ventilation has become the standard treatment strategy for patients with acute respiratory distress syndrome (ARDS). The physiological basis of prone positioning seems to act beneficially in most pathophysiological disorders of ARDS improving hemodynamics, gas exchange and respiratory mechanics. Moreover prone positioning seems to exert an additional beneficial effect against ventilator-induced lung injury. In patients with severe ARDS, early use of

prolonged prone positioning in conjunction with lung-protective strategies decreases mortality significantly.

Koulouras V, Papathanakos G, Papathanasiou A, Nakos G. Efficacy of prone position in acute respiratory distress syndrome patients: A pathophysiology-based review. *World J Crit Care Med* 2016; 5(2): 121-136 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/121.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.121

INTRODUCTION

The adult respiratory distress syndrome was first described during Vietnam War in 1960s as a new distinctive clinical entity of hypoxemic respiratory failure affecting both lungs. This term was later modified to acute respiratory distress syndrome (ARDS) characterized by a diffuse inflammatory condition of the lungs, decreased respiratory system compliance, bilateral pulmonary infiltrates and rapid onset of hypoxemic respiratory failure following a variety of lung insults.

ARDS is a clinical syndrome with heterogeneous underlying pathological processes; it can arise from direct (pulmonary) injury to the lung parenchyma or from indirect (extrapulmonary) systemic insults transmitted by circulation. Regardless of the underlying insult, the development of diffuse alveolar damage involves neutrophil activation and endothelial injury, leading to noncardiogenic pulmonary edema and atelectasis.

In 1994, the American and European Consensus Conference (AECC) established specific criteria for acute lung injury (ALI) and ARDS, with ARDS being the most severe form of the syndrome[1,2]. These criteria included acute onset, bilateral lung infiltrates on chest radiograph, no evidence of elevated left atrial pressure and severe hypoxaemia, assessed by the arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2) ratio. According to these guidelines, ARDS existed when the PaO_2/FiO_2 ratio was $\leqslant$ 200 mmHg and ALI when the PaO_2/FiO_2 ratio was $\leqslant$ 300 mmHg. The AECC definition for ARDS remained the basis for enrollment in most of the landmark trials over the past 20 years.

Based on the limitations of diagnostic reliability and stratification of patients with ARDS/ALI according to severity by AECC criteria, the European Society of Intensive Care Medicine proposed the Berlin ARDS definition in 2011 (Table 1). This new "Berlin" definition is not substantially different from the old, but defines the criteria more specifically including timing, chest imaging, origin of edema and oxygenation, and classifies the severity of disease on the basis of the degree of hypoxemia and positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP)[3].

ARDS represents a common clinical problem in intensive care unit patients[4]. It has a varying incidence from 5-7.2 in Europe to 33.8 new cases/100000 population/year in the United States (150000-200000 cases/year)[5-7]. In the ICU setting, 7%-10% of admitted patients and 5%-8% of the mechanically ventilated ones meet criteria for ALI/ARDS[8]. After continued progress in understanding ARDS pathophysiology and the application of lung protective ventilation, mortality rate significantly decreased from a rate of 65%-70% in the early 1980s to 35%-40% to date in RCTs and consistently higher in real word observational studies[7,9,10].

ARDS APPROACH: PROTECTIVE LUNG VENTILATION

The majority of patients with ARDS will require mechanical ventilation. The goals of mechanical ventilation for ARDS patients are to minimize iatrogenic lung injury [ventilator-induced lung injury (VILI)] while providing acceptable oxygenation and carbon dioxide (CO_2) clearance.

Numerous studies provided clear evidence of large mortality benefit when patients with ARDS were ventilated with a lung-protective strategy: Avoidance of alveolar overdistention using tidal volumes of 6 mL/kg predicted body weight, with plateau pressures $\leqslant$ 30 cmH_2O, and allowing a low pH in order to achieve these targets[11,12].

A major and controversial aspect of mechanical ventilation regards PEEP; the appropriate levels of PEEP and proper method of titration remain controversial[13-17]. Some authors recommend the lowest level (5-10 cm H_2O) of PEEP to be used to support oxygenation and maintain FiO_2 at or below 0.6. A recent meta-analysis, which included data from ALVEOLI, LOVS, and EXPRESS clinical trials, revealed that higher levels of PEEP were associated with improved survival and oxygenation among patients with moderate to severe ARDS[18,19].

ARDS AND PRONE POSITIONING

Conceptually, prone position may result to a more uniform distribution of lung stress and strain, leading to improved ventilation-perfusion matching and regional improvement in lung and chest wall mechanics. Prior clinical trials showed that prone positioning improves oxygenation in patients with ARDS, without benefits in terms of survival[20-22]. A recent multicenter prospective controlled trial (the PROSEVA study) showed that prone positioning decreased 28-d and 90-d mortality, increased ventilator-free days and decreased time to extubation[23]. Based on these data, ventilation in the prone position is recommended for the first week in moderate to severe ARDS patients.

Other adjunctive strategies used in the ARDS setting include recruitment maneuvers, conservative fluid strategy[24], neuromuscular blocking agents[25], extracorporeal membrane oxygenation, high-frequency ventilation[26,27], corticosteroids[28], and inhaled pharma-

Table 1 The Berlin definition of the acute respiratory distress syndrome

Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[1]	Bilateral opacities - not fully explained by effusions, lobar/lung collage, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure of fluid overload. Need objective assessment (*e.g.*, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[2]	
Mild	200 mmHg < PaO_2/FiO_2 ⩽ 300 mmHg with PEEP or CPAP ⩾ 5 cmH_2O[3]
Moderate	100 mmHg < PaO_2/FiO_2 ⩽ 200 mmHg with PEEP or CPAP ⩾ 5 cmH_2O
Severe	PaO_2/FiO_2 ⩽ 100 mmHg with PEEP or CPAP ⩾ 5 cmH_2O

[1]Chest radiograph or computed tomography scan; [2]If attitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)]. [3]This may be delivered noninvasively in the mild acute respiratory distress syndrome group. CPAP: Continuous positive airway pressure; FiO_2: Fraction of inspired oxygen; PaO_2: Partial pressure of arterial oxygen; PEEP: Positive-end expiratory pressure.

cologic agents.

In this review article, we describe the ARDS pathophysiological models supporting the prone position, we highlight the physiological and lung protective effects of prone positioning and we review the most recent clinical trials on prone position in ARDS patients.

HISTORICAL BACKGROUND OF PRONE POSITION

The possible benefits of prone positioning were first speculated in 1974 from studies on the effects of sedation and paralysis on the diaphragm. Bryan *et al*[29] suggested that anaesthetized and paralyzed patients in the prone position should exhibit a better expansion of the dependent (dorsal) lung regions with consistent improvement in oxygenation, indicating prone's potential beneficial impact on lung mechanics. Two years later, Piehl *et al*[30] reported dramatic effects on oxygenation improvement by prone position in five patients with ARDS and in the following year Douglas *et al*[31] reported similar findings in six ARDS patients, confirming that prone positioning could effectively improve oxygenation in this patient group. Although the first reports were very promising, the following years the clinical application of prone positioning in ARDS patients was not very popular. Not until 1986, when Maunder *et al*[32] with their chest computed tomography scans study challenged the previously commonly held assumption that ARDS is a homogeneous process (as usually shown by anteroposterior radiography), associated with generalized and relatively uniform damage to the alveolar capillary membrane. The same year Gattinoni *et al*[33] demonstrated that in ARDS, affected areas primarily occur in the dependent portion of the lung parenchyma. This was soon accompanied by the finding that in ARDS, respiratory compliance is also well correlated with the amount of normally aerated (nondependent) tissue and not with the amount of nonaerated (dependent) tissue[34]. ARDS lung is not stiff but "small" ("baby lung"), and the elasticity of the residual inflated lung is nearly normal. At first physicians, believed that "baby lung" was something well defined, constant and anatomically confined in the ventral (nondependent) regions of the lungs. They turned ARDS patients to the prone position, trying to redistribute the blood flow from the posterior unventilated lung to the previously nondependent baby lung, in order to improve lung's perfusion, to minimize the resulted shunt and to improve the oxygenation[35,36]. Although the physiologic mechanisms leading to improved oxygenation during prone positioning proved to be different as first suggested, and the redistribution concerned the alveolar gas more, the interest in prone positioning remained strong and prone position proved to be beneficial for both oxygenation and outcome of ARDS patients.

ARDS PATHOPHYSIOLOGICAL LUNG MODELS SUPPORTING THE PRONE POSITION

From 1988 to 1991 computerized tomograms of ARDS patients being in the prone position revealed an unexpected finding: The disappearance of the posterobasal densities after prone positioning and their redistribution to the new dependent lung regions[37,38]. This finding changed the concept of "baby lung" from an anatomically confined- to a functional entity, and led to the development of an early pathophysiological model known as "sponge lung" model[35,39].

When someone removes a sponge from the water and holds it flat, the water drains from it and then slows to a stop. If the sponge is turned from horizontal to vertical position, the drainage begins again and then slows again to a stop. As it slows, the sponge is not equally wet from top to bottom, with the top having more empty pores than the bottom. This is pretty much what the "sponge lung" model in ARDS patients suggested: Edema increases the lung weight and squeezes the gas out of the dependent lung regions producing alveolar collapse and increasing the CT densities in dependent regions (compression atelectasis)[40,41]; the size of open airway and the amount of gas decr-

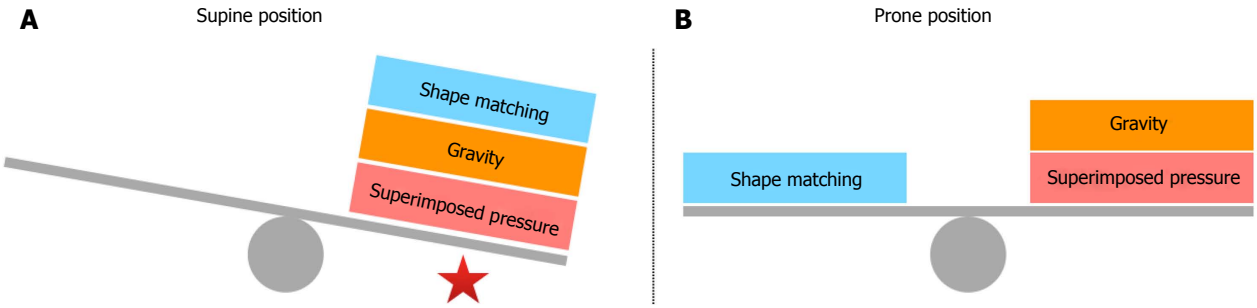


Figure 1 Relationship between gravity, superimposed pressure and shape matching. A: In supine position gravity, superimposed pressure, and shape matching act to the same detrimental direction; B: In prone position, shape matching counterbalances gravity and superimposed pressure allowing a more homogeneous inflation of the dependent lung areas.

eases along the vertical axis. Although in ARDS the edema has a nongravitational distribution and is quite homogeneously distributed throughout the lung parenchyma[40,42], the "sponge lung" model provided, at that time, a satisfying explanation for three different things. Firstly, how the increased lung mass in ARDS patients due to edema and the increased superimposed pressure, including the heart weight squeeze out the gas of the gravity-dependent lung regions leading to loss of lung aeration[35]. Secondly, why the lung densities shift from dorsal to ventral regions during prone position in ARDS lung[37,43]: The superimposed hydrostatic pressure is reversed and the ventral regions, as the result of the gravitational forces, are newly compressed (this can happen within minutes). And thirdly, "sponge lung" model explained the mechanism through which PEEP acts as a counterforce to oppose the collapsing, compressing forces: PEEP greater than the superimposed pressure keeps the most dependent lung regions open[36,41].

Some years later the "sponge lung" model and the opinion that in ARDS patients the lung edema causes the lung to collapse under its own weight in dependent regions was challenged as a hypothesis by some authors[44,45] and a new supplementary hypothesis was proposed. In ARDS patients in supine position, the dependent areas of the lung collapse not only due to edema and the increased superimposed pressure but also due to the different shape existing between the lung and the chest wall and the resulted nonhomogeneous expansion of alveolar units. The isolated lung normally has a conical shape with the dependent side being bigger than the nondependent side (in supine position). On the other hand, the chest wall has a cylindrical shape and the problem proves to be a shape-matching problem (the fitting of an elastic cone into a rigid cylinder). Because the two structures have the same volume, the lung must expand its upper regions more than the lower ones and this condition results to a greater expansion of the nondependent alveolar units or otherwise to a lesser expansion of the dependent ones[46]. In ARDS patients who are in supine position, the gravitational forces, the increased superimposed pressure, and the shape matching of the lung into the chest cavity act to the same direction having a detrimental effect on dependent alveolar units. On the contrary, in ARDS patients, who are turned in the prone position, shape matching counterbalances gravity and superimposed pressure allowing a more homogeneous inflation of the dependent lung areas (Figure 1). In addition, prone position eliminates compression of the lungs by the heart[47,48] and relieves the dependent lung area from the abdominal pressure[45,49].

The "shape matching" model enlightens two aspects of prone positioning. If lungs would not have a conical shape and were just symmetrical, the degree of shunt and hypoxia would not vary between supine and prone position if perfusion would remain the same. After the rotation of the patient to the prone position the shunt lessens and the oxygenation improves because the recruitment of the dorsal areas overcomes the de-recruitment of the ventral regions due to "shape matching"[44]. Secondly this model takes into account an inherent nonuniform alveolar stress that is not gravitationally determined and explains in part why the application of prone positioning diminishes alveolar hyperinflation and protects the lungs from high shearing forces and eventually from ventilator induced lung injury (VILI)[50].

PHYSIOLOGICAL EFFECTS OF PRONE POSITIONING

Effects of prone position on gas exchange

Oxygenation: It is well known that there is normally a regional difference in intrapleural pressure, being more subatmospheric at the apex and at the nondependent lung areas. This is clearly a gravity dependent phenomenon and results in exponentially regional differences in transpulmonary pressure and thus in the size of alveoli; the transpulmonary pressure, *i.e.,* the distending forces of the lung, decreases along the ventral-to-dorsal axis and the size of the alveolar units decreases toward the dependent areas.

It was found that by turning the patient to the prone position due to thoracic-lung shape modifications the intrapleural pressure becomes less negative in non-

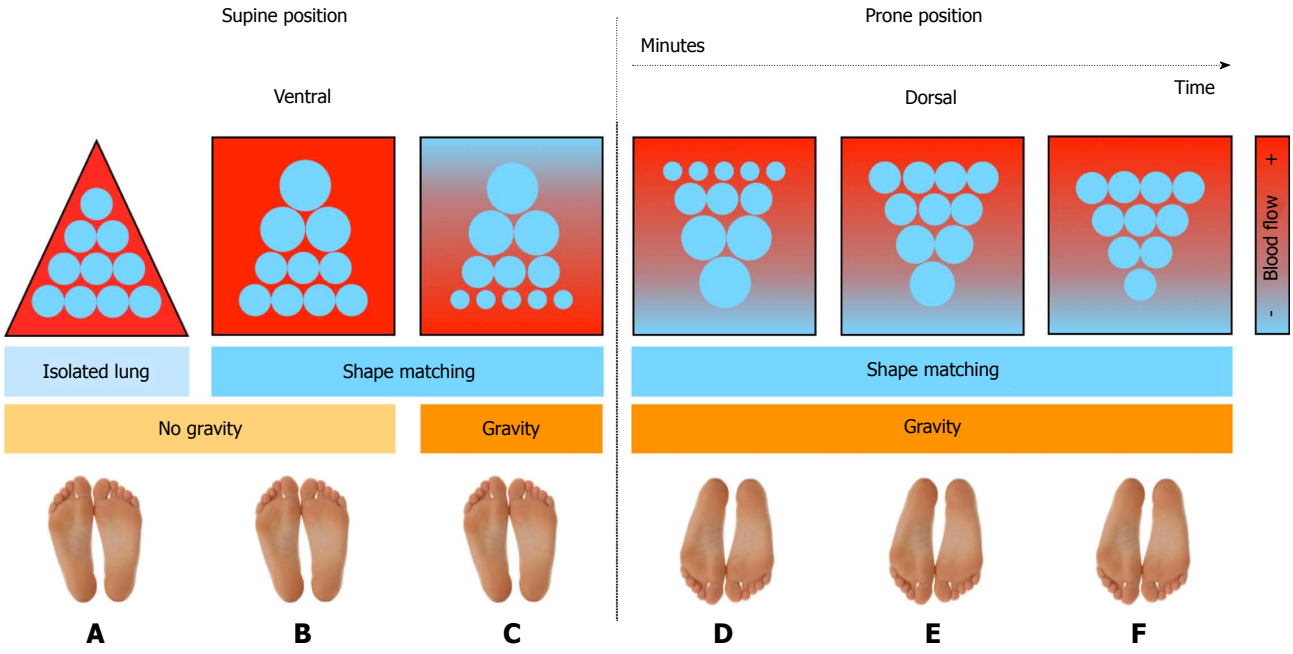


Figure 2 A summary showing the sequential effects of prone position on acute respiratory distress syndrome diseased lung. A: Original shape of the isolated lung; the dorsal side is bigger than the ventral one (no gravity); B: The result of shape matching: alveolar units have bigger size ventrally and smaller size dorsally (no gravity); C: The additive effect of gravity on ventilation and perfusion: blood flow is being diverted toward dependent regions, while dependent pulmonary units close; D: Immediately after turning to the prone position, pulmonary blood flow in dorsal regions of the lung is maintained unmodified; E: Dorsal lung recruitment follows (greater than ventral de-recruitment), gravitational forces compress the ventral region, but this effect is damped by regional expansion due to shape matching; F: Transpulmonary pressure and regional inflation distribution become more homogeneous throughout the lung resulting finally to better oxygenation.

dependent and less positive in dependent regions[51,52]. The net effect of prone positioning is not only the increase of regional inflation distribution in dorsal regions and decrease in ventral regions respectively, but intrapleural pressure, transpulmonary pressure and regional inflation distribution become more homogeneous throughout the lung (Figure 2)[53]. It was early suggested that this could be explained by the reversal of lung weight gradients, the direct transmission of the weight of the heart to subjacent regions, direct transmission of the weight of abdominal contents to caudal regions of the dorsal lung and/or regional mechanical properties and shape of the chest wall and lung[54].

In addition, although in healthy lung pulmonary perfusion is distributed along a ventral-dorsal gradient and progressively increases down the lung, data suggest that in the diseased lung, blood flow is being diverted toward the nondependent regions. This is caused by several mechanisms including hypoxic vasoconstriction, vessel obliteration and extrinsic vessel compression[55-57]. Also, human and animal studies have shown that in the conversion from the supine to prone ventilation, pulmonary blood flow in dorsal regions of the lung is maintained unmodified and prevalent in lung dorsal areas (Figure 2)[46,53,58-63]. Besides, in patients with ARDS, the increased lung weight due to serious inflammation and pulmonary edema would act also as hypergravity to squeeze the blood flow as well as ventilation out of the dependent area to the nondependent region[16,64]. Thus, the reduction in intrapulmonary shunt and the increase in oxygenation observed in patients with ARDS who are turned in the prone position mainly results from better ventilated well-perfused lung areas with dorsal recruitment being in parallel greater than ventral de-recruitment (Figure 2)[36,51,53]. Animal data had early suggested that during prone position homogeneity of ventilation increases V/Q as well as the correlation between regional ventilation and perfusion[65]. Very important is the finding that prone position, when combined, is followed by an improved and/or a more sustained response to recruiting maneuvers[50,66-68].

Albert *et al*[47] in their study determined the fraction of lung that might be subjected to the weight of the heart when patients are in the supine *vs* the prone position. The study included only non-ARDS patients, but it was found that turning patients to the prone position eliminates the compressive force of the heart on dorsal lung regions redirecting it to only a small portion of the ventral lung regions (Figure 3). This is in agreement with the results of previous studies. In a study conducted by our group it was shown that ARDS patients with congestive heart failure and cardiomegaly after being turned to the prone positioning exhibited a significant, rapid, and persistent improvement in oxygenation. This improvement could be partly due to the decompression of the left lower lobe by the enlarged heart[69]. Wiener *et al*[70] had early found that patients with cardiomegaly exhibited reduced left mid- and lower zone ventilation in the supine but not in the prone position.

Figure 3 Prone positioning allows the heart to lay on the sternum and the compressive force of the heart on dorsal lung regions to be eliminated.

It is worth to mention that the interaction between PEEP and posture on regional distribution of ventilation was recently examined in anesthetized human volunteers. It was found that after the addition of PEEP in the prone position there is a much greater redistribution to ventral areas for blood flow than for ventilation, causing increased V/Q mismatch. In the study of Petersson *et al*[71], without PEEP, the vertical ventilation-to-perfusion gradient was less in prone postures than in supine, but with PEEP, the gradient was similar. Although this finding supports prior studies, which have shown that lower PEEP is needed to maintain oxygenation in the prone posture than in the supine[66,72], reductions of PEEP are inappropriate, at least when V/Q matching and systemic oxygenation are being evaluated[73,74].

CO_2 clearance: During the course of ARDS the CO_2 clearance is becoming impaired due to structural changes of the lung[75-77] and the increase in dead space proves to be a prognostic marker of ARDS mortality[78]. Interestingly, turning the ARDS patient to prone position does not always result in decrease in arterial CO_2 because the presence of aerated alveoli doesn't necessarily mean that they are also well ventilated. In fact, it has been suggested that oxygen and carbon dioxide responses to prone position are independent and a decrease in $PaCO_2$ to the first pronation rather than an increase in PaO_2/FiO_2, is significantly associated with lung recruitability and a better outcome[79,80].

It has been proposed that in $PaCO_2$ nonresponders, the primary mechanism of the PaO_2 increase is diversion of the blood flow, whereas in $PaCO_2$ responders the primary mechanism is greater dorsal recruitment in comparison to ventral derecruitment, combined with reduced alveolar overinflation[46,79]. The $PaCO_2$ responders seem to have a higher potential to be recruited with prone positioning than with nonresponders, revealing a difference in underlying lung pathologies[81]. It has also been suggested that when PaO_2 increases and $PaCO_2$ does not simultaneously decrease, it is a sign that either cardiac output is lowered or alveolar dead space ventilation is increased by PEEP, reflecting lung overdistention[63].

EFFECTS OF PRONE POSITION ON RESPIRATORY MECHANICS

Total respiratory system mechanics in general are not modified during prone position and it has been shown that respiratory mechanics improve after returning to supine position, suggesting the potential beneficial structural effects of prone positioning[20,54]. Although chest wall compliance decreases[20,40] prone position does not affect total respiratory system compliance[54]. The only exception may be patients with secondary ARDS (nonpulmonary insult), who have shown an increase in respiratory system compliance[22,82,83].

EFFECTS OF PRONE POSITION ON STRESS/STRAIN AND VILI

Low tidal volume ventilation[11], high PEEP and recruitment maneuvers are commonly used in the ARDS setting as protective ventilation strategies to minimize lung overdistention and ventilation heterogeneity, but ventilation at low tidal volumes can also cause injury through repetitive opening and closing of the small airways and lung units[84,85], effects on surfactant function[86], and regional hypoxia[87]. Stress is the tension developed in the lungs' fibrous skeleton when a distending force is applied, and strain is the volume increase caused by the applied force relative to the resting volume of the lungs[88]. The clinical equivalent of stress is transpulmonary pressure (airway pressure minus pleural pressure) and the clinical equivalent of strain is the ratio of volume change (ΔV) to the functional residual capacity (FRC), which is the resting lung volume[89]. Under mechanical ventilation with PEEP, lung strain may be calculated as: Strain = (V_T + PEEP volume)/FRC, and stress and strain are linked by the formula: Stress = k x strain, where k is the lung-specific elastance (approximately equal 13 cmH_2O in either healthy or acutely injured lungs)[89-91].

As already mentioned, prone positioning results to a more homogeneous distribution of transpulmonary pressure and regional inflation throughout the lung. By favoring such a homogenization, turning ARDS patients to prone position could help eliminate lung overdistention, which proves to be the main component of VILI (volutrauma). In the prone position, air is distributed more homogeneously throughout the lungs, and stress and strain are decreased. Indeed, there are several levels of evidence supporting the preventive effect of prone position on VILI. Animal studies suggest that prone positioning decreases or delays the progression of VILI[92-95], while human studies have confirmed the relevant beneficial effect of prone positioning in the ARDS setting. In a study conducted by our group, Galiatsou *et al*[50] compared lung CT scans in ARDS patients in supine and prone position and found that prone position is associated with significant alveolar recruitment and less hyperinflation compared to the supine position; this process was more prevalent in lobar than in diffuse ARDS patients. This finding was confirmed and even more extended in the study by Cornejo *et al*[96]; the authors concluded that prone positioning enchases lung recruitment and decreases tidal hyperinflation, even in those ARDS patients classified as having low potential for lung recruitment. The same study also suggested that prone positioning decreases alveolar instability and cyclic alveolar recruitment/derecruitment. This proves to be particularly important, as intra-airway shear forces due to cyclical airspace opening and closing of airway and pulmonary units result to injury of airway epithelial cells (atelectrauma), which is the second component of VILI pathogenesis[90].

Another component of VILI is biotrauma (lung inflammation). It follows the application of unphysiological mechanical forces to lung tissue, the release of proinflammatory cytokines and the recruitment of white cells; it can lead to multi-organ failure[88,97]. Papazian *et al*[98] compared neutrophil counts and interleukin-8 levels in the bronchoalveolar lavage fluid of ARDS patients being in the supine and in the prone position and found that prone position reduced lung inflammation in ARDS patients. In an experimental study conducted by our group, we examined whether the prone position of the patients affects histological changes and apoptosis in the lung and "end organs", including the brain, heart, diaphragm, liver, kidneys and small intestine. We found that prone position appears to reduce the severity and the extent of lung injury, and is associated with decreased apoptosis in the lung and "end organs"[99]. It is also known that mechanical ventilation induces heterogeneous lung injury by mitogen-activated protein kinase (MAPK). Park *et al*[100] in their experimental study on rodent lungs exposed to injurious ventilation found that the prone positioning has a protective lung effect by increasing the expression of MAPK-phosphatase 1, while the supine position has an opposite effect.

The prone positioning has extra protective lung effects: It improves the mobilization and postural drainage of secretions from the posterior lung segments[54,101-103], and it has been shown to reduce the risk of ventilator-associated pneumonia (VAP)[76,104-108]. Finally, by enchasing oxygenation, proning reduces the need of sustaining high toxic levels of inspired oxygen[109].

EFFECTS OF PRONE POSITION ON HEMODYNAMICS AND HEMODYNAMIC MONITORING

Vieillard-Baron *et al*[110] investigated the short-term effects of prone positioning on right ventricular function in patients with severe ARDS and it was found that proning unloads the right ventricle by decreasing right ventricular enlargement and mean septal dyskinesia. Recently, Jozwiack *et al*[111] confirmed the beneficial hemodynamic effects of prone positioning in patients with ARDS as it was shown that prone positioning increases cardiac preload, reduces right ventricular afterload and increases left ventricular preload; this resulted to increased cardiac index only in patients with preload reserve. During the prone positioning, pulmonary arterial occlusion pressure is also increased and the transpulmonary pressure gradient (the difference of mean pulmonary arterial pressure relative to pulmonary artery occlusion pressure) is reduced[111]. Elevated transpulmonary pressure gradient defines pulmonary vascular dysfunction and is independently related to increased ARDS mortality[51,112,113]. Besides, the increased pulmonary arterial occlusion pressure transfers some lung regions from West zone 2 to zone 3, thus having the potential to decrease dead space ventilation, another factor independently related to ARDS mortality[51,78,111]. Prone positioning serves both the lung and the "right ventricle protective approach" of mechanical ventilation[112].

Brücken *et al*[114] investigated the influence of prone positioning on the measurement of transpulmonary thermodilution-derived variables in ARDS patients and found that although extravascular lung water index (EVLWI) and global end-diastolic volume index measurements are possibly influenced by prone positioning, the differences are minor and presumably of no clinical relevance. The positive effect of prone positioning on EVLWI was demonstrated by McAuley *et al*[115], where an initial transient increase was followed by a statistically significant decrease on EVLWI.

Grensenmann *et al*[116] investigated the influence of modified prone positioning (135°) on the accuracy of pulse contour-derived calibrated cardiac index and uncalibrated cardiac index in ARDS patient with transpulmonary thermodilution as reference technique. They found that the prone positioning only marginally influences calibrated pulse contour-derived cardiac index measurements, while uncalibrated pulse contour analysis showed a degree of error higher than considered

acceptable[116].

CLINICAL RESPONSE TO PRONE POSITIONING

Although prone positioning in ARDS setting is generally associated with increased arterial oxygenation, the truth is that patients' response is quite variable and hard to predict. There are few patients, who after being turned to the prone position show no improvement at all or even a deterioration.

According to arterial blood gas changes after their proning, ARDS patients can be classified as "responders" or not "responders"; "PaO_2 responders" are those whose PaO_2/FiO_2 ratio increases by at least 20% or by $\geqslant$ 20 mmHg, whereas $PaCO_2$ responders are those whose $PaCO_2$ decreases by $\geqslant$ 1 mmHg. These are the thresholds most selected in previous studies[69,79,102,117-121]. Expected $PaCO_2$ changes are relatively smaller than PaO_2 changes because of the different slopes of the content/tension relationship.

ARDS responders can also be classified as "persistent" or "not persistent" based upon whether arterial oxygenation is partially maintained or not respectively when they are turned supine again[37,102]. These patients may exhibit one of three different responses: (1) Display an improved oxygenation compared to prone positioning; (2) maintain a good oxygenation compared to how they were before prone positioning, but not so good as during prone (the majority of the patients); and (3) display a deterioration and return to basal supine oxygenation. The last patients are also called "prone dependent"[122]. When a patient is turned to the prone position repeatedly or the prone position is prolonged, the effect of prone positioning may change with time and be highly variable (during prone position the patient can unpredictably display either improvement or deterioration in oxygenation).

Unfortunately, the factors that influence the time course of alveolar recruitment and the improvement in oxygenation during prone positioning have not been well characterized. These may include the stage of ARDS (early *vs* late), the cause (pulmonary *vs* extrapulmonary), the radiologic pattern (patchy *vs* diffuse), the severity of hypoxia, the size of initial intrapulmonary shunt, and the patient's body habitus[22,123-129]. Morphological characteristics from CT scans have also failed to predict the response to prone positioning[130]. Although patient's response remains still unpredictable, a trial of prone positioning should be performed in all suitable candidates.

Our group has examined the effect of prone positioning in patients with persistent hypoxemia having either hydrostatic pulmonary edema (HPE), ARDS or pulmonary fibrosis[69]. All patients with HPE and 75% of patients with ARDS exhibited improvement of oxygenation when positioned prone. In contrast none of the patients with pulmonary fibrosis responded favorably to prone positioning. We have also found that patients with HPE and early ARDS responded better to prone positioning than patients with late ARDS and pulmonary fibrosis did. This suggests that prone positioning should be applied as early as possible after the onset of the disease when edema, lung recruitability, and absence of structural alterations of the lung are most represented[22,69].

EFFECT OF PRONE POSITIONING ON CLINICAL OUTCOME - MORTALITY

Prone positioning in ARDS patients with refractory hypoxemia has been studied for over three decades and more than 300 articles can be found in PUBMED under the terms "prone position" and "ARDS". In recent years, several clinical studies have evaluated the safety and efficacy of prone positioning in mechanically ventilated patients with ARDS, but only few were randomized and enrolled an adequate number of patients[23,73,75,76,131]. Former studies on prone positioning had several limitations. Small sample size, initiation of positioning, length of time and type of proning, and the absence of use of lung protective ventilation in conjunction with proning were identified as limitations.

Gattinoni *et al*[75] studied 304 patients with ARDS and PaO_2/FiO_2 ratio less than 200 mmHg as an inclusion criterion. Patients were randomized in conventional treatment (in the supine position) and predefined strategy of placing patients in a prone position for six or more hours daily for 10 d. Although prone positioning improved oxygenation of patients, the relative risk of death did not significantly differ between the two study groups: In the prone group as compared with the supine group the relative risk was 0.84 at the end of the study period (95%CI: 0.56 to 1.27), 1.05 at the time of discharge from the intensive care unit (95%CI: 0.84 to 1.32), and 1.06 at six months (95%CI: 0.88 to 1.28). A significant limitation of this study was that no lung protective ventilation protocol was used[75].

Guerin *et al*[76] included 802 patients with acute respiratory failure and PaO_2/FiO_2 ratio less than 300 mmHg in a prospective, unblinded, multicenter controlled trial. Patients were randomly assigned to prone positioning, that was applied as early as possible for at least 8 h/d, or to supine positioning. In this study, prone positioning improved oxygenation and reduced the risk of VAP, but no significant difference between the two study groups was evident in regard to mortality. A lung protective ventilation protocol was not used in this study as well[76].

Mancebo *et al*[132] enrolled 136 patients with severe ARDS (mean PaO_2/FiO_2 ratio 105 mmHg) and randomized them to prone or supine positioning. In this study, the duration of prone was significantly higher in comparison to the previously mentioned trials. In particular, the prone group was targeted to receive continuous prone ventilation treatment for 20 h/d contin-

uously until the patients were ready for weaning from mechanical ventilation. In addition, a lung protective ventilation protocol was used. According to the results of this trial, prone positioning followed a trend for reduced ICU mortality although the difference was not statistically significant[132].

In The Prone-Supine Ⅱ study, a multicenter, unblinded, randomized controlled trial, Taccone *et al*[73] assigned 342 adult patients with ARDS, receiving mechanical ventilation, with a lung protective protocol, to undergo either supine or prone (for 20 h/d) positioning during ventilation. In this study, the long duration of prone positioning failed to demonstrate any benefit on survival in all study patients[73].

The only study to date that showed that prone positioning improves mortality in ARDS patients is the Proning Severe ARDS Patients (PROSEVA) study[23]. The PROSEVA study is a randomized controlled trial designed to determine whether prone-position ventilation, applied early, would improve the outcome in patients with severe ARDS. In this study, 466 patients with severe ARDS (defined as a PaO_2/FiO_2 ratio < 150 mmHg) underwent either at least 16 h of prone positioning or were left in the supine position after 12 to 24 h of initial conventional mechanical ventilation. The primary outcome that was investigated was the rate of death at 28 d. The unadjusted 28-d mortality rate was 16.0% in the prone group compared with 32.8% in the supine group ($P < 0.001$)[23]. The distinctively different findings in the PROSEVA study can be attributed to several factors. According to the investigators, the improvement in the outcome found in this study compared to the previous ones was related to the shorter period of enrollment (less than 24 h since ARDS criteria were confirmed), the longer prone-positioning sessions used (the prone position was applied for 73% of the time ascribed to the intervention and was concentrated over a period of a few days) and the lung protective mechanical ventilation protocol than was applied[23].

The findings of the PROSEVA study are in accordance with the conclusions of recent meta-analyses including trials where prone positioning sessions and days of treatment were prolonged together with the use of lung protective ventilation protocol, with or without similar PEEP between the two strategies[12,133-135]. All these meta-analyses showed an overall survival benefit of prone positioning[133,134,136-138]. The benefit on survival in these meta-analyses was mainly evident when prolonged sessions of prone positioning were initiated in combination with small tidal volumes in patients with severe hypoxemia[133,134,136-139]. Finally, in the most recent Cochrane review, Bloomfield *et al*[140] included a total of nine randomized clinical trials. In this meta-analysis, there was no convincing evidence of benefit nor harm from universal application of prone positioning in adults ARDS patients mechanically ventilated in intensive care units[140]. However, in the same review, in three subgroups, early implementation, prolonged adoption of prone positioning and severe hypoxemia at study entry, prone positioning may confer a statistically significant mortality advantage[140]. The basic characteristics of these meta-analyses are shown in Table 2.

Clinicians intending to use prone positioning therapy face the question of optimal duration of prone positioning sessions, which still remains controversial. Early studies were characterized by short prone positioning session of no more than 10 h, ranging between 1-10 h in the majority of the patients[75,76,134]. Later studies used prolonged session of prone positioning, usually more than 12 h[23,72-75,137,139] showing better results on mortality or morbidity but the majority of them did not achieve statistical significance. In their meta-analysis, Beitler *et al*[134] stratified analysis by high (≥ 12 h/d) or low (< 12 h/d) proning dose and demonstrated a significant reduction in mortality with high doses (RR = 0.71; 95%CI: 0.56-0.90; $P = 0.004$) but not low doses (RR = 1.05; 95%CI: 0.92-1.19; $P = 0.472$)[134]. Lee *et al*[137] showed a negative trend for overall mortality when the actual duration of prone positioning was longer, but the effect of the duration of prone positioning on mortality did not achieve statistical significance (RC = -0.037; 95%CI: -0.089 to 0.013; $P = 0.130$)[137].

Thus, although data regarding optimal exact duration of prone positioning is far from being sufficient, it seems that periods of more than 12 h of prone positioning are needed in order to improve outcome. According to our experience and the findings of the PROSEVA study, prolonged duration of proning even more than 24-36 h, or a protocol of short period (*i.e.,* 1-2 h) of supine positioning for daily nursing care between 24-h prone sessions for 3-5 d are safe and seems to improve outcome in patients with severe ARDS under lung protective mechanical ventilation (unpublished preliminary data).

In summary, despite former small non-randomized observational studies not showing any beneficial outcome in regard to prone position in ARDS patients, newer large randomized trials and recent meta-analyses show that prone position, when performed early and in sufficient duration, may improve survival in patients with severe hypoxemia and in patients ventilated with a restrict lung protective ventilation protocol characterized by small tidal volumes.

CONTRAINDICATIONS AND COMPLICATIONS OF PRONE POSITIONING

There are only few absolute contraindications to prone positioning, such as unstable vertebral fractures and unmonitored or significantly increased intracranial pressure. Hemodynamic and cardiac rhythm disturbances are strong relative contraindications, since immediate access for cardiopulmonary resuscitation is limited. Except for conditions that would make proning impractical (*e.g.,* the presence of external fixators), for other relative contraindications (Table 3) one should take into account the team expertise, and potential complications

Table 2 Meta-analyses on prone position in acute respiratory distress syndrome patients

Meta-analysis	No. of studies included	Total number of patients	Main findings
Sud *et al*[138]	10	1867	Prone ventilation reduces mortality in patients with severe hypoxemia
Gattinoni *et al*[136]	4	1573	The individual patient meta-analysis of the four major clinical trials available clearly shows that with prone positioning, the absolute mortality of severely hypoxemic ARDS patients may be reduced by approximately 10%
Lee *et al*[137]	11	2246	Ventilation in the prone position significantly reduced overall mortality in patients with severe acute respiratory distress syndrome. Sufficient duration of prone positioning was statistically significant in associated with a reduction in overall mortality
Beitler *et al*[134]	7	2119	Prone positioning was associated with a significant decrease in RR of death only among studies with low baseline tidal volume
Tonelli *et al*[133]	159 (93 with overall mortality reported) (44 trials reported mortality as a primary outcome)	20671	Limited supportive evidence that specific interventions can decrease mortality in ARDS, while low tidal volumes and prone positioning in severe ARDS seem effective
Park *et al*[139]	8	2141	Prone positioning tends to reduce the mortality rates in ARDS patients, especially when used in conjunction with a lung protective strategy and longer prone position durations. Prone positioning for ARDS patients should be prioritized over other invasive procedures because related life-threatening complications are rare
Bloomfield *et al*[140]	9	2165	No convincing evidence of benefit nor harm from universal application of prone positioning in adults with hypoxaemia mechanically ventilated in intensive care units Three subgroups (early implementation of prone positioning, prolonged adoption of prone positioning and severe hypoxaemia at study entry) suggested that prone positioning may confer a statistically significant mortality advantage

ARDS: Acute respiratory distress syndrome.

Table 3 Absolute and relative contraindications to prone positioning

Absolute
Unmonitored or significantly increased intracranial pressure
Unstable vertebral fractures
Relative
Difficult airway management
Tracheal surgery or sternotomy during the previous 15 d
New tracheostomy (less than 24 h)
Single anterior chest tube with air leaks
Serious facial trauma or facial surgery during the previous 15 d
Increased intraocular pressure
Hemodynamic instability or recent cardiopulmonary arrest
Cardiac pacemaker inserted in the last 2 d
Ventricular assist device
Intra-aortic balloon pump
Deep venous thrombosis treated for less than 2 d
Massive hemoptysis requiring an immediate surgical or interventional radiology procedure
Continuous dialysis
Severe chest wall lesions ± rib fractures
Recent cardiothoracic surgery/unstable mediastinum or open chest
Multiple trauma with unstabilized fractures
Femur, or pelvic fractures ± external pelvic fixation
Pregnant women
Recent abdominal surgery or stoma formation
Kyphoscoliosis
Advanced osteoarthritis or rheumatoid arthritis
Body weight greater than 135 kg

Table 4 Potential complications of prone positioning

Edema (facial, airway, limbs, thorax)
Pressure sores
Conjunctival hemorrhage
Compression of nerves and retinal vessels
Endotracheal tube dislocation (main stem intubation or non-scheduled extubation), obstruction or kinking
Airway suctioning difficulty
Transient hypotension or oxygen desaturation
Worsening gas exchange
Pneumothorax
Thoracic drain kinking or obstruction
Cardiac events
Inadvertent dislodging of Swan-Ganz catheter
Vascular catheter kinking or removal
Vascular catheter malfunction during continuous veno-venous hemofiltration
Deep venous thrombosis
Urinary bladder catheter or nasogastric feeding tube displacement
Enteral nutrition intolerance; vomiting; feeding complications
Need for increased sedation or muscle paralysis
Difficulty in instituting cardiopulmonary resuscitation

should be weighed against the feasibility of recruiting a potentially life-saving treatment[23,46,81,97,141-146].

Although the safety of proning has long been a concern because of the risk of serious complications (Table 4), data from clinical studies indicate that the maneuver is safe and has a minimal risk profile when performed by skilled personnel and in well-selected patients[23,46,53,54,73,75,76,97,104,117,121,131,132,134,137,139,143-145,147-159]. The use of special devices and beds (*e.g.*, Vollman Proning Device or RotoProne™. Therapy System) can facilitate the mechanics of safe proning[81,142,158]. Manual prone positioning proves to be cost-effective since it can be achieved with a sheet or an assistive device (*e.g.*, Vollman Proning Device). It is a simple

technique and allows full access to the patient. The main disadvantage of the method is that it requires additional highly skilled nursing resources. The patient's size and the number of lines will eventually determine the number of people required for the turn; it can take four or more staff members to accomplish safely. On the other hand, automated prone-positioning needs one man, minimizes risk during turning and can provide continuous rotation if required according to patient's needs and responses. Unfortunately, the cost of automated prone-positioning beds is very high. Besides, quick access to the patient and abdomen release during mechanical ventilation in prone position are also a concern. To the best of our knowledge, in the literature there are no studies comparing manual and automated prone positioning and the user experience for automated prone positioning remains limited.

CONCLUSION

This review strongly supports the use of prone positioning in the early management of ARDS systematically and not as a rescue maneuver or a last-ditch effort. Large randomized trials and recent meta-analyses show that prone position, when performed early and in sufficient duration, may improve survival in patients with severe ARDS and in patients ventilated with a restrict lung protective ventilation protocol characterized by small tidal volumes. The physiological basis of prone positioning seems to act beneficially in most pathophysiological disorders of ARDS improving hemodynamics, gas exchange and respiratory mechanics. Moreover prone positioning seems to exert an additional beneficial effect against ventilator-induced lung injury. The mechanisms by which prone positioning improves with survival, are likely related to its physiologic effects.

REFERENCES

1 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818-824 [PMID: 7509706 DOI: 10.1164/ajrccm.149.3.7509706]

2 **Li G**, Malinchoc M, Cartin-Ceba R, Venkata CV, Kor DJ, Peters SG, Hubmayr RD, Gajic O. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *Am J Respir Crit Care Med* 2011; **183**: 59-66 [PMID: 20693377 DOI: 10.1164/rccm.201003-0436OC]

3 **Ranieri VM**, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**: 2526-2533 [PMID: 22797452 DOI: 10.1001/jama.2012.5669]

4 **Ashbaugh DG**, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319-323 [PMID: 4143721 DOI: 10.1016/S0140-6736(67)90168-7]

5 **Linko R**, Okkonen M, Pettilä V, Perttilä J, Parviainen I, Ruokonen E, Tenhunen J, Ala-Kokko T, Varpula T. Acute respiratory failure in intensive care units. FINNALI: a prospective cohort study. *Intensive Care Med* 2009; **35**: 1352-1361 [PMID: 19526218 DOI: 10.1007/s00134-009-1519-z]

6 **Villar J**, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, Gandía F, Carriedo D, Mosteiro F, Basaldúa S, Fernández RL, Kacmarek RM. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med* 2011; **37**: 1932-1941 [PMID: 21997128 DOI: 10.1007/s00134-011-2380-4]

7 **Sigurdsson MI**, Sigvaldason K, Gunnarsson TS, Moller A, Sigurdsson GH. Acute respiratory distress syndrome: nationwide changes in incidence, treatment and mortality over 23 years. *Acta Anaesthesiol Scand* 2013; **57**: 37-45 [PMID: 23216361 DOI: 10.1111/aas.12001]

8 **Esteban A**, Ferguson ND, Meade MO, Frutos-Vivar F, Apezteguia C, Brochard L, Raymondos K, Nin N, Hurtado J, Tomicic V, González M, Elizalde J, Nightingale P, Abroug F, Pelosi P, Arabi Y, Moreno R, Jibaja M, D'Empaire G, Sandi F, Matamis D, Montañez AM, Anzueto A. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med* 2008; **177**: 170-177 [PMID: 17962636 DOI: 10.1164/rccm.200706-893OC]

9 **Phua J**, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, Scales DC, Stather DR, Li A, Jones A, Gattas DJ, Hallett D, Tomlinson G, Stewart TE, Ferguson ND. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *Am J Respir Crit Care Med* 2009; **179**: 220-227 [PMID: 19011152 DOI: 10.1164/rccm.200805-722OC]

10 **Villar J**, Sulemanji D, Kacmarek RM. The acute respiratory distress syndrome: incidence and mortality, has it changed? *Curr Opin Crit Care* 2014; **20**: 3-9 [PMID: 24309954 DOI: 10.1097/MCC.0000000000000057]

11 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]

12 **Putensen C**, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med* 2009; **151**: 566-576 [PMID: 19841457 DOI: 10.7326/0003-4819-151-8-200910200-00011]

13 **Fish E**, Novack V, Banner-Goodspeed VM, Sarge T, Loring S, Talmor D. The Esophageal Pressure-Guided Ventilation 2 (EPVent2) trial protocol: a multicentre, randomised clinical trial of mechanical ventilation guided by transpulmonary pressure. *BMJ Open* 2014; **4**: e006356 [PMID: 25287106 DOI: 10.1136/bmjopen-2014-006356]

14 **Talmor DS**, Fessler HE. Are esophageal pressure measurements important in clinical decision-making in mechanically ventilated patients? *Respir Care* 2010; **55**: 162-172; discussion 172-174 [PMID: 20105342]

15 **Hedenstierna G**. Esophageal pressure: benefit and limitations. *Minerva Anestesiol* 2012; **78**: 959-966 [PMID: 22699701]

16 **Ochiai R**. Mechanical ventilation of acute respiratory distress syndrome. *J Intensive Care* 2015; **3**: 25 [PMID: 26045965 DOI: 10.1186/s40560-015-0091-6]

17 **Amato MB**, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; **372**: 747-755 [PMID: 25693014 DOI: 10.1056/NEJMsa1410639]

18 **Briel M**, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; **303**: 865-873 [PMID: 20197533 DOI: 10.1001/jama.2010.218]

19 **Santa Cruz R**, Rojas JI, Nervi R, Heredia R, Ciapponi A. High versus low positive end-expiratory pressure (PEEP) levels for mechanically ventilated adult patients with acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2013; **6**: CD009098 [PMID: 23740697 DOI: 10.1002/14651858.CD009098.pub2]

20 **Pelosi P**, Tubiolo D, Mascheroni D, Vicardi P, Crotti S, Valenza F, Gattinoni L. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *Am J Respir Crit Care Med* 1998; **157**: 387-393 [PMID: 9476848 DOI: 10.1164/ajrccm.157.2.97-04023]

21 **Mure M**, Martling CR, Lindahl SG. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. *Crit Care Med* 1997; **25**: 1539-1544 [PMID: 9295829 DOI: 10.1097/00003246-199709000-00022]

22 **Blanch L**, Mancebo J, Perez M, Martinez M, Mas A, Betbese AJ, Joseph D, Ballús J, Lucangelo U, Bak E. Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 1997; **23**: 1033-1039 [PMID: 9407238 DOI: 10.1007/s001340050453]

23 **Guérin C**, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 2159-2168 [PMID: 23688302 DOI: 10.1056/NEJMoa1214103]

24 **Wiedemann HP**, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354**: 2564-2575 [PMID: 16714767 DOI: 10.1056/NEJMoa062200]

25 **Papazian L**, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; **363**: 1107-1116 [PMID: 20843245 DOI: 10.1056/NEJMoa1005372]

26 **Ferguson ND**, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matte A, Walter SD, Lamontagne F, Granton JT, Arabi YM, Arroliga AC, Stewart TE, Slutsky AS, Meade MO. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 795-805 [PMID: 23339639 DOI: 10.1056/NEJMoa1215554]

27 **Young D**, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 806-813 [PMID: 23339638 DOI: 10.1056/NEJMoa1215716]

28 **Meduri GU**, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, Bokhari F, Zaloga G, Annane D. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2008; **34**: 61-69 [PMID: 18000649 DOI: 10.1007/s00134-007-0933-3]

29 **Bryan AC**. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. *Am Rev Respir Dis* 1974; **110**: 143-144 [PMID: 4440945]

30 **Piehl MA**, Brown RS. Use of extreme position changes in acute respiratory failure. *Crit Care Med* 1976; **4**: 13-14 [PMID: 1253612 DOI: 10.1097/00003246-197601000-00003]

31 **Douglas WW**, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: the prone position. *Am Rev Respir Dis* 1977; **115**: 559-566 [PMID: 322557]

32 **Maunder RJ**, Shuman WP, McHugh JW, Marglin SI, Butler J. Preservation of normal lung regions in the adult respiratory distress syndrome. Analysis by computed tomography. *JAMA* 1986; **255**: 2463-2465 [PMID: 3701964 DOI: 10.1001/jama.1986.03370180089038]

33 **Gattinoni L**, Presenti A, Torresin A, Baglioni S, Rivolta M, Rossi F, Scarani F, Marcolin R, Cappelletti G. Adult respiratory distress syndrome profiles by computed tomography. *J Thorac Imaging* 1986; **1**: 25-30 [PMID: 3298678 DOI: 10.1097/00005382-198607000-00005]

34 **Gattinoni L**, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis* 1987; **136**: 730-736 [PMID: 3307572 DOI: 10.1164/ajrccm/136.3.730]

35 **Gattinoni L**, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005; **31**: 776-784 [PMID: 15812622 DOI: 10.1007/s00134-005-2627-z]

36 **Gattinoni L**, Pesenti A, Carlesso E. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure: impact and clinical fallout through the following 20 years. *Intensive Care Med* 2013; **39**: 1909-1915 [PMID: 24026295 DOI: 10.1007/s00134-013-3066-x]

37 **Langer M**, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients. A clinical study. *Chest* 1988; **94**: 103-107 [PMID: 3383620 DOI: 10.1378/chest.94.1.103]

38 **Gattinoni L**, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991; **74**: 15-23 [PMID: 1986640 DOI: 10.1097/00000542-199101000-00004]

39 **Bone RC**. The ARDS lung. New insights from computed tomography. *JAMA* 1993; **269**: 2134-2135 [PMID: 8468771 DOI: 10.1001/jama.1993.03500160104042]

40 **Pelosi P**, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; **149**: 8-13 [PMID: 8111603 DOI: 10.1164/ajrccm.149.1.8111603]

41 **Gattinoni L**, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA* 1993; **269**: 2122-2127 [PMID: 8468768 DOI: 10.1001/jama.1993.03500160092039]

42 **Glenny RW**, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol* (1985) 1991; **71**: 620-629 [PMID: 1938736]

43 **Pelosi P**, Crotti S, Brazzi L, Gattinoni L. Computed tomography in adult respiratory distress syndrome: what has it taught us? *Eur Respir J* 1996; **9**: 1055-1062 [PMID: 8793469 DOI: 10.1183/09031936.96.09051055]

44 **Hubmayr RD**. Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story. *Am J Respir Crit Care Med* 2002; **165**: 1647-1653 [PMID: 12070067 DOI: 10.1164/rccm.2001080-01CP]

45 **Rouby JJ**, Puybasset L, Nieszkowska A, Lu Q. Acute respiratory distress syndrome: lessons from computed tomography of the whole lung. *Crit Care Med* 2003; **31**: S285-S295 [PMID: 12682454 DOI: 10.1097/01.CCM.0000057905.74813.BC]

46 **Gattinoni L**, Taccone P, Carlesso E, Marini JJ. Prone position in acute respiratory distress syndrome. Rationale, indications, and limits. *Am J Respir Crit Care Med* 2013; **188**: 1286-1293 [PMID: 24134414 DOI: 10.1164/rccm.201308-1532CI]

47 **Albert RK**, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. *Am J Respir Crit Care Med* 2000; **161**: 1660-1665 [PMID: 10806172 DOI: 10.1164/ajrccm.161.5.9901037]

48 **Malbouisson LM**, Busch CJ, Puybasset L, Lu Q, Cluzel P, Rouby JJ. Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group. *Am J Respir Crit Care Med* 2000; **161**: 2005-2012 [PMID: 10852781 DOI: 10.1164/ajrccm.161.6.9907067]

49 **Mure M**, Glenny RW, Domino KB, Hlastala MP. Pulmonary gas exchange improves in the prone position with abdominal distension. *Am J Respir Crit Care Med* 1998; **157**: 1785-1790 [PMID: 9620906 DOI: 10.1164/ajrccm.157.6.9711104]

50 **Galiatsou E**, Kostanti E, Svarna E, Kitsakos A, Koulouras V, Efremidis SC, Nakos G. Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006; **174**: 187-197 [PMID: 16645177 DOI: 10.1164/rccm.200506-899OC]

51 **Guerin C**, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. *Intensive Care Med* 2014; **40**: 1634-1642 [PMID: 25266133 DOI: 10.1007/s00134-014-3500-8]

52 **Tawhai MH**, Nash MP, Lin CL, Hoffman EA. Supine and prone differences in regional lung density and pleural pressure gradients in the human lung with constant shape. *J Appl Physiol* (1985) 2009; **107**: 912-920 [PMID: 19589959 DOI: 10.1152/japplphysiol.00324.2009]

53 **Guérin C**. Prone ventilation in acute respiratory distress syndrome. *Eur Respir Rev* 2014; **23**: 249-257 [PMID: 24881080 DOI: 10.1183/09059180.00001114]

54 **Pelosi P**, Brazzi L, Gattinoni L. Prone position in acute respiratory distress syndrome. *Eur Respir J* 2002; **20**: 1017-1028 [PMID: 12412699 DOI: 10.1183/09031936.02.00401702]

55 **Arborelius M**, Lundin G, Svanberg L, Defares JG. Influence of unilateral hypoxia on blood flow through the lungs in man in lateral position. *J Appl Physiol* 1960; **15**: 595-597 [PMID: 13794044]

56 **Greene R**, Zapol WM, Snider MT, Reid L, Snow R, O'Connell RS, Novelline RA. Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. *Am Rev Respir Dis* 1981; **124**: 593-601 [PMID: 7305115]

57 **Gattinoni L**, Pelosi P, Pesenti A, Brazzi L, Vitale G, Moretto A, Crespi A, Tagliabue M. CT scan in ARDS: clinical and physiopathological insights. *Acta Anaesthesiol Scand Suppl* 1991; **95**: 87-94; discussion 94-6 [PMID: 1927233]

58 **Richard JC**, Janier M, Lavenne F, Berthier V, Lebars D, Annat G, Decailliot F, Guerin C. Effect of position, nitric oxide, and almitrine on lung perfusion in a porcine model of acute lung injury. *J Appl Physiol* (1985) 2002; **93**: 2181-2191 [PMID: 12391113 DOI: 10.1152/japplphysiol.00313.2002]

59 **Nyrén S**, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. *J Appl Physiol* (1985) 1999; **86**: 1135-1141 [PMID: 10194194]

60 **Guérin C**. Prone position. *Curr Opin Crit Care* 2014; **20**: 92-97 [PMID: 24366167 DOI: 10.1097/MCC.0000000000000059]

61 **Wiener CM**, Kirk W, Albert RK. Prone position reverses gravitational distribution of perfusion in dog lungs with oleic acid-induced injury. *J Appl Physiol* (1985) 1990; **68**: 1386-1392 [PMID: 2347780]

62 **Lamm WJ**, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994; **150**: 184-193 [PMID: 8025748 DOI: 10.1164/ajrccm.150.1.8025748]

63 **Guérin C**. Ventilation in the prone position in patients with acute lung injury/acute respiratory distress syndrome. *Curr Opin Crit Care* 2006; **12**: 50-54 [PMID: 16394784]

64 **Petersson J**, Rohdin M, Sánchez-Crespo A, Nyrén S, Jacobsson H, Larsson SA, Lindahl SG, Linnarsson D, Glenny RW, Mure M. Paradoxical redistribution of pulmonary blood flow in prone and supine humans exposed to hypergravity. *J Appl Physiol* (1985) 2006; **100**: 240-248 [PMID: 16150840 DOI: 10.1152/japplphysiol.01430.2004]

65 **Mure M**, Domino KB, Lindahl SG, Hlastala MP, Altemeier WA, Glenny RW. Regional ventilation-perfusion distribution is more uniform in the prone position. *J Appl Physiol* (1985) 2000; **88**: 1076-1083 [PMID: 10710406]

66 **Cakar N**, der Kloot TV, Youngblood M, Adams A, Nahum A. Oxygenation response to a recruitment maneuver during supine and prone positions in an oleic acid-induced lung injury model. *Am J Respir Crit Care Med* 2000; **161**: 1949-1956 [PMID: 10852772 DOI: 10.1164/ajrccm.161.6.9907113]

67 **Rival G**, Patry C, Floret N, Navellou JC, Belle E, Capellier G. Prone position and recruitment manoeuvre: the combined effect improves oxygenation. *Crit Care* 2011; **15**: R125 [PMID: 21575205 DOI: 10.1186/cc10235]

68 **Oczenski W**, Hörmann C, Keller C, Lorenzl N, Kepka A, Schwarz S, Fitzgerald RD. Recruitment maneuvers during prone positioning in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; **33**: 54-61; quiz 62 [PMID: 15644648]

69 **Nakos G**, Tsangaris I, Kostanti E, Nathanail C, Lachana A, Koulouras V, Kastani D. Effect of the prone position on patients with hydrostatic pulmonary edema compared with patients with acute respiratory distress syndrome and pulmonary fibrosis. *Am J Respir Crit Care Med* 2000; **161**: 360-368 [PMID: 10673172 DOI: 10.1164/ajrccm.161.2.9810037]

70 **Wiener CM**, McKenna WJ, Myers MJ, Lavender JP, Hughes JM. Left lower lobe ventilation is reduced in patients with cardiomegaly in the supine but not the prone position. *Am Rev Respir Dis* 1990; **141**: 150-155 [PMID: 2136978 DOI: 10.1164/ajrccm/141.1.150]

71 **Petersson J**, Ax M, Frey J, Sánchez-Crespo A, Lindahl SG, Mure M. Positive end-expiratory pressure redistributes regional blood flow and ventilation differently in supine and prone humans. *Anesthesiology* 2010; **113**: 1361-1369 [PMID: 21068656 DOI: 10.1097/ALN.0b013e3181fcec4f]

72 **Gainnier M**, Michelet P, Thirion X, Arnal JM, Sainty JM, Papazian L. Prone position and positive end-expiratory pressure in acute respiratory distress syndrome. *Crit Care Med* 2003; **31**: 2719-2726 [PMID: 14668607 DOI: 10.1097/01.CCM.0000094216.49129.4B]

73 **Taccone P**, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, Caspani L, Raimondi F, Bordone G, Iapichino G, Mancebo J, Guérin C, Ayzac L, Blanch L, Fumagalli R, Tognoni G, Gattinoni L. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009; **302**: 1977-1984 [PMID: 19903918 DOI: 10.1001/jama.2009.1614]

74 **Gattinoni L**, Caironi P. Prone positioning: beyond physiology. *Anesthesiology* 2010; **113**: 1262-1264 [PMID: 21042196 DOI: 10.1097/ALN.0b013e3181fcd97e]

75 **Gattinoni L**, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, Malacrida R, Di Giulio P, Fumagalli R, Pelosi P, Brazzi L, Latini R. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; **345**: 568-573 [PMID: 11529210 DOI: 10.1056/NEJMoa010043]

76 **Guerin C**, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, Palmier B, Le QV, Sirodot M, Rosselli S, Cadiergue V, Sainty JM, Barbe P, Combourieu E, Debatty D, Rouffineau J, Ezingeard E, Millet O, Guelon D, Rodriguez L, Martin O, Renault A, Sibille JP, Kaidomar M. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004; **292**: 2379-2387 [PMID: 15547166 DOI: 10.1001/jama.292.19.2379]

77 **Gattinoni L**, Bombino M, Pelosi P, Lissoni A, Pesenti A, Fumagalli R, Tagliabue M. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA* 1994; **271**: 1772-1779 [PMID: 8196122 DOI: 10.1001/jama.1994.03510460064035]

78 **Kallet RH**, Alonso JA, Pittet JF, Matthay MA. Prognostic value of the pulmonary dead-space fraction during the first 6 days of acute respiratory distress syndrome. *Respir Care* 2004; **49**: 1008-1014 [PMID: 15329171]

79 **Gattinoni L**, Vagginelli F, Carlesso E, Taccone P, Conte V, Chiumello D, Valenza F, Caironi P, Pesenti A. Decrease in PaCO2 with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; **31**: 2727-2733 [PMID: 14668608 DOI: 10.1097/01.CCM.0000098032.34052.F9]

80 **Protti A**, Chiumello D, Cressoni M, Carlesso E, Mietto C, Berto V, Lazzerini M, Quintel M, Gattinoni L. Relationship between gas exchange response to prone position and lung recruitability during acute respiratory failure. *Intensive Care Med* 2009; **35**: 1011-1017 [PMID: 19189081 DOI: 10.1007/s00134-009-1411-x]

81 **Dirkes S**, Dickinson S, Havey R, O'brien D. Prone positioning: is it safe and effective? *Crit Care Nurs Q* 2012; **35**: 64-75 [PMID: 22157493 DOI: 10.1097/CNQ.0b013e31823b20c6]

82 **Servillo G**, Roupie E, De Robertis E, Rossano F, Brochard L, Lemaire F, Tufano R. Effects of ventilation in ventral decubitus position on respiratory mechanics in adult respiratory distress syndrome. *Intensive Care Med* 1997; **23**: 1219-1224 [PMID: 9470076]

83 **Guerin C**, Badet M, Rosselli S, Heyer L, Sab JM, Langevin B, Philit F, Fournier G, Robert D. Effects of prone position on alveolar recruitment and oxygenation in acute lung injury. *Intensive Care Med* 1999; **25**: 1222-1230 [PMID: 10654205 DOI: 10.1007/s001340051050]

84 **Slutsky AS**. Lung injury caused by mechanical ventilation. *Chest*

1999; **116**: 9S-15S [PMID: 10424561 DOI: 10.1378/chest.116.suppl_1.9S-a]
85 **Bilek AM**, Dee KC, Gaver DP. Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. *J Appl Physiol* (1985) 2003; **94**: 770-783 [PMID: 12433851 DOI: 10.1152/japplphysiol.00764.2002]
86 **Albert RK**. The role of ventilation-induced surfactant dysfunction and atelectasis in causing acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2012; **185**: 702-708 [PMID: 22227381 DOI: 10.1164/rccm.201109-1667PP]
87 **Slutsky AS**, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013; **369**: 2126-2136 [PMID: 24283226 DOI: 10.1056/NEJMra1208707]
88 **Gattinoni L**, Protti A. Ventilation in the prone position: for some but not for all? *CMAJ* 2008; **178**: 1174-1176 [PMID: 18427093 DOI: 10.1503/cmaj.080359]
89 **Chiumello D**, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; **178**: 346-355 [PMID: 18451319 DOI: 10.1164/rccm.200710-1589OC]
90 **Gattinoni L**, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. *Crit Care Med* 2010; **38**: S539-S548 [PMID: 21164395 DOI: 10.1097/CCM.0b013e3181f1fcf7]
91 **Gattinoni L**, Carlesso E, Caironi P. Stress and strain within the lung. *Curr Opin Crit Care* 2012; **18**: 42-47 [PMID: 22157254 DOI: 10.1097/MCC.0b013e32834f17d9]
92 **Valenza F**, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, Aletti G, Porro GA, Irace M, Carlesso E, Carboni N, Lazzerini M, Gattinoni L. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005; **33**: 361-367 [PMID: 15699840 DOI: 10.1097/01.ccm.0000150660.45376.7c]
93 **Broccard A**, Shapiro RS, Schmitz LL, Adams AB, Nahum A, Marini JJ. Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Crit Care Med* 2000; **28**: 295-303 [PMID: 10708156 DOI: 10.1097/00003246-200002000-00001]
94 **Du HL**, Yamada Y, Orii R, Suzuki S, Sawamura S, Suwa K, Hanaoka K. Beneficial effects of the prone position on the incidence of barotrauma in oleic acid-induced lung injury under continuous positive pressure ventilation. *Acta Anaesthesiol Scand* 1997; **41**: 701-707 [PMID: 9241328]
95 **Broccard AF**, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit Care Med* 1997; **25**: 16-27 [PMID: 8989171 DOI: 10.1097/00003246-199701000-00007]
96 **Cornejo RA**, Díaz JC, Tobar EA, Bruhn AR, Ramos CA, González RA, Repetto CA, Romero CM, Gálvez LR, Llanos O, Arellano DH, Neira WR, Díaz GA, Zamorano AJ, Pereira GL. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013; **188**: 440-448 [PMID: 23348974 DOI: 10.1164/rccm.201207-1279OC]
97 **Roche-Campo F**, Aguirre-Bermeo H, Mancebo J. Prone positioning in acute respiratory distress syndrome (ARDS): when and how? *Presse Med* 2011; **40**: e585-e594 [PMID: 22078089 DOI: 10.1016/j.lpm.2011.03.019]
98 **Papazian L**, Gainnier M, Marin V, Donati S, Arnal JM, Demory D, Roch A, Forel JM, Bongrand P, Brégeon F, Sainty JM. Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; **33**: 2162-2171 [PMID: 16215365 DOI: 10.1097/01.ccm.0000181298.05474.2b]
99 **Nakos G**, Batistatou A, Galiatsou E, Konstanti E, Koulouras V, Kanavaros P, Doulis A, Kitsakos A, Karachaliou A, Lekka ME, Bai M. Lung and 'end organ' injury due to mechanical ventilation in animals: comparison between the prone and supine positions. *Crit Care* 2006; **10**: R38 [PMID: 16507176 DOI: 10.1186/cc4840]
100 **Park MS**, He Q, Edwards MG, Sergew A, Riches DW, Albert RK, Douglas IS. Mitogen-activated protein kinase phosphatase-1 modulates regional effects of injurious mechanical ventilation in rodent lungs. *Am J Respir Crit Care Med* 2012; **186**: 72-81 [PMID: 22582160 DOI: 10.1164/rccm.201109-1593OC]
101 **Mackenzie CF**. Anatomy, physiology, and pathology of the prone position and postural drainage. *Crit Care Med* 2001; **29**: 1084-1085 [PMID: 11378626 DOI: 10.1097/00003246-200105000-00046]
102 **Chatte G**, Sab JM, Dubois JM, Sirodot M, Gaussorgues P, Robert D. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am J Respir Crit Care Med* 1997; **155**: 473-478 [PMID: 9032181 DOI: 10.1164/ajrccm.155.2.9032181]
103 **Gillart T**, Bazin JE, Guelon D, Constantin JM, Mansoor O, Conio N, Schoeffler P. [Effect of bronchial drainage on the improvement in gas exchange observed in ventral decubitus in ARDS]. *Ann Fr Anesth Reanim* 2000; **19**: 156-163 [PMID: 10782238 DOI: 10.1016/S0750-7658(00)00199-4]
104 **Voggenreiter G**, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, Bock E, Gotzen L, Obertacke U, Nast-Kolb D. Prone positioning improves oxygenation in post-traumatic lung injury--a prospective randomized trial. *J Trauma* 2005; **59**: 333-341; discussion 341-343 [PMID: 16294072 DOI: 10.1097/01.ta.0000179952.95921.49]
105 **Drakulovic MB**, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet* 1999; **354**: 1851-1858 [PMID: 10584721 DOI: 10.1016/S0140-6736(98)12251-1]
106 **Li Bassi G**, Zanella A, Cressoni M, Stylianou M, Kolobow T. Following tracheal intubation, mucus flow is reversed in the semirecumbent position: possible role in the pathogenesis of ventilator-associated pneumonia. *Crit Care Med* 2008; **36**: 518-525 [PMID: 18176317 DOI: 10.1097/01.CCM.0000299741.32078.E9]
107 **Li Bassi G**, Torres A. Ventilator-associated pneumonia: role of positioning. *Curr Opin Crit Care* 2011; **17**: 57-63 [PMID: 21169827 DOI: 10.1097/MCC.0b013e3283428b31]
108 **Pappert D**, Rossaint R, Slama K, Grüning T, Falke KJ. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. *Chest* 1994; **106**: 1511-1516 [PMID: 7956412 DOI: 10.1378/chest.106.5.1511]
109 **Sinclair SE**, Altemeier WA, Matute-Bello G, Chi EY. Augmented lung injury due to interaction between hyperoxia and mechanical ventilation. *Crit Care Med* 2004; **32**: 2496-2501 [PMID: 15599157]
110 **Vieillard-Baron A**, Charron C, Caille V, Belliard G, Page B, Jardin F. Prone positioning unloads the right ventricle in severe ARDS. *Chest* 2007; **132**: 1440-1446 [PMID: 17925425 DOI: 10.1378/chest.07-1013]
111 **Jozwiak M**, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013; **188**: 1428-1433 [PMID: 24102072 DOI: 10.1164/rccm.201303-0593OC]
112 **Repessé X**, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. *Chest* 2015; **147**: 259-265 [PMID: 25560864 DOI: 10.1378/chest.14-0877]
113 **Bull TM**, Clark B, McFann K, Moss M. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med* 2010; **182**: 1123-1128 [PMID: 20558628 DOI: 10.1164/rccm.201002-0250OC]
114 **Brücken U**, Grensemann J, Wappler F, Sakka SG. Influence of prone positioning on the measurement of transpulmonary thermodilution-derived variables in critically ill patients. *Acta Anaesthesiol Scand* 2011; **55**: 1061-1067 [PMID: 22092202 DOI: 10.1111/j.1399-6576.2011.02519.x]
115 **McAuley DF**, Giles S, Fichter H, Perkins GD, Gao F. What is the optimal duration of ventilation in the prone position in acute lung injury and acute respiratory distress syndrome? *Intensive Care Med* 2002; **28**: 414-418 [PMID: 11967594 DOI: 10.1007/s00134-002-1248-z]
116 **Grensemann J**, Bruecken U, Treszl A, Wappler F, Sakka SG. The

influence of prone positioning on the accuracy of calibrated and uncalibrated pulse contour-derived cardiac index measurements. *Anesth Analg* 2013; **116**: 820-826 [PMID: 23460570 DOI: 10.1213/ANE.0b013e31827fe77e]

117 **De Jong A**, Molinari N, Sebbane M, Prades A, Futier E, Jung B, Chanques G, Jaber S. Feasibility and effectiveness of prone position in morbidly obese patients with ARDS: a case-control clinical study. *Chest* 2013; **143**: 1554-1561 [PMID: 23450309 DOI: 10.1378/chest.12-2115]

118 **Albert RK**, Keniston A, Baboi L, Ayzac L, Guérin C. Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014; **189**: 494-496 [PMID: 24528322 DOI: 10.1164/rccm.201311-2056LE]

119 **Papazian L**, Paladini MH, Bregeon F, Huiart L, Thirion X, Saux P, Jammes Y, Auffray JP. Is a short trial of prone positioning sufficient to predict the improvement in oxygenation in patients with acute respiratory distress syndrome? *Intensive Care Med* 2001; **27**: 1044-1049 [PMID: 11497137 DOI: 10.1007/s001340000799]

120 **Mebazaa MS**, Abid N, Frikha N, Mestiri T, Ben Ammar MS. [The prone position in acute respiratory distress syndrome: a critical systematic review]. *Ann Fr Anesth Reanim* 2007; **26**: 307-318 [PMID: 17289334 DOI: 10.1016/j.annfar.2006.11.017]

121 **Kopterides P**, Siempos II, Armaganidis A. Prone positioning in hypoxemic respiratory failure: meta-analysis of randomized controlled trials. *J Crit Care* 2009; **24**: 89-100 [PMID: 19272544 DOI: 10.1016/j.jcrc.2007.12.014]

122 **Marik PE**, Iglesias J. A "prone dependent" patient with severe adult respiratory distress syndrome. *Crit Care Med* 1997; **25**: 1085-1087 [PMID: 9201066 DOI: 10.1097/00003246-199706000-00030]

123 **Fessler HE**, Talmor DS. Should prone positioning be routinely used for lung protection during mechanical ventilation? *Respir Care* 2010; **55**: 88-99 [PMID: 20040127]

124 **Collins SR**, Blank RS. Approaches to refractory hypoxemia in acute respiratory distress syndrome: current understanding, evidence, and debate. *Respir Care* 2011; **56**: 1573-1582 [PMID: 22008398 DOI: 10.4187/respcare.01366]

125 **Lim CM**, Kim EK, Lee JS, Shim TS, Lee SD, Koh Y, Kim WS, Kim DS, Kim WD. Comparison of the response to the prone position between pulmonary and extrapulmonary acute respiratory distress syndrome. *Intensive Care Med* 2001; **27**: 477-485 [PMID: 11355115 DOI: 10.1007/s001340000848]

126 **Lee DL**, Chiang HT, Lin SL, Ger LP, Kun MH, Huang YC. Prone-position ventilation induces sustained improvement in oxygenation in patients with acute respiratory distress syndrome who have a large shunt. *Crit Care Med* 2002; **30**: 1446-1452 [PMID: 12130960]

127 **Reutershan J**, Schmitt A, Dietz K, Unertl K, Fretschner R. Alveolar recruitment during prone position: time matters. *Clin Sci* (Lond) 2006; **110**: 655-663 [PMID: 16451123 DOI: 10.1042/CS20050337]

128 **Jolliet P**, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med* 1998; **26**: 1977-1985 [PMID: 9875907 DOI: 10.1097/00003246-199812000-00023]

129 **Rialp G**, Betbesé AJ, Pérez-Márquez M, Mancebo J. Short-term effects of inhaled nitric oxide and prone position in pulmonary and extrapulmonary acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2001; **164**: 243-249 [PMID: 11463595 DOI: 10.1164/ajrccm.164.2.2002087]

130 **Papazian L**, Paladini MH, Bregeon F, Thirion X, Durieux O, Gainnier M, Huiart L, Agostini S, Auffray JP. Can the tomographic aspect characteristics of patients presenting with acute respiratory distress syndrome predict improvement in oxygenation-related response to the prone position? *Anesthesiology* 2002; **97**: 599-607 [PMID: 12218526 DOI: 10.1097/00000542-200209000-00013]

131 **Girard R**, Baboi L, Ayzac L, Richard JC, Guérin C. The impact of patient positioning on pressure ulcers in patients with severe ARDS: results from a multicentre randomised controlled trial on prone positioning. *Intensive Care Med* 2014; **40**: 397-403 [PMID: 24352484 DOI: 10.1007/s00134-013-3188-1]

132 **Mancebo J**, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, Rodríguez F, Garro P, Ricart P, Vallverdú I, Gich I, Castaño J, Saura P, Domínguez G, Bonet A, Albert RK. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; **173**: 1233-1239 [PMID: 16556697 DOI: 10.1164/rccm.200503-353OC]

133 **Tonelli AR**, Zein J, Adams J, Ioannidis JP. Effects of interventions on survival in acute respiratory distress syndrome: an umbrella review of 159 published randomized trials and 29 meta-analyses. *Intensive Care Med* 2014; **40**: 769-787 [PMID: 24667919 DOI: 10.1007/s00134-014-3272-1]

134 **Beitler JR**, Shaefi S, Montesi SB, Devlin A, Loring SH, Talmor D, Malhotra A. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014; **40**: 332-341 [PMID: 24435203 DOI: 10.1007/s00134-013-3194-3]

135 **Alsaghir AH**, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med* 2008; **36**: 603-609 [PMID: 18216609 DOI: 10.1097/01.CCM.0000299739.98236.05]

136 **Gattinoni L**, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. *Minerva Anestesiol* 2010; **76**: 448-454 [PMID: 20473258]

137 **Lee JM**, Bae W, Lee YJ, Cho YJ. The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2014; **42**: 1252-1262 [PMID: 24368348 DOI: 10.1097/CCM.0000000000000122]

138 **Sud S**, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guérin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010; **36**: 585-599 [PMID: 20130832 DOI: 10.1007/s00134-009-1748-1]

139 **Park SY**, Kim HJ, Yoo KH, Park YB, Kim SW, Lee SJ, Kim EK, Kim JH, Kim YH, Moon JY, Min KH, Park SS, Lee J, Lee CH, Park J, Byun MK, Lee SW, Rlee C, Jung JY, Sim YS. The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *J Thorac Dis* 2015; **7**: 356-367 [PMID: 25922713 DOI: 10.3978/j.issn.2072-1439.2014.12.49]

140 **Bloomfield R**, Noble DW, Sudlow A. Prone position for acute respiratory failure in adults. *Cochrane Database Syst Rev* 2015; **11**: CD008095 [PMID: 26561745 DOI: 10.1002/14651858.CD008095.pub2]

141 **Modrykamien AM**, Gupta P. The acute respiratory distress syndrome. *Proc* (Bayl Univ Med Cent) 2015; **28**: 163-171 [PMID: 25829644]

142 **Vollman KM**. Prone positioning for the ARDS patient. *Dimens Crit Care Nurs* 1997; **16**: 184-193 [PMID: 9248377 DOI: 10.1097/00003465-199707000-00002]

143 **Benson AB**, Albert RK. Prone positioning for acute respiratory distress syndrome. *Clin Chest Med* 2014; **35**: 743-752 [PMID: 25453422 DOI: 10.1016/j.ccm.2014.08.011]

144 **Henderson WR**, Griesdale DE, Dominelli P, Ronco JJ. Does prone positioning improve oxygenation and reduce mortality in patients with acute respiratory distress syndrome? *Can Respir J* 2014; **21**: 213-215 [PMID: 24927376]

145 **Athota KP**, Millar D, Branson RD, Tsuei BJ. A practical approach to the use of prone therapy in acute respiratory distress syndrome. *Expert Rev Respir Med* 2014; **8**: 453-463 [PMID: 24832577 DOI: 10.1586/17476348.2014.918850]

146 **Samanta S**, Samanta S, Wig J, Baronia AK. How safe is the prone position in acute respiratory distress syndrome at late pregnancy? *Am J Emerg Med* 2014; **32**: 687.e1-687.e3 [PMID: 24412021 DOI: 10.1016/j.ajem.2013.12.021]

147 **Guérin C**, Mancebo J. Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: yes. *Intensive Care Med* 2015; **41**: 2195-2197 [PMID: 26399890

DOI: 10.1007/s00134-015-3918-7]
148 **Sud S**, Friedrich JO, Adhikari NK, Taccone P, Mancebo J, Polli F, Latini R, Pesenti A, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L, Guérin C. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2014; **186**: E381-E390 [PMID: 24863923 DOI: 10.1503/cmaj.140081]
149 **Tekwani SS**, Murugan R. 'To prone or not to prone' in severe ARDS: questions answered, but others remain. *Crit Care* 2014; **18**: 305 [PMID: 25042412 DOI: 10.1186/cc13893]
150 **Soo Hoo GW**. In prone ventilation, one good turn deserves another. *N Engl J Med* 2013; **368**: 2227-2228 [PMID: 23688300 DOI: 10.1056/NEJMe1304349]
151 Prone positioning can save lives. *BMJ* 2013; **346**: f3302 [PMID: 23697748 DOI: 10.1136/bmj.f3302]
152 **Hale DF**, Cannon JW, Batchinsky AI, Cancio LC, Aden JK, White CE, Renz EM, Blackbourne LH, Chung KK. Prone positioning improves oxygenation in adult burn patients with severe acute respiratory distress syndrome. *J Trauma Acute Care Surg* 2012; **72**: 1634-1639 [PMID: 22695433 DOI: 10.1097/TA.0b013e318247cd4f]
153 **Abroug F**, Ouanes-Besbes L, Dachraoui F, Ouanes I, Brochard L. An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. *Crit Care* 2011; **15**: R6 [PMID: 21211010 DOI: 10.1186/cc9403]
154 **Wright AD**, Flynn M. Using the prone position for ventilated patients with respiratory failure: a review. *Nurs Crit Care* 2011; **16**: 19-27 [PMID: 21199551 DOI: 10.1111/j.1478-5153.2010.00425.x]
155 **Sud S**, Sud M, Friedrich JO, Adhikari NK. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ* 2008; **178**: 1153-1161 [PMID: 18427090 DOI: 10.1503/cmaj.071802]
156 **Fernandez R**, Trenchs X, Klamburg J, Castedo J, Serrano JM, Besso G, Tirapu JP, Santos A, Mas A, Parraga M, Jubert P, Frutos F, Añon JM, Garcia M, Rodriguez F, Yebenes JC, Lopez MJ. Prone positioning in acute respiratory distress syndrome: a multicenter randomized clinical trial. *Intensive Care Med* 2008; **34**: 1487-1491 [PMID: 18427774 DOI: 10.1007/s00134-008-1119-3]
157 **Abroug F**, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. *Intensive Care Med* 2008; **34**: 1002-1011 [PMID: 18350271 DOI: 10.1007/s00134-008-1062-3]
158 **Davis JW**, Lemaster DM, Moore EC, Eghbalieh B, Bilello JF, Townsend RN, Parks SN, Veneman WL. Prone ventilation in trauma or surgical patients with acute lung injury and adult respiratory distress syndrome: is it beneficial? *J Trauma* 2007; **62**: 1201-1206 [PMID: 17495725 DOI: 10.1097/TA.0b013e31804d490b]
159 **Agrawal SP**, Goel AD. Prone position ventilation in Acute Respiratory Distress Syndrome: An overview of the evidences. *Indian J Anaesth* 2015; **59**: 246-248 [PMID: 25937653 DOI: 10.4103/0019-5049.155004]

P- Reviewer: Chen XL, Qiu HB
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.137

World J Crit Care Med 2016 May 4; 5(2): 137-142
ISSN 2220-3141 (online)

MINIREVIEWS

Antimicrobial-impregnated catheters for the prevention of catheter-related bloodstream infections

Leonardo Lorente

Leonardo Lorente, Intensive Care Unit, Hospital Universitario de Canarias, 38320 La Laguna, Santa Cruz de Tenerife, Spain

Author contributions: The author solely contributed to this paper.

Conflict-of-interest statement: None declared.

Correspondence to: Leonardo Lorente, MD, PhD, Intensive Care Unit, Hospital Universitario de Canarias, Ofra, s/n, 38320 La Laguna, Santa Cruz de Tenerife, Spain. lorentemartin@msn.com
Telephone: +34-922-678000
Fax: +34-922-647112

Received: June 1, 2015
Peer-review started: June 7, 2015
First decision: August 16, 2015
Revised: December 21, 2015
Accepted: January 27, 2016
Article in press: January 29, 2016
Published online: May 4, 2016

Abstract

Central venous catheters are commonly used in critically ill patients. Such catheterization may entail mechanical and infectious complications. The interest in catheter-related infection lies in the morbidity, mortality and costs that it involved. Numerous contributions have been made in the prevention of catheter-related infection and the current review focuses on the possible current role of antimicrobial impregnated catheters to reduce catheter-related bloodstream infections (CRBSI). There is evidence that the use of chlorhexidine-silver sulfadiazine (CHSS), rifampicin-minocycline, or rifampicin-miconazol impregnated catheters reduce the incidence of CRBSI and costs. In addition, there are some clinical circumstances associated with higher risk of CRBSI, such as the venous catheter access and the presence of tracheostomy. Current guidelines for the prevention of CRBSI recommended the use of a CHSS or rifampicin-minocycline impregnated catheter in patients whose catheter is expected to remain in place > 5 d and if the CRBSI rate has not decreased after implementation of a comprehensive strategy to reduce it.

Key words: Catheter; Venous; Prevention; Impregnated; Bloodstream

Core tip: The catheter-related bloodstream infections (CRBSI) are associated with an increase of mortality and costs. Thus it is necessary to adopt preventive measures to reduce it. In my opinion of view, the use of antimicrobial impregnated catheters could be considered in some clinical circumstances associated with higher risk of CRBSI, such as vascular accesses with higher risk of CRBSI (such as internal jugular venous site with tracheostomy or femoral venous site) or patients with higher risk of CRBSI (such as immunocompromised patients or patients with disorders of skin integrity).

Lorente L. Antimicrobial-impregnated catheters for the prevention of catheter-related bloodstream infections. *World J Crit Care Med* 2016; 5(2): 137-142 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/137.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.137

INTRODUCTION

Some central venous catheter (CVC) could be needed by different reasons, such as administration of fluids, parenteral nutrition, blood products, medications and/or monitor the hemodynamic status. Critically ill patients frequently needed some CVC, and the 78% of them had inserted some CVC[1]. The catheterization of CVC may have different complications, such as infection, thrombosis and haemorrhage[2]. Catheter-related infection lead to an increase of mortality, morbidity, and costs[3-10].

Numerous contributions have been made to analyse the efficacy of different measures to prevent catheter-related infection[11]. In addition, there have been found that the implementation of different bundles have reduced the incidence of catheter-related bloodstream infections (CRBSI)[12-15]. This review focuses on the possible current role of antimicrobial impregnated catheters to reduce CRBSI.

BUNDLES TO REDUCE CRBSI

The first published experience reducing CRBSI with the implementation of a bundle was that by Pronovost *et al*[12], and afterwards other experiences reported lower CRBSI incidence with the implementation of bundles with this proposal[13-15].

The Keystone Intensive Care Unit (ICU) project by Pronovost *et al*[12] was carried out in the Michigan state in 103 ICUs between March 2004 and September 2005. In this project was found that 3 mo after intervention implementation was reduced the median incidence of CRBSI from 2.7 (mean of 7.7) infections per 1000 d of catheter to 0 (mean of 2.3) ($P \leqslant 0.002$) and that during the follow-up of 18 mo was maintained at 0 (mean of 1.4). The prevention measures were avoid the femoral site if possible, the use of full-barrier precautions for CVC insertion, hand washing, chlorhexidine to clean the skin, and remove unnecessary CVC. In addition, an intervention to ventilator-associated pneumonia prevention, the use of a daily goals sheet to improve the communication between clinician within the ICU, and a program to improve the safety culture were implemented.

Afterwards to Michigan experience was carried out the Spanish experience, which was developed in 192 ICUs between April 2008 and June 2010[13]. The bundle to reduce CRBSI proposed by BZ project included the subclavian venous access as the site of choice (while in Keystone project was recommended to avoid the femoral venous site) and added a measure on the catheter maintenance (such isopropyl alcohol 70° to clean injection ports system and reduce the handling of hubs). In this project was found, that after 18 mo of intervention implementation, a significant decrease ($P < 0.001$) on the overall median CRBSI rate from 3.07 to 1.12 infections per 1000 catheter-days.

There are other experiences showing the beneficial effect of the implementation of bundles to reduce CRBSI incidence. In a project in 29 pediatric ICUs across the United States, carried out between October 2006 to September 2007, the implementation of a bundle reduce CRBSI incidence from 5.4 *vs* 3.1 per 1000 catheter-days ($P < 0.001$)[14]. In other project in 12 ICUs across the United States, the CRBSI incidence decreased from 11.2 to 8.9 infections per 1000 catheter-days (RR = 0.79; 95%CI: 0.67-0.93) after the implementation of a bundle[15].

EVIDENCE ON ANTIMICROBIAL-IMPREGNATED CATHETERS

CVC impregnated in antimicrobial agents, such as cefazolin, vancomycin, chlorhexidine-silver sulfadiazine (CHSS), rifampicin-minocycline, or rifampicin-miconazol, has been proposed for the prevention of CRBSI[16].

First generation of CVC impregnated in CHSS (external surface impregnation) compared with non impregnated catheters have reduced CRBSI risk in a meta-analysis (OR = 0.56; 95%CI: 0.37-0.84; $P = 0.005$)[17]. Afterwards CHSS impregnated catheters of second generation (impregnated in the external and internal surfaces) reduced the CRBSI incidence compared to standard catheters, according the findings of a meta-analysis[18] including 3 randomised controlled trials (RCTs) and 1176 patients[19-21].

In addition, other meta-analysis was found a reduction of CRBSI with the use of CVC impregnated on antimicrobial agents compared with non-coated catheters[22]. In this meta-analysis were included 3452 CVCs from 8 RCTs, 7 RCTs using rifampicin-minocycline impregnated catheters and one using rifampicin-miconazole impregnated catheters.

A multicenter RCT showed that CVC impregnated in rifampicin-minocycline had a lower risk of CRBSI compared to first generation CHSS impregnated[23]. However, there is not reported a comparison in the incidence of CRBSI between rifampicin-minocycline and CHSS impregnated catheters of second generation.

Antimicrobial impregnated catheters have reduced the CRBSI risk and costs associated with CVC in several cost-effectiveness analyses[18,24,25]. The cost related to the increase of hospital stay was included in all those cost-effectiveness studies[18,24,25]. The cost associated to CRBSI was approximately $10000[18,24,25]; however, this cost in some studies was as high as $40000[5] and $71000[7] due to hospital stay increase. To simply the cost-effectiveness analyses, our team carried out several studies to compare the costs associated with CVC using antimicrobial impregnated catheters or standard catheters (including only the cost related to the diagnosis of CRBSI, the antimicrobials used for the treatment of CRBSI, and avoiding the cost due to increased hospital stay)[26-31].

Initially, we carried out performed one study to analyze the efficacy of rifampicin-miconazole (RM)

impregnated catheters to decrease the CRBSI risk[26]. There were included 73 RM in femoral site, 111 standard catheters in femoral site, 114 RM in jugular site and 127 standard catheters in jugular site. We found RM impregnated catheters showed a lower risk of CRBSI than standard catheters femoral venous access and in jugular venous access. Afterwards, we found that the use of RM impregnated catheters compared to standard catheters was associated with lower costs related to CVC in the jugular venous access with tracheostomy[27], and in the femoral venous access[28].

Afterwards, we studied the cost-effectiveness analyses of second generation of CVC impregnated in CHSS in different venous accesses[29-31]. We included 64 CHSS during 569 d and 190 standard catheters during 1626 d in femoral venous site; and there was found a lower CRBSI incidence and lower cost related to CVC in patients with CVC impregnated in CHSS than in patients with standard catheters[29]. In the jugular venous access analysis were included 245 CHSS impregnated catheters during 1685 d of catheter and 391 standard catheters during 1586 d of catheter; and there was found that patients with CVC impregnated in CHSS in comparison with patients with standard catheter showed a lower CRBSI incidence and a lower cost related to CVC[30]. In the analysis of subclavian venous including 353 patients with CHSS impregnated catheters during 2743 d and 518 with standard catheters during 3297 d, we found a lower incidence of CRBSI and lower CVC related cost per day of catheter in those patients with CHSS impregnated catheters than in those with standard catheters[31].

RECOMMENDATION OF GUIDELINES ABOUT THE USE OF ANTIMICROBIAL-IMPREGNATED CATHETERS

The 2011 published guidelines for CRBSI prevention recommended CVC impregnated in CHSS or rifampicin-minocycline impregnated catheter in patients whose catheter is expected to remain in place during more than 5 d and the incidence of CRBSI has not been reduced after the implementation of a comprehensive strategy[11].

I would like to make some comments about some issues of those recommendations. First, the recommendation about the use of CVC impregnated on rifampicin-minocycline was based on two RCTs showing that the use of CVC impregnated on rifampicin-minocycline reduced the risk of CRBSI[32,33]. However, the guidelines do not mentioned the meta-analysis by Falagas *et al*[22], which included also other four RCTs, and showing that CVC impregnated on rifampicin-minocycline reduced CRBSI rate. Besides, in those guidelines was not mentioned the published observational study reporting the reduction of CRBSI incidence with CVC impregnated on RM[26]. Second, there was recommended by those guidelines the use of CHSS impregnated based on 3 RCTs showing second generation of CVC impregnated in CHSS decreased catheter tip colonisation rate[19-21]. However, there was not specified which generation (first, second or both) of CHSS impregnated catheter was recommended. In addition, in those RCTs were not found significant differences in CRBSI rate with second generation of CVC impregnated in CHSS. Besides, in those guidelines was not mentioned the meta-analysis published by Hockenhull *et al*[18], which included those 3 RCTs and reported a lower risk of CRBSI using second generation of CVC impregnated in CHSS.

FACTORS ASSOCIATED WITH HIGHER RISK OF CRBSI

I believe that antimicrobial impregnated catheters could be used in some clinical circumstances associated with high CRBSI incidence. About this issue, I will focus in the CRBSI risk according to the venous catheter access and the presence of tracheostomy.

Risk of CRBSI according the CVC access

In a systematic, which included 2 RCTs and 8 observational studies, was concluded that there is no significant difference in the CRBSI incidence between subclavian and femoral venous accesses, and between internal jugular and femoral venous accesses[34]. To establish those conclusions, the authors excluded two studies from the analysis (one of our team[35], and other from the team of Nagashima *et al*[36]), and the criteria that motivate the exclusion of those 2 studies are no clear[37]. The authors remove these 2 studies due to heterogeneity of the analysis; however, the heterogeneity analysis showed I^2 = 35% and P = 0.14 (and in methods section the authors statement that I^2 < 49% suggested low heterogeneity and that $P \leqslant$ 0.10 was considered as significant heterogeneity), the same direction on the effect was found in the results of seven of studies included in the review (with a tendency to higher CRBSI risk in femoral venous access than in internal jugular venous access), and the two studies deleted showed the same effect. When these two studies were included, then femoral venous access exhibit a higher risk of CRBSI than internal jugular sites[34].

In a study published by our team including 2595 CVC (including 917 subclavian, 1390 internal jugular and 288 femoral venous accesses) was reported a higher risk of CRBSI in femoral than in jugular and subclavian accesses, and in jugular than in subclavian access[35].

In addition, in a study of our team was found a higher CRBSI risk in the central access than in the posterior access of internal jugular vein[38]. We believed that those findings could be probably due to lower risk of contamination in the posterior access group by oropharyngeal secretion. Critically ill patient undergoing to mechanical ventilation are in a semirecumbent

position to decrease esophageal reflux risk and aspiration risk, according the recommendation by the guidelines of the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America for the prevention of ventilator associated pneumonia[39]. Thus, in that position the oropharyngeal secretions due to gravity could reach easily the internal jugular vein by the central than by the posterior access.

Afterwards, we found a higher CRBSI risk in femoral venous site than in internal jugular vein by central access[40]. In addition, we did not find significant differences in CRBSI risk between subclavian venous site and internal jugular vein by posterior access[41].

Risk of CRBSI according the existence of tracheostomy

Tracheostomy has been found as risk factor of CRBSI[42,43]. In a study published by the team of Garnacho-Montero *et al*[42], including 1211 subclavian or jugular venous catheters, the presence of tracheostomy was found to be associated with CRBSI; however, the authors did not report the comparison between the both venous accesses with the presence of tracheostomy[42]. In another study by our team, which included 89 subclavian venous catheters with tracheostomy, 788 subclavian venous catheters without tracheostomy, 52 central internal jugular venous catheters with tracheostomy and 463 central internal jugular venous catheters without tracheostomy, was found that tracheostomy was associated with higher CRBSI risk. In addition, we found a higher incidence of CRBSI in patients with the presence of tracheostomy in the jugular venous access than in subclavian venous site[43].

Afterwards, we found that internal jugular venous site by central access and tracheostomy had a higher CRBSI risk than femoral venous site[44]. In addition, we found a lower CRBSI risk in the subclavian venous site with tracheostomy than in femoral venous site[45]. Besides, we found a higher CRBSI risk in internal jugular venous site by posterior access with tracheostomy than without tracheostomy[46].

The guidelines for CRBSI prevention recommend avoid the femoral venous access, and recommended the subclavian venous access rather than jugular or femoral venous accesses to reduce CRBSI risk for non-tunneled CVC placement[11]. However, there any recommendation about the different internal jugular venous sites and the venous access with tracheostomy.

CONCLUSION

In my opinion, antimicrobial impregnated catheters could be used in some clinical circumstances associated with higher risk of CRBSI, such as vascular sited with high CRBSI risk (femoral venous access or internal jugular venous access with tracheostomy) or patients with high CRBSI risk (patients with disorders of skin integrity or immunocompromised patients).

REFERENCES

1 **Vincent JL**, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. *JAMA* 1995; **274**: 639-644 [PMID: 7637145 DOI: 10.1001/jama.1995.03530080055041]

2 **Lorente L**, León C. [Femoral venous catheterization. Does it really need to be avoided?]. *Med Intensiva* 2009; **33**: 442-449 [PMID: 19922826 DOI: 10.1016/j.medin.2009.03.009]

3 **Smith RL**, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections. *Chest* 1991; **100**: 164-167 [PMID: 2060337 DOI: 10.1378/chest.100.1.164]

4 **Collignon PJ**. Intravascular catheter associated sepsis: a common problem. The Australian Study on Intravascular Catheter Associated Sepsis. *Med J Aust* 1994; **161**: 374-378 [PMID: 8090116]

5 **Pittet D**, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994; **271**: 1598-1601 [PMID: 8182812 DOI: 10.1001/jama.1994.03510440058033]

6 **Haley RW**, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. *Am J Med* 1981; **70**: 51-58 [PMID: 7457491 DOI: 10.1016/0002-9343(81)90411-3]

7 **Dimick JB**, Pelz RK, Consunji R, Swoboda SM, Hendrix CW, Lipsett PA. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. *Arch Surg* 2001; **136**: 229-234 [PMID: 11177147 DOI: 10.1001/archsurg.136.2.229]

8 **Rello J**, Ochagavia A, Sabanes E, Roque M, Mariscal D, Reynaga E, Valles J. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med* 2000; **162**: 1027-1030 [PMID: 10988125 DOI: 10.1164/ajrccm.162.3.9911093]

9 **Arnow PM**, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. *Clin Infect Dis* 1993; **16**: 778-784 [PMID: 8329510 DOI: 10.1093/clind/16.6.778]

10 **Lambert ML**, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis* 2011; **11**: 30-38 [PMID: 21126917 DOI: 10.1016/S1473-3099(10)70258-9]

11 **O'Grady NP**, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp ME, Saint S. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2011; **52**: e162-e193 [PMID: 21460264 DOI: 10.1093/cid/cir257]

12 **Pronovost P**, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, Bander J, Kepros J, Goeschel C. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725-2732 [PMID: 17192537 DOI: 10.1056/NEJMoa061115]

13 **Palomar M**, Álvarez-Lerma F, Riera A, Díaz MT, Torres F, Agra Y, Larizgoitia I, Goeschel CA, Pronovost PJ. Impact of a national multimodal intervention to prevent catheter-related bloodstream infection in the ICU: the Spanish experience. *Crit Care Med* 2013; **41**: 2364-2372 [PMID: 23939352 DOI: 10.1097/CCM.0b013e3182923622]

14 **Miller MR**, Griswold M, Harris JM, Yenokyan G, Huskins WC, Moss M, Rice TB, Ridling D, Campbell D, Margolis P, Muething S, Brilli RJ. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. *Pediatrics* 2010; **125**: 206-213 [PMID: 20064860 DOI: 10.1542/peds.2009-1382]

15 **Warren DK**, Cosgrove SE, Diekema DJ, Zuccotti G, Climo MW, Bolon MK, Tokars JI, Noskin GA, Wong ES, Sepkowitz KA, Herwaldt LA, Perl TM, Solomon SL, Fraser VJ. A multicenter intervention to prevent catheter-associated bloodstream infections. *Infect Control Hosp Epidemiol* 2006; **27**: 662-669 [PMID: 16807839 DOI: 10.1086/506184]

16 **Ramritu P**, Halton K, Collignon P, Cook D, Fraenkel D, Battistutta D, Whitby M, Graves N. A systematic review comparing the relative effectiveness of antimicrobial-coated catheters in intensive care units. *Am J Infect Control* 2008; **36**: 104-117 [PMID: 18313512 DOI: 10.1016/j.ajic.2007.02.012]

17 **Veenstra DL**, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999; **281**: 261-267 [PMID: 9918482 DOI: 10.1001/jama.281.3.261]

18 **Hockenhull JC**, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, Gamble C, McLeod C, Walley T, Dickson R. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technol Assess* 2008; **12**: iii-iv, xi-xii, 1-154 [PMID: 18405471 DOI: 10.3310/hta12120]

19 **Brun-Buisson C**, Doyon F, Sollet JP, Cochard JF, Cohen Y, Nitenberg G. Prevention of intravascular catheter-related infection with newer chlorhexidine-silver sulfadiazine-coated catheters: a randomized controlled trial. *Intensive Care Med* 2004; **30**: 837-843 [PMID: 15060765 DOI: 10.1007/s00134-004-2221-9]

20 **Ostendorf T**, Meinhold A, Harter C, Salwender H, Egerer G, Geiss HK, Ho AD, Goldschmidt H. Chlorhexidine and silver-sulfadiazine coated central venous catheters in haematological patients--a double-blind, randomised, prospective, controlled trial. *Support Care Cancer* 2005; **13**: 993-1000 [PMID: 15834740 DOI: 10.1007/s00520-005-0812-9]

21 **Rupp ME**, Lisco SJ, Lipsett PA, Perl TM, Keating K, Civetta JM, Mermel LA, Lee D, Dellinger EP, Donahoe M, Giles D, Pfaller MA, Maki DG, Sherertz R. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections: a randomized, controlled trial. *Ann Intern Med* 2005; **143**: 570-580 [PMID: 16230723 DOI: 10.7326/0003-4819-143-8-200510180-00007]

22 **Falagas ME**, Fragoulis K, Bliziotis IA, Chatzinikolaou I. Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2007; **59**: 359-369 [PMID: 17255143 DOI: 10.1093/jac/dkl522]

23 **Darouiche RO**, Raad II, Heard SO, Thornby JI, Wenker OC, Gabrielli A, Berg J, Khardori N, Hanna H, Hachem R, Harris RL, Mayhall G. A comparison of two antimicrobial-impregnated central venous catheters. Catheter Study Group. *N Engl J Med* 1999; **340**: 1-8 [PMID: 9878638 DOI: 10.1056/NEJM199901073400101]

24 **Pai MP**, Pendland SL, Danziger LH. Antimicrobial-coated/bonded and -impregnated intravascular catheters. *Ann Pharmacother* 2001; **35**: 1255-1263 [PMID: 11675856 DOI: 10.1345/aph.10416]

25 **Saint S**, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter-related infection: are antimicrobial catheters useful? *Infect Control Hosp Epidemiol* 2000; **21**: 375-380 [PMID: 10879567 DOI: 10.1086/501776]

26 **Lorente L**, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. The use of rifampicin-miconazole-impregnated catheters reduces the incidence of femoral and jugular catheter-related bacteremia. *Clin Infect Dis* 2008; **47**: 1171-1175 [PMID: 18808356 DOI: 10.1086/592253]

27 **Lorente L**, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. Rifampicin-miconazole-impregnated catheters save cost in jugular venous sites with tracheostomy. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1833-1836 [PMID: 22187350 DOI: 10.1007/s10096-011-1508-3]

28 **Lorente L**, Lecuona M, Ramos MJ, Jiménez A, Mora ML, Sierra A. Lower associated costs using rifampicin-miconazole–impregnated catheters compared with standard catheters. *Am J Infect Control* 2011; **39**: 895-897 [PMID: 21741122 DOI: 10.1016/j.ajic.2011.01.018]

29 **Lorente L**, Lecuona M, Jiménez A, Santacreu R, Raja L, Gonzalez O, Mora ML. Chlorhexidine-silver sulfadiazine-impregnated venous catheters save costs. *Am J Infect Control* 2014; **42**: 321-324 [PMID: 24581021 DOI: 10.1016/j.ajic.2013.09.022]

30 **Lorente L**, Lecuona M, Jiménez A, Lorenzo L, Diosdado S, Marca L, Mora ML. Cost/benefit analysis of chlorhexidine-silver sulfadiazine-impregnated venous catheters for femoral access. *Am J Infect Control* 2014; **42**: 1130-1132 [PMID: 25278411 DOI: 10.1016/j.ajic.2014.06.027]

31 **Lorente L**, Lecuona M, Jiménez A, Lorenzo L, Santacreu R, Ramos S, Hurtado E, Buitrago M, Mora ML. Efficiency of chlorhexidine-silver sulfadiazine-impregnated venous catheters at subclavian sites. *Am J Infect Control* 2015; **43**: 711-714 [PMID: 25934065 DOI: 10.1016/j.ajic.2015.03.019]

32 **Raad I**, Darouiche R, Dupuis J, Abi-Said D, Gabrielli A, Hachem R, Wall M, Harris R, Jones J, Buzaid A, Robertson C, Shenaq S, Curling P, Burke T, Ericsson C. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Ann Intern Med* 1997; **127**: 267-274 [PMID: 9265425 DOI: 10.7326/0003-4819-127-4-199708150-00002]

33 **Hanna H**, Benjamin R, Chatzinikolaou I, Alakech B, Richardson D, Mansfield P, Dvorak T, Munsell MF, Darouiche R, Kantarjian H, Raad I. Long-term silicone central venous catheters impregnated with minocycline and rifampin decrease rates of catheter-related bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol* 2004; **22**: 3163-3171 [PMID: 15284269 DOI: 10.1200/JCO.2004.04.124]

34 **Marik PE**, Flemmer M, Harrison W. The risk of catheter-related bloodstream infection with femoral venous catheters as compared to subclavian and internal jugular venous catheters: a systematic review of the literature and meta-analysis. *Crit Care Med* 2012; **40**: 2479-2485 [PMID: 22809915 DOI: 10.1097/CCM.0b013e318255d9bc]

35 **Lorente L**, Henry C, Martín MM, Jiménez A, Mora ML. Central venous catheter-related infection in a prospective and observational study of 2,595 catheters. *Crit Care* 2005; **9**: R631-R635 [PMID: 16280064 DOI: 10.1186/cc3824]

36 **Nagashima G**, Kikuchi T, Tsuyuzaki H, Kawano R, Tanaka H, Nemoto H, Taguchi K, Ugajin K. To reduce catheter-related bloodstream infections: is the subclavian route better than the jugular route for central venous catheterization? *J Infect Chemother* 2006; **12**: 363-365 [PMID: 17235641 DOI: 10.1007/s10156-006-0471-X]

37 **Lorente L**, Jiménez A. Central venous catheter site: should we really stop avoiding the femoral vein? *Crit Care Med* 2013; **41**: e34 [PMID: 23528774 DOI: 10.1097/CCM.0b013e318278b48e]

38 **Lorente L**, Jiménez A, Castedo J, Galván R, García C, Martín MM, Mora ML. Internal jugular venous catheter-related bacteremia according to central and posterior accesses. *Intensive Care Med* 2007; **33**: 1071-1075 [PMID: 17457569]

39 **Coffin SE**, Klompas M, Classen D, Arias KM, Podgorny K, Anderson DJ, Burstin H, Calfee DP, Dubberke ER, Fraser V, Gerding DN, Griffin FA, Gross P, Kaye KS, Lo E, Marschall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, Saint S, Salgado CD, Weinstein RA, Wise R, Yokoe DS. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol* 2008; **29** Suppl 1: S31-S40 [PMID: 18840087 DOI: 10.1086/591062]

40 **Lorente L**, Jiménez A, García C, Galván R, Castedo J, Martín MM, Mora ML. Catheter-related bacteremia from femoral and central internal jugular venous access. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 867-871 [PMID: 18386084 DOI: 10.1007/s10096-008-0507-5]

41 **Lorente L**, Jiménez A, Galván R, García C, Castedo J, Martín MM, Mora ML. Equivalence of posterior internal jugular and subclavian accesses in the incidence of central venous catheter

related bacteremia. *Intensive Care Med* 2007; **33**: 2230-2231 [PMID: 17885747]

42 **Garnacho-Montero J**, Aldabó-Pallás T, Palomar-Martínez M, Vallés J, Almirante B, Garcés R, Grill F, Pujol M, Arenas-Giménez C, Mesalles E, Escoresca-Ortega A, de Cueto M, Ortiz-Leyba C. Risk factors and prognosis of catheter-related bloodstream infection in critically ill patients: a multicenter study. *Intensive Care Med* 2008; **34**: 2185-2193 [PMID: 18622596 DOI: 10.1007/s00134-008-1204-7]

43 **Lorente L**, Jiménez A, Martín MM, Castedo J, Galván R, García C, Brouard MT, Mora ML. Influence of tracheostomy on the incidence of central venous catheter-related bacteremia. *Eur J Clin Microbiol Infect Dis* 2009; **28**: 1141-1145 [PMID: 19370367 DOI: 10.1007/s10096-009-0742-4]

44 **Lorente L**, Jiménez A, Naranjo C, Martínez J, Iribarren JL, Jiménez JJ, Santacreu R, Martín MM, Mora ML. Higher incidence of catheter-related bacteremia in jugular site with tracheostomy than in femoral site. *Infect Control Hosp Epidemiol* 2010; **31**: 311-313 [PMID: 20109074 DOI: 10.1086/651065]

45 **Lorente L**, Jiménez A, Martín MM, Palmero S, Jiménez JJ, Mora ML. Lower incidence of catheter-related bloodstream infection in subclavian venous access in the presence of tracheostomy than in femoral venous access: prospective observational study. *Clin Microbiol Infect* 2011; **17**: 870-872 [PMID: 21682804 DOI: 10.1111/j.1469-0691.2010.03406.x]

46 **Lorente L**, Jiménez A, Roca I, Martín MM, Mora ML. Influence of tracheostomy on the incidence of catheter-related bloodstream infection in the catheterization of jugular vein by posterior access. *Eur J Clin Microbiol Infect Dis* 2011; **30**: 1049-1051 [PMID: 21301912 DOI: 10.1007/s10096-011-1190-5]

P- Reviewer: Cotogni P, Kriebardis AG
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.143

World J Crit Care Med 2016 May 4; 5(2): 143-149
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Can PC-9 Zhong chong replace K-1 Yong quan for the acupunctural resuscitation of a bilateral double-amputee? Stating the "random criterion problem" in its statistical analysis

Adrián Ángel Inchauspe

Adrián Ángel Inchauspe, Department of Reseach, HINEA Interzonal Neuropsychiatric Hospital Dr. Alejandro Korn, Melchor Romero, La Plata, Buenos Aires, Aires B1884CUB, Argentina

Author contributions: Inchauspe AÁ solely contributed to this manuscript.

Institutional review board statement: Having consulted on the specific issue with Professor Carlo Guinzburg-Emeritus Professor at Bologna University and promoter of the Index Paradigm - and then submitted this proposal as regards the subjectivity of randomness in scientific research, a protocol for a pilot study was presented to the authorities of the Joint Committee on Health Research and the Central Ethics Committee of the Province of Buenos Aires-the highest authorities in our region-for its approval.

Informed consent statement: Regarding that these victims are unable to give their consent during an "impending death situation", quoted Central Ethics Committee proposed the publication in regional mass media to inform its population about that hospitals will adhere to this protocol.

Conflict-of-interest statement: The author reports no conflict of interest.

Data sharing statement: Consent was not obtained but the potential benefits of sharing these data outweigh the potential harms because, as mentioned before, Central Ethics Committee proposed the publication in regional mass media to inform its population about that hospitals will adhere to this protocol.

Correspondence to: Adrián Ángel Inchauspe, MD, PhD, Department of Reseach, HINEA Interzonal Neuropsychiatric Hospital Dr. Alejandro Korn, Melchor Romero, La Plata, Buenos Aires, 14-4079, Berazategui B1884CUB, Argentina. adrian.inchauspe@yahoo.com.ar
Telephone: +54-11-42561616
Fax: +54-11-42561616

Received: June 3, 2015
Peer-review started: June 8, 2015
First decision: December 4, 2015
Revised: December 13, 2015
Accepted: January 16, 2016
Article in press: January 19, 2016
Published online: May 4, 2016

Abstract

AIM: To present an inclusion criterion for patients who have suffered bilateral amputation in order to be treated with the supplementary resuscitation treatment which is hereby proposed by the author.

METHODS: This work is based on a Retrospective Cohort model so that a certainly lethal risk to the control group is avoided.

RESULTS: This paper presents a hypothesis on acupunctural PC-9 Zhong chong point, further supported by previous statistical work recorded for the K-1 Yong quan resuscitation point.

CONCLUSION: Thanks to the application of the resuscitation maneuver herein proposed on the previously

mentioned point, patients with bilateral amputation would have another alternative treatment available in case basic and advanced CPR should fail.

Key words: PC-9 Zhong chong; Alternative emergency point; Cardiac arrest; Double; Amputee patients

Core tip: The aforementioned inclusion criterion for the impossibility of stimulating K-1 Yong quan introduce PC-9 Zhong chong stimulation, so that the Shao Yin energetic level may be reactivated, restarting this biological pacemaker and the cardiac function. Diabetes increases risk of cardiovascular and cerebrovascular diseases from 50% to 80%; and every three seconds, a diabetic foot is amputated in the world. The proposed study upon a prospective non-intervention group, considering the "patients that may be deceased", states a Retrospective Cohort Study model that will allow us to efface the contingentiality of a possible "fatal damage".

Inchauspe AÁ. Can PC-9 Zhong chong replace K-1 Yong quan for the acupunctural resuscitation of a bilateral double-amputee? Stating the "random criterion problem" in its statistical analysis. *World J Crit Care Med* 2016; 5(2): 143-149 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/143.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.143

INTRODUCTION

Research on K-1 was presented back in 2005, during an official account at the Congress Celebrating the Fiftieth Anniversary of the Argentine Acupuncture Association[1], which encouraged us to continue doing research on efficiency criteria derived from its application.

That account was published by *Resuscitation*[2] in April 2010 to an important global repercussion. To date, ever more rescue cases through Yong quan are recorded and several hospitals resort to replacing their protocol due to the increased interest its extraordinary results generate.

This research project was edited first as a cover note in the *World Journal of Critical Care Medicine*[3], whose editorial presented then the validation of its statistical sequence, and now requests the publication of a new, original, paper on this issue of paramount importance.

We shall review the anatomical and functional bases for our hypothesis as well as the parameters which justify its use from the point of view of Traditional Chinese Medicine.

Topographic anatomy of PC-9 Zhong chong

Traditionally, the point is located 0.1 cm from the base of the nail on the radial side of the hand's middle finger. This soft region is innervated by the palmo-digital arteriovenous net which is irrigated by the digital branch of the median nerve[4].

Rather curiously, the finger we refer to is also known as "cordial or heart finger" in Spanish [*dedo cordial* or *corazón*], thus discarding any causal nominative association from its anatomic-functional value. To a certain extent, such names in Spanish connote a close relationship between such finger and the organ it protects[4].

Functions of Zhong chong

PC-9 Zhong chong is the Tsing-well point of the Xin Bao meridian, or "Heart Protector". It is also the Wood-Cheng point of a Fire channel and, as such, it should not surprise its additional function of Stimulating Point of that channel, precisely because it precedes the Fire element in the Five Movement Theory of Traditional Chinese Medicine[4].

Maybe what has been stated before justifies its capacity to reduce the Heart Fire (*Xin*) on that channel: Deriving from either its ignition by excess or the plenitude of its Mother element in the generative cycle, *i.e.,* Wood[5] (Table 1).

This may explain the therapeutic possibility of acting on said channel in order to alleviate every cardiovascular condition resulting from affecting Fire, as well as those effects proper to its state of Well point, which enables restoring the biological pacemaker of the organism. This may either derive from considering gastro-entero-colonic peristalsis to even the very cardiac pacemaker present at the sinoauricular node. This meridian has -under the parameters of Chinese Medicine - the justified property of recovering the Heart from its most severe nosological conditions.

Thus, the Xin Bao channel is provided with points with *Yin/Yang* energy rebalancing properties for the body, consequently harmonizing its biological rhythms. As we previously stated, this enables this point to act as an effective cardiac pacemaker. For this reason, it has been chosen as an Alternative Emergency Point (in case of coma, sudden death or cardiac arrest*)* because of its direct connection with the Shao Yin energetic plane through a short channel branch running between PC-1 to K-27 (Figure 1).

That is the case of another point, namely, PC6-*Nei guan*, *Luo* meridian link and root, able to open up the *Extraordinary Yin Wei Vessel* and, consequently, to regulate the cardiovascular, respiratory and digestive activity of our body. That is why we understand its specific antiemetic property, comparable in strength to that of a well-known medicine ondansetron, widely used as palliative for said collateral effect during anti blastic therapies[6].

MATERIALS AND METHODS

Materials

Materials for the purposes of this paper are a wide range of patients who, for different reasons, have no lower limbs, that situation being the result of a

Table 1 Heat patterns affecting pericardium[5]

Pattern	Heat colapsing pericardium	Murky mucosity obstructing pericardium
Consciousness	Coma; convulsions	Coma; patient sometimes awake
Fever	High fever	Low fever
Fæces	Constipated or no change	Inconsistent
Pulse	Weak or tense and fast	Sunken or unstable and fast
Tongue	Scarlet, with yellow fur	Red, with white or greasy fur

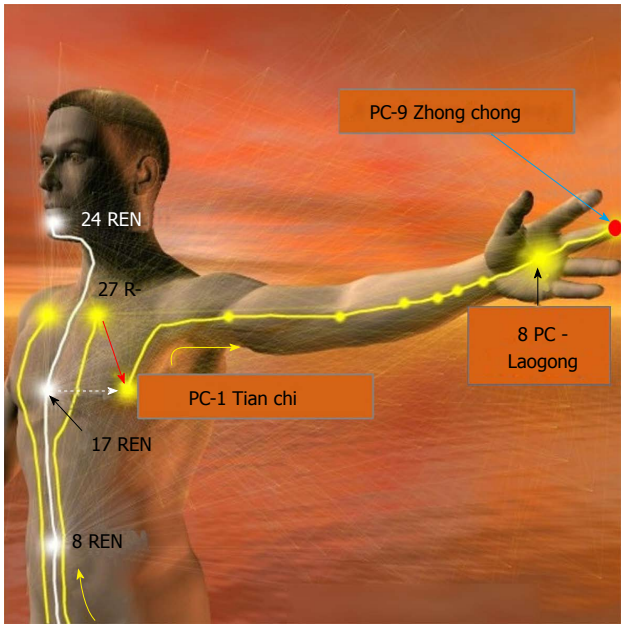


Figure 1 Establishing the connection between Xin Bao and Shao Yin. Source (modif.): http://www.ktthome.com/teorias/mtc/teorias_mtc_1_1_2_8.html.

congenital cause or as a consequence of the evolution of a number of diverse pathologies (*e.g.,* diabetes, traumas, neurologic diseases, toxic causes, *etc.*).

The status of this patient-population - previously set aside from possibility of integration between the supplementary Yong quan resuscitation maneuver and ILCOR's CPR-can now be reconsidered among this new proposal of inclusion criteria. Quoted criteria have been made possible thanks to the development and design of a new, alternative praxis to assist this patient group during imminent death situations[3].

Methods

Those subjects within the Inclusion criterion above mentioned shall be those to whom-because of the impossibility of stimulating K-1 Yong quan-shall undergo stimulation at PC-9 Zhong chong, so that their Shao Yin energetic level may be reactivated as well as their survival axis, thus enabling the resetting and restarting their biological pacemaker and their cardiac function[7].

Stimulation maneuver for PC-9 Zhong chong

In spite of its habitual location described before, whenever in an emergency situation, it may prove convenient to unify topographical criteria and locate the very tip of the middle finger in order to stimulate the point by direct pressure in the distal extremity of its third phalanx, thus a more efficient stimulus is obtained and there is no confusion for the rescuer as to the location of the life-saving point.

It is worth mentioning that Traditional Chinese Medicine also considers valid this location we are proposing[4].

The Chinese indicated bleeding the point to make the maneuver effective; that is why it is better to apply direct pressure on the tip of the middle finger. However, we have been able to verify that the pressure exerted by the nail of the rescuer might be enough to achieve efficient stimulations and positive results on the cardiac pacemaker.

Initially, as in the case of Yong quan, a methodological design was proposed during the investigation in which a certain group would receive the treatment and another would not be benefited (*control group*). Such type of study makes reference to the *random criterion* in order to measure differences and, in that way, establish causal associations which may better determine the intervention mechanism.

Stating the random criterion problem

The randomness principle requires an ever increasing sample - following a *quantitative* interest - in order to get away from uncertainty, thus reducing the variability of fate. Being that generally the case in the validation of any statistical methodology applied in Medicine, it has to make an effort to prove if any association visible through observation is a product of fate or not[3,8].

As inferred by quoted criterion, the control group would not profit from the benefit of providing a second chance by means of the proposed maneuver during rescue. Such determination leaves those included in the control group *deserted to their own ill-fate* should basic and advanced CPR fail.

Application of statistical analysis based on the index paradigm[9]

As was the case while analyzing the Yong quan maneuver statistical tendencies-in spite of what has been so far stated, we have assigned priority to what, in our view, is singular and of qualitative nature. As such, the proposal of a Retrospective Cohort Study model has been able to prove the following suggested affirmation[9].

In statistics, a null hypothesis (Ho) is one made up

with the purpose of supporting another, alternative one (Ha). To develop any medical study necessarily implies determining an association between such two variables under research.

Any statistical treatment contemplates the possibility of a standard error (SE). That is why, the wider the sample, the more precise it becomes; consequently the possibility of results being random is greatly reduced [this analysis was previously published in *WJCCM* August 2013 - ISSN 2220-3141 (online)[3]].

In order to select one of these hypotheses (either Ho or Ha), a security level is required which, in clinical studies, has been standardized at 95%.

Statistical testing functions this way: The scale of difference that exists between the methods to be compared (A and B) needs to be verified. Should such scale be higher than a defined SE multiplied by a security coefficient - which is also given - we can then conclude that the difference between methods A and B is statistically significant. Such statement enables us to reject Ho hypothesis and accept Ha hypothesis[3].

First, we compared classical CPR by manual cardiac massage (method A) with the complementary resuscitation maneuver on Yong quan (method B). By August, 2013, the following values were obtained (out of 58 patients looked after and 9 dead ones):

Method A (Manual CPR) = 6.4% Method B: (Yong quan rescue) = 85%

Thus, if *P* = [PA - PB] = [0.064 - 0.85] = 0.786[3] (where *P* stands for Probability).

To this result, SE is applied, E = $\sqrt{P}$ (1 - P) × (1/n1 + 1/n2). Then, SE × 1.96 = 0.098.

Therefore, 0.786 is higher than 0.098, which demonstrates the difference between PA and PB to be significant, thus concluding that Yong quan rescue is quality sure.

In order to further verify the previous analysis, the sample obtained in May 2015 (with 76 patients looked after and 12 dead ones), rendered the following values:

Method A (Manual CPR) = 6.4% Method B (Yong quan praxis) = 84.21%

Thus, P = [PA - PB] = [0.064 - 0.8421] = 0.778

Again, the result verifies that 0.778 is higher than 0.098, which further debunks Ho hypothesis and once more verifies the alternative hypothesis (Ha).

Furthermore, in August 2013 we also compared the use of defibrillation (Method "A'" - meaning CPR + defibrillation) against the complementary Yong quan resuscitation maneuver (Method "B"). Afterlife indexes on both treatments were as follows:

Method "A'" (CPR + defibrillation): 48% response

Method "B" (Yong quan maneuver: 84.84% response

Thus, [PA' - PB] = 0.48 - 0.84 = 0.36

That, multiplied by SE: SE (0.0076) × 1.96 = 0.0148

Because this result is also higher than SE multiplied by 1.96, it provides a value of 0.00148, a figure which is also statistically significant. This, again, proves the statistical value of the supplementary resuscitation K-1 Yong quan point by means of comparative analysis[3].

Let us compare new values in these two methods provided in May, 2015:

Defibrillator method (Method A') = 30%

Yong quan method (Method B) = 84%

P = [PA - PB]; that is, P = [0.30 - 0.8421] = 0.542

Applying the same process of multiplication by SE: SE × 1.96 = 0.0148

Consequently, as 0.542 is higher than 0.0148, it can be deduced that the difference in P once more becomes significant, rejecting Ho hypothesis and giving support to Ha hypothesis, which implies that this sequence of studies is far from being a random, chance product.

The difference here is also confirmed to be statistically significant; thus, all of the considerations from the previous example are valid, demonstrating once more the comparative value of the Yong quan method[3] (Figure 2).

Even though today there are updated statistics in which manual CPR reached 17% survival rate (see, *e.g.*, www.ymca.org.ar), it is in fact estimated that the actual survival rate would be noticeably lower, this deriving from what results studies indicate.

According to what Dr. Custodio Calvo, member of the Spanish Cardiopulmonary Resuscitation Association, has mentioned, such estimated indices of survival would not for cardiac massage, if truth be told, go further than 5%[10]. Other studies later claim a rise up in survival rate to 10%[11] which, they estimate, may result in an increased value if population had more knowledge on CPR technique and use.

As for the survival percentages due to the application of cardioversion, recent studies presented by Dr. Emilio Marín-Huerta show that premature defibrillation increased this scale from 24% to 30% in cases of cardiac arrest[11]. It is worth noticing that the 2013 statistics made reference to the resuscitation carried out at casinos in Las Vegas, where there is a defibrillator available every 40 m.

As a matter of fact, statistics referring to extra-hospital resuscitations seem to have stuck at a 6.4%, a figure which coincides with the former evaluation of the previous statistical analysis which was presented by this author in this very same publication in August 2013.

It should be mentioned that, if cumulative rates of positive responses to the maneuver be considered (verified by pulse recovery and ECG record), the rate reached a 92.10%; *i.e.,* over 76 cases, 70 patients could manifest objective responses to K-1 stimulation.

Consequently, all the above has made clear that there actually exists a difference if one takes into account as control the group of "deceased patients" instead of considering among them "patients that may be deceased". Stating such consideration into a Retrospective Cohort Study model[9] will allow us to efface the contingentiality of a possible "fatal damage" as proposed by the randomness principle upon a prospective non-intervention group in both K-1 Yong quan

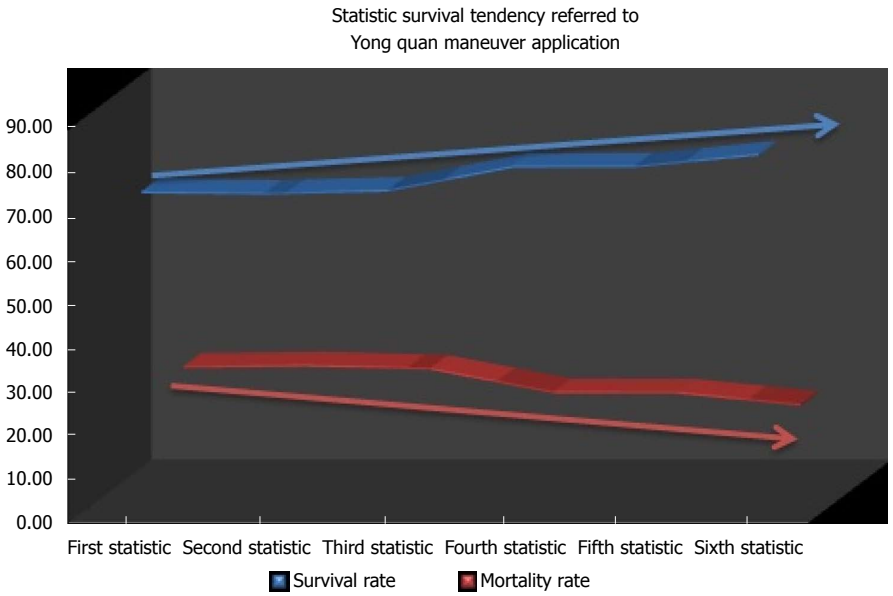


Figure 2 Statistic Survival Trend referred to the Yong quan Maneuver application[3].

and future PC-9 Zhong chong research.

RESULTS

Having had an experience of more than 75 cases treated when basic and advanced CPR had failed, the supplementary K-1 Yong quan maneuver has shown a most promising survival rate (84.84%) once the classic CPR protocols have been proved of no use, thus validating the action of the Shao Yin (heart-kidney) circuit during its support to life maintaining maneuvers[3].

As regards diabetes, the WHO has currently established the following statistics[12]: (1) one in 10 individuals is diabetic (*i.e.,* 10% of world population - about 347 million people worldwide have diabetes); (2) it is estimated that in 2012 diabetes was the direct cause of 1.5 million deaths, mainly due to sugar excess in the blood sample while fasting; and (3) every three seconds, a diabetic foot is amputated in the world these days.

Diabetes has become a major cause for an increased risk of cardiovascular and cerebrovascular diseases - between 50% and 80% of deaths in people with diabetes - making this condition the one which predisposes the most to suffering a stroke (this being, at the same time, cause and effect of cardiac arrest)[7].

From the aforementioned, one can fairly deduce that the group which this hypothesis addresses is one in constant growth, a global trend which apparently shall be only on the rise in the short and long run and make even more frequent the cases under study, quite similar to those already mentioned and studied.

DISCUSSION

The effect on the Shao Yin plane has been irrefutably demonstrated - through the resuscitations published-by stimulation the K-1 Yong quan. We have already made clear that this circuit is part of the so-called "survival axis", which has been confirmed in the Western tradition by the works carried out by Cannon and Seyle on the "fight or flight" or "stress" reaction[7,10] (Figure 3).

Likewise, there also exist relationships that establish their link for the heart governor channel as well. One of them is that Xin Bao has been found to be the "pulse wife" to kidney, located at the same height but on the left wrist or Yang.

Besides, it needs to be remembered that there exists a small collateral branch from K-27 - to the end of the external trajectory of the kidney meridian-through which it receives its daily chrono-biological legacy with the Well and Alarm point of the same *Heart Governor* channel, PC 1 - *Tian chi* (see illustration). According to the descriptions found on Acupuncture norms, the presence of such connection with the Shao Yin energetic plane fully justifies acting on that point when confronted to emergency situations caused by cardiac arrest.

Physiological testing in a bilateral double amputee and healthy volunteers showed significant changes as regards heart rate variation on stimulating PC-9 Zhong chong, very much like what took place when validation for the supplementary resuscitation maneuver on Yong quan was required.

All this justifies our assumption that in those cases in which K-1 stimulus is impossible, we can try successful stimulation when confronted with the unfortunate failure of both basic and advanced CPR. Its categorization as "alternative supplementary pacemaker" when stimulation on K-1 point is rendered impossible shall eventually be more accurately established by a pilot study that shall reliably verify the statistical value of its effects, as was required from the supplementary practice on the Yong quan.

In conclusion, the Heart Governor meridian-through

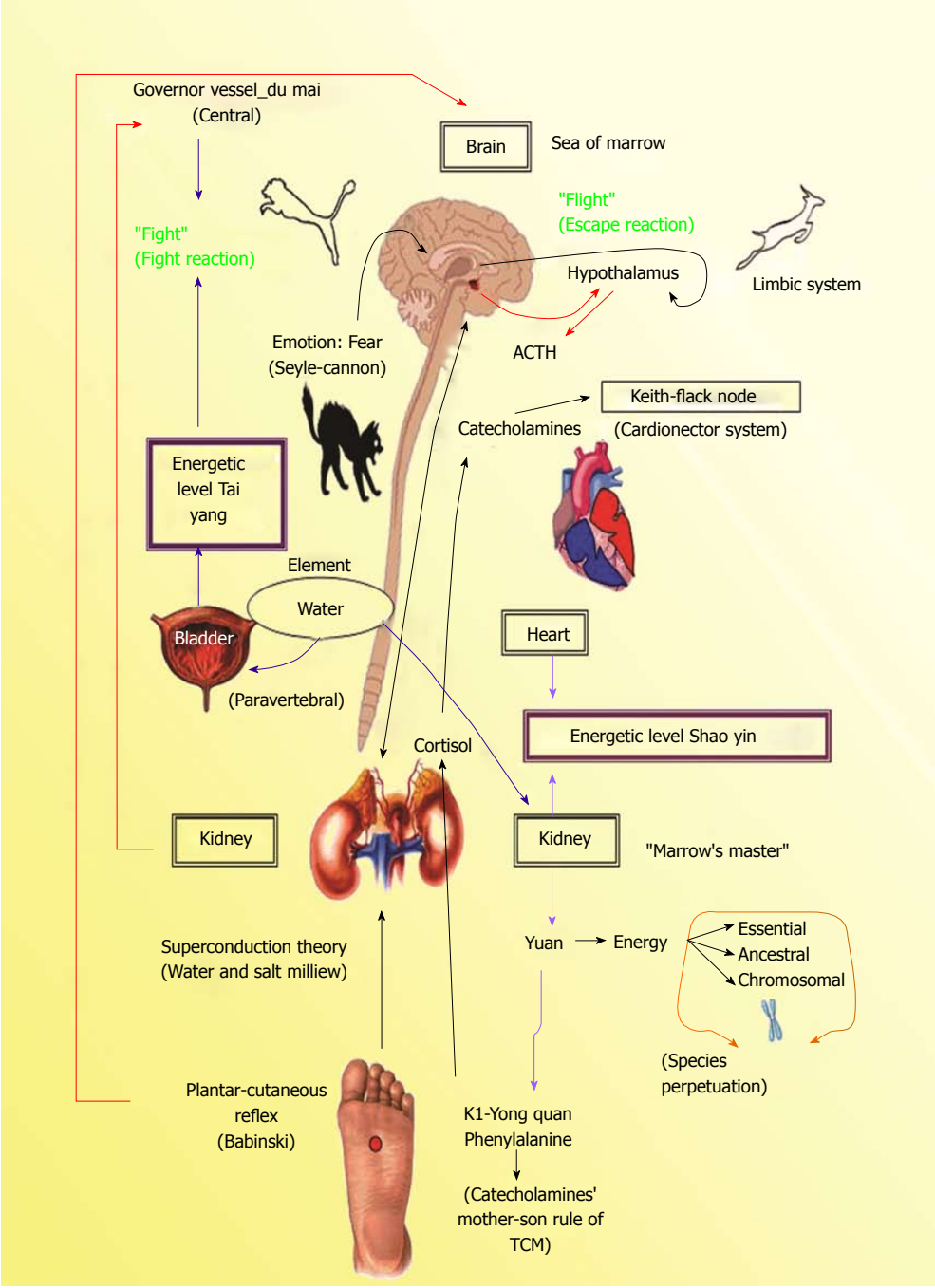


Figure 3 Survival axis as described by Inchauspe Adrián Ángel[13]. TCM: Traditional chinese medicine; ACTH: Adrenocorticotropic hormone.

inner and outer collaterals-ensures blood provision and distribution to the Heart; consequently, it rules the channeling through which both Qi and Heart irrigation flow as regards their function of blood admission and propulsion.

In some way, Xin Bao-according to Dr. Carlos Zaringolami-is a reflection of Xin's drive of Qi; consequently, it shall be directly involved in every circulatory ailment related to pumping disruption: *i.e.,* palpitations, precordalgia, angor pectoris and cardiorespiratory arrest.

As we have previously seen, PC-9 Zhong chong fulfills every prerogative of stimulating the correct paths in order to explain and achieve the expected results so that the unfortunate group of patients, whose condition is already limited, should not be confronted to a most surely fatal situation in case basic and advanced CPR fail.

As in the case of K-1 Yong quan, the proposed new maneuver that is herein contained-on the pertinent section above-offers an extremely simple solution during an emergency situation to a very severe prognostic problem at no cost whatsoever.

COMMENTS

Background

In the authors' 28-year-career resuscitating through the K-1 Yong quan, different situations as to sustaining its supplementary application during life supporting protocol use. However, double-amputee diabetic patients were

considered excluded from Yong quan CPR method in case of basic and advanced CPR failure. This challenge demanded an urgent solution in order to eliminate these patients from the exclusion criteria in the supplementary reanimation maneuver protocols on Yong quan for such unfortunate cases. The proposal of this hypothesis for the use of PC-9 Zhong chong as an alternative resuscitation point will certainly benefit those subjects in whom Yong quan is either anatomically non-existent or impossible to access.

Research frontiers

Statistics from the experimental plan proposed herein shall enable assessment of the real value of PC-9 Zhong chong as an alternative resuscitation point to consider in double amputee patients in whom failure of basic and advanced CPR protocol would leave them hopeless.

Innovations and breakthroughs

This work aims at adding an alternative point to the supplementary resuscitation system designed by the author and endorsed within Traditional Chinese Medicine parameters so that precisely the most unfortunate patients may have another resource in case they need rescue.

Applications

The methodology proposed shall offer yet another therapeutical alternative to add to current life support international protocols available at emergency services.

Peer-review

The author performed a retrospective analysis in order to estimate an inclusion criterion for patients who have suffered bilateral amputation whether they could be treated with the supplementary resuscitation treatment like acupunctural of PC-9 Zhong chong point, further supported by previous statistical work recorded for the K-1 Yong quan resuscitation point. Patients with bilateral amputation independently of the cause were included in the study. The author concludes that thanks to the application of the resuscitation maneuver herein proposed on the previously mentioned point, patients with bilateral amputation would have another alternative treatment available in case basic and advanced CPR should fail.

REFERENCES

1 **Inchauspe AA.** El Efecto Lázaro: mi experiencia con Yongquan en la Reanimación Cardiovascular. Tema de Relato del Congreso del Cincuentenario de la Asociación Argentina de Acupuntura. *Revista Argentina de Acupuntura* 2006; **117:** 5-11

2 **Inchauspe AA.** Traditional Chinese Medicine K-1 Yongquan and resuscitation: another Kind of "Lazarus phenomenon. *Resuscitation* 2010; **81**: 505-506 [DOI: 10.1016/j.resuscitation.2009.12.009]

3 **Inchauspe AA.** Drawing the yongquan protocol into the different stages of the cardiopulmonary resuscitation sequence**.** *World J Crit Care Med* 2013; **2**: 17-20 [PMID: 24701412 DOI: 10.5492/wjccm.v2.i3.17]

4 **Inchauspe AA.** Systematized Integration of Therapeutic Acupunctural Knowledge. New York: Nova Publishers, 2014

5 **Kaptchuck T.** Medicina China: una Trama sin Tejedor. Appendix A: El Modelo de las Cuatro Fases. Barcelona: Libros de la Liebre de Marzo, 1995

6 **PC-6 vs ondansestron.** Available from: URL: http://www.bdigital.unal.edu.co/2326/1/597982.2009.pdf

7 **Inchauspe AA.** "Traditional Chinese and Brain Protection: Can its principles be consistent with Western Science?" Poster Presentation, 9th IBIA International Brain Injury Association Congress. Edinburgh, Scotland, 2012

8 **Apreda GA.** "La Psicopatología, la Psiquiatría y la Salud Mental - Sus paradigmas y su integración" Ed. de la Universidad Nacional de La Plata, 2010: 46

9 **Inchauspe AA.** Resuscitation on the K-1 Yongquan: Ethical and Methodological Aspects of its Pilot Study. *Health* 2015; **7**: 809-818 [DOI:10.4236/health.2015.77095]

10 **Calvo C.** La tasa de supervivencia tras la aplicación de la RCP básica no supera el 5 por ciento, según se desprende de estudios. Available from: URL: http://www.e-mergencia.com/threads/la-tasa-de-supervivencia-tras-la-aplicacion-de-la-rcp-basica-no-supera-el-5-por-ciento-segun-se-des.16167/

11 **Marín-Huerta E,** Rafael Peinado, Antonio Asso, Ángel Loma, Julián P Villacastín. Muerte súbita cardíaca extrahospitalaria y desfibrilación precoz. *Rev Esp Cardiol* 2000; **53**: 851-865 [DOI: 10.1016/S0300-8932(00)75165-7]

12 **Diabetes**. Available from: URL: http://www.who.int/diabetes/facts

13 **Inchauspe AA.** Traditional Chinese Medical Criteria about the Use of Yongquan as a Life-Support Maneuver. In: Haixue Kuang, Recent Advances in Theories and practice of Chinese Medicine. Croatia: InTech Publications, 2011

P- Reviewer: Kouraklis G
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.150

World J Crit Care Med 2016 May 4; 5(2): 150-164
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Prospective Study

Cost effectiveness of intensive care in a low resource setting: A prospective cohort of medical critically ill patients

Hajrunisa Cubro, Rabija Somun-Kapetanovic, Guillaume Thiery, Daniel Talmor, Ognjen Gajic

Hajrunisa Cubro, Guillaume Thiery, Medical Intensive Care Unit, Sarajevo University Clinical Center, Sarajevo 71000, Bosnia and Herzegovina

Rabija Somun-Kapetanovic, Department of Quantitative Economics, Faculty of Economics, Sarajevo 71000, Bosnia and Herzegovina

Daniel Talmor, Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215, United States

Ognjen Gajic, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN 55905, United States

Author contributions: Cubro H, Somun-Kapetanovic R and Thiery G collected and analyzed the data; Cubro H, Talmor D and Gajic O designed the work; Cubro H, Talmor D and Gajic O interpreted the results; Cubro H wrote the first draft; Cubro H, Thiery G, Talmor D and Gajic O revised the manuscript for important intellectual content and gave approval for publication.

Institutional review board statement: The study was reviewed and approved by the Institutional review board of Sarajevo University Clinical Center and Ehics commitee of the Sarajevo University Faculty of Medicine.

Informed consent statement: All study participants, or their legal guardian, provided written informed consent prior to study enrollment.

Conflict-of-interest statement: The authors of this study declare that they have no conflict of interest to disclose.

Data sharing statement: There is no additional data.

Correspondence to: Ognjen Gajic, MD, Professor of Medicine, Division of Pulmonary and Critical Care, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States. gajic.ognjen@mayo.edu
Telephone: +1-507-2556051
Fax: +1-507-2554267

Received: April 9, 2015
Peer-review started: April 9, 2015
First decision: September 14, 2015
Revised: October 20, 2015
Accepted: November 13, 2015
Article in press: November 17, 2015
Published online: May 4, 2016

Abstract

AIM: To calculate cost effectiveness of the treatment of critically ill patients in a medical intensive care unit (ICU) of a middle income country with limited access to ICU resources.

METHODS: A prospective cohort study and economic evaluation of consecutive patients treated in a recently established medical ICU in Sarajevo, Bosnia and Herzegovina. A cost utility analysis of the intensive care of critically ill patients compared to the hospital ward treatment from the perspective of the health care system was subsequently performed. Incremental cost effectiveness was calculated using estimates of ICU *vs* non-ICU treatment effectiveness based on a formal systematic review of published studies. Decision analytic modeling was used to compare treatment alternatives. Sensitivity analyses of the key model parameters were performed.

RESULTS: Out of 148 patients, seventy patients (47.2%) survived to one year after critical illness with a median

quality of life index 0.64 [interquartile range(IQR) 0.49-0.76]. Median number of life years gained per patient was 30 (IQR 16-40) or 18 quality adjusted life years (QALYs) (IQR 7-28). The cost of treatment of critically ill patients varied between 1820 dollar and 20109 dollar per hospital survivor and between 100 dollar and 2514 dollar per QALY saved. Mean factors that influenced costs were: Age, diagnostic category, ICU and hospital length of stay and number and type of diagnostic and therapeutic interventions. The incremental cost effectiveness ratio for ICU treatment was estimated at 3254 dollar per QALY corresponding to 35% of per capita GDP or a Very Cost Effective category according to World Health Organization criteria.

CONCLUSION: The ICU treatment of critically ill medical patients in a resource poor country is cost effective and compares favorably with other medical interventions. Public health authorities in low and middle income countries should encourage development of critical care services.

Key words: Cost benefit analysis; Intensive care; Quality of life; Intensive care unit; Mortality; Decision analysis; Economics

Core tip: The first of a kind prospective cost effectiveness study in the intensive care unit in low resource settings. The study provides important evidence that critical care is cost effective medical intervention that favorably compares with most standard medical treatments but is unfortunately grossly underdeveloped in low resource settings.

Cubro H, Somun-Kapetanovic R, Thiery G, Talmor D, Gajic O. Cost effectiveness of intensive care in a low resource setting: A prospective cohort of medical critically ill patients. *World J Crit Care Med* 2016; 5(2): 150-164 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/150.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.150

INTRODUCTION

Cost-effectiveness analysis (CEA) and related techniques are methods for evaluating the economic efficiency of health-related programs and interventions[1,2].

CEA is designed to incorporate the medical and economic aspects of health care programs or interventions, to examine these interventions from perspectives of different actors and to allow objective comparisons with alternative interventions or programs[3]. In an environment with limited resources, it is crucial to ensure fairness in the allocation of resources on the one hand and efficiency on the other[4]. Health care providers, public health officials, and other decision makers require accurate information about economic efficiency, or "cost-effectiveness", of different options in order to maximize the impact of health care spending[5]. Ideally this will lead to the most effective allocation of resources. For a post-war developing country such as Bosnia and Herzegovina optimal allocation of resources is crucial.

Treatment of critically ill patients includes expensive equipment, highly skilled personnel, and often costly procedures to save lives. Studies that deal with the outcome of treatment in an intensive care unit (ICU), have reported mortality of critically ill patients between 8% and 33%, with a further 11% to 64% mortality rate on general hospital wards after ICU treatment[6,7].

Intensive care is an expensive specialty due to its need for highly trained personnel and modern technology[8] and is a low priority for public health authorities in resource limited countries[9-11]. Objective analysis of costs and outcomes is needed to determine whether an admission to an ICU is a reasonable use of limited resources in a population of critically ill patients[12].

The high mortality of ICU patients, high cost, and a certain possibility of survival of patients without intensive care raise a question of whether the treatment in an ICU provides good value for invested resources, especially in a resource limited country such as Bosnia and Herzegovina?

A search of the literature on the analysis of costs and effectiveness in the field of intensive care medicine found no studies published from the Balkans, South-Eastern Europe or other resource limited settings. The objective of this study was to calculate the incremental cost per quality-adjusted life year (QALY) obtained by the treatment of medical critically ill patients in the ICU compared to the treatment without intensive care at the Sarajevo University Clinical Center. We sought to understand whether the recently established medical ICU provides a good value for the invested resources by the health care system of a developing country.

Our original hypothesis was that critical care is cost-effective even in a resources poor setting.

MATERIALS AND METHODS

Design and setting

We performed a prospective cohort study and an economic evaluation of consecutive medical critically ill patients treated in a recently established five bed medical ICU in a tertiary care medical institution with around 1800 beds in Sarajevo, the capital city of Bosnia and Herzegovina. The ICU has approximately 140-180 admissions annually.

Study population

Consecutive medical critically ill patients treated between June 1 2011 and June 29 2012 was included. Patients that stayed in the ICU less than 24 h and hospital readmissions were excluded from the analysis. Critical care survivors were interviewed at one year

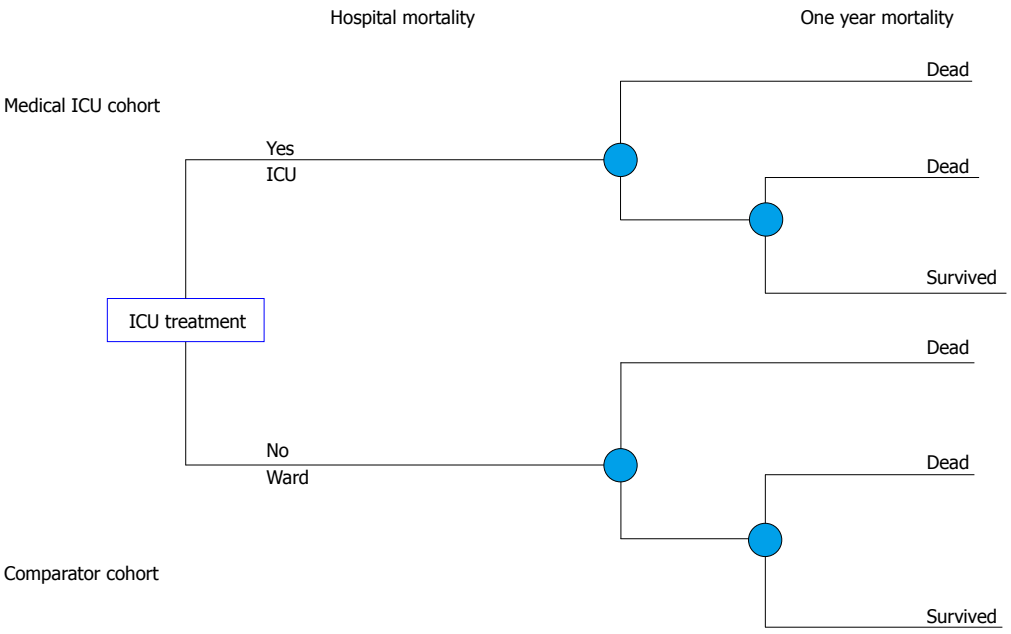


Figure 1 The decision tree in the decision analysis. Two branches of the decision tree represent two cohorts of critically ill patients. First one is represented with the patients that were treated in the medical ICU. The other branch represents comparator model of the same patients and shows the treatment outcomes if patients were treated on the hospital ward instead of the ICU. data on treatment outcomes for the comparator were extracted from the systemetic review of the literature. ICU: Intensive care unit.

follow up after hospital release.

Patient characteristics, acute illness severity scores[13-15], diagnostic and therapeutic interventions along with costs were prospectively recorded. Data were recorded in a predefined paper form and afterwards entered in a specially constructed database.

Control group of patients

Ethical and administrative constraints precluded the use of historical or concurrent control group of the critically ill patients without access to the ICU in our institution. To overcome these constraints and to increase the generalizability of our findings, we calculated the incremental cost effectiveness using estimates of ICU *vs* non-ICU treatment effectiveness based on a formal systematic review of published studies.

Outcome definitions

Primary outcome measure was one year survival. Secondary outcome measures were: 28 d ventilator free days, 28 d ICU free days, 30 d and 60 d mortality, the health related quality of life (HRQOL) and incremental cost effectiveness ratio (ICER). Ventilator-free days were defined as the number of days between successful weaning from mechanical ventilation and 28 d after study enrollment[16]. ICU-free days were defined as the number of days between successful transfer to a normal ward and 28 d after study enrollment[16].

ICER is the ratio of the difference in costs and difference in effects between two competing choices[17].

Economic evaluation

Recommendations of the Panel of Cost-effectiveness in Health and Medicine adjusted for critical care were followed for economic evaluation[18].

With primary data obtained, a full economic evaluation in the form of cost utility analysis of intensive care of critically ill patients compared to hospital ward treatment from the perspective of the health care system was performed. The analytical horizon was the life time of patients. Decision analytic modeling was used to construct a decision tree (Figure 1), which served to calculate the ICER.

Model: The decision tree

Two branches of the decision tree present two cohorts of critically ill patients. First one is represented with the medical ICU patients (Figure 1). The other branch represents the comparator model of the patients with the same characteristics and shows treatment outcomes if patients were treated on the hospital ward instead of the ICU.

The data on the treatment outcomes of the comparator cohort were extracted from a systematic review of the literature.

Systematic review

A systematic review of the available literature was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[19].

A comprehensive search strategy was developed in order to identify the studies that dealt with outcomes of the treatment of adult critically ill patients in and out of an ICU. The following electronic databases were searched: PubMed, EBSCO and Web of science. The

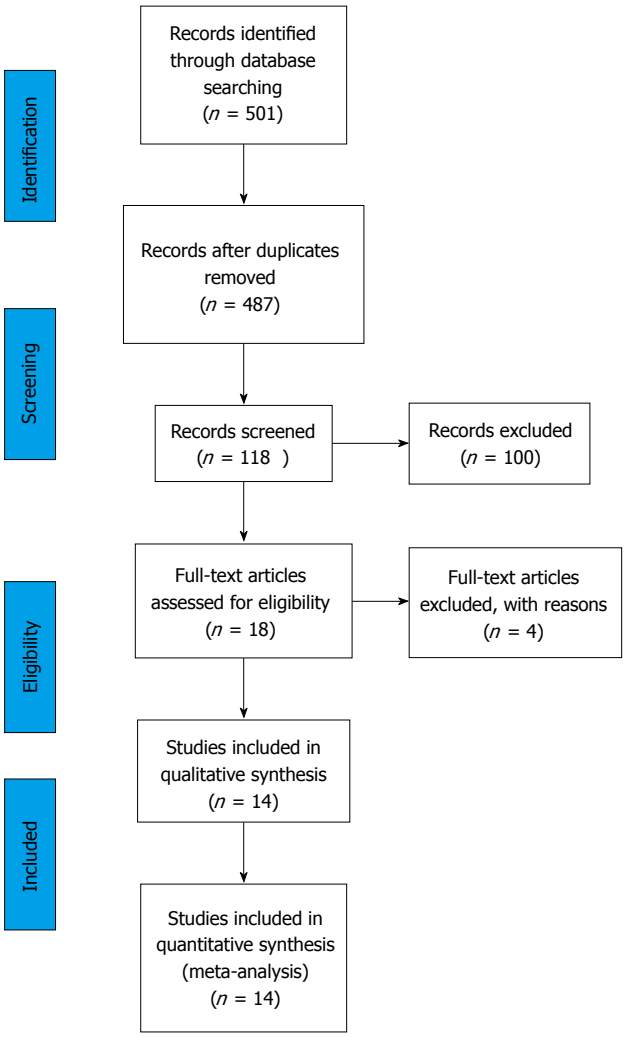


Figure 2 The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram. The information flow in the different phases of the systematic review is presented. The first search through the data bases returned 501 studies, or 487 after the duplicates were removed. A total of 118 studies were screened based on the abstract and title and 18 full text articles were reviewed. Among them 14 studies were included in the meta-analysis.

search targeted original articles, published in English on adult patient population (≥ 19 years) in the date range from the year 1990 to May 31, 2012.

The following terms were used: Critical OR acute AND ill AND rationing OR selection OR withholding treatment OR refusal to treat OR triage OR utilization AND mortality OR outcome OR statistics OR numerical data OR economics. In addition we searched through related articles on PubMed and also found additional articles from the reference lists of retrieved articles.

Comparative, validation, evaluation, observational studies, clinical trials and controlled trials were included in the study screening process. Review articles, letters to the editor, commentaries, expert opinions and studies for which the full text was unavailable were excluded.

The search process is presented on Figure 2 (PRISMA flow diagram). The first search returned 501 studies or 487 after the duplicates were removed. Studies that did not fulfill the inclusion criteria or the ones that met the exclusion criteria (n = 369) were excluded. A total of 118 articles were screened based on the title and abstract and among them full texts of 18 studies were identified and reviewed. Secondarily, the studies that showed highly increased mortality among ICU treated critically ill were excluded from the selection, since it was very unlikely that such outcome would be possible in the case of the Clinical Center University of Sarajevo. A total of 14 studies were included[12,20-32] (Figure 3 and Table 1). The following data were recorded: The year of publication, country of origin, patient population, reasons for ICU refusal, and mortality of critically ill patients treated within the ICU and outside of an ICU. Data were extracted in a previously defined form.

Data from the above mentioned studies were used for the calculation of an Odds Ratio for mortality of critically ill patients when treated on the general hospital wards instead of the ICU. Similar calculations were previously done by Ridley *et al*[8], further details in the Electronic data supplement.

For discounting of costs and health effects an annual rate of 3% was used, with sensitivity analysis for 0% and 6%. Uncertainty was controlled by the use of sensitivity analysis of the key model parameters: The attributable risk reduction of death for ICU treatment, the daily ICU cost, the daily standard care general ward cost, the discount rate, and the quality of life after critical illness, the quality of life index calculation method, the adjustment for excess mortality after critical illness (Post-ICU survival rate, PICUS).

One and two-way sensitivity analysis was performed; along with best and worst case scenarios. A simplified overview of methodology used is presented in Figure 4.

Costing methodology

From the perspective of health system Costs consist of costs of hospitalization and long term post-hospitalization costs.

The cost of hospital stay was calculated for the ICU patient cohort and for the comparator cohort. The ICU patient cohort hospital stay cost was calculated as the sum of the ICU cost and the post-ICU ward cost. The cost of the ICU stay was calculated as the product of the cost per ICU day and the length of ICU stay. The daily ICU cost was calculated based on fixed ICU cost and patient specific variable costs and costing methodology recommended by the Health Insurance Institute of Federation of Bosnia and Herzegovina.

The fixed cost was an estimate made by the Health insurance Institute after an analysis of costs of personnel, equipment amortization, overheads, cost of a hospital bed-maintenance, costs of routine laboratory and X-ray and microbiology. The Health Insurance institute of Federation of Bosnia and Herzegovina is the main financier of the Clinical center University of Sarajevo.

Patient variable costs were prospectively recorded

Table 1 Characteristics of the studies included in the systematic review

Ref.	Patients population and country	Year of publication	Refusal reasons	No. of deaths with ICU support out of total patients treated in ICU (% mortality)	No. of deaths without ICU support out of total patients not treated in ICU (% mortality)	Difference in mortality rates (%)	OR (95%CI)
Frisho-Lima *et al*[20]	General, Israel	1994	Moribund, no beds	7/62 (11.3)	31/65 (47.7)	36.4	7.16 (2.84-18.07)
Metcalfe *et al*[21]	6 general, United Kingdom	1997	Lack of beds or staff or other	178/480 (37.1)	75/165 (45.5)	8.4	1.41 (0.99-2.02)
Sprung *et al*[22]	General, Israel	1999	Too good or too poor prognosis, no beds, more data required, another crit. care area more appropriate	51/321 (15.9)	28/61 (45.9)	30	4.49 (2.50-8.07)
Joynt *et al*[23]	General, Hong Kong	2001	Triage, futility, inappropriate referral.	142/388 (36.6)	145/236 (61.4)	24.8	2.76 (1.98-3.85)
Garrouste-Oregas *et al*[24]	Medical and surgical, France	2003	too well/too sick	46/189 (24.3)	38/141 (27.0)	2.6	1.15 (0.70-1.89)
Simchen *et al*[25]	5 ICUs. Medical and surgical, Israel	2004	All hospital patients screened	80/190 (42.1)	192/349 (55.0)	12.9	1.68 (1.18-2.40)
Garrouste-Oregas *et al*[12]	4 medical and 7 general, France	2005	Too well/too sick, patients refusal, ICU occupied	120/412 (29.1)	49/128 (38.3)	9.2	1.51 (1.00-2.29)
Thiéry G *et al*[26]	Medical ICU, cancer patients 30 d mortality, France	2005	Too sick	57/105 (54.3)	39/54 (74.0)	19.7	2.19 (1.08-4.45)
Simchen *et al*[27]	5 acute care hospitals, medical and surgical patients Israel	2007	Died > 24 h deteriorated on ward	23/97 (23.7)	44/169 (26.0)	2.3	1.13 (0.63-2.02)
			Died < 24 h	4/97 (4.1)	55/414 (13.3)	9.2	3.56 (1.26-10.08)
Iapichino *et al*[28]	11 university hospitals from 7 countries: Denmark, France, Israel, Italy, The Netherlands, Spain, United Kingdom	2010	28 d mortality	1482/6708 (22.1)	197/600 (32.8)	10.7	1.72 (1.44-2.06)
Edbrooke *et al*[29]	11 hospitals in 7 EU countries	2011	28 d mortality	1389/6312 (22.0)	375/1137 (33.0)	11.0	1.74 (1.52-2.00)
Robert *et al*[30]	10 medical ICUs, France	2012	Too good or too sick 28 d	277/1,139 (24.3)	58/193 (30.1)	5.7	1.34 (0.96-1.87)
Cabrini *et al*[31]	Early ICU transfer, medical patients Italy	2012	Too well/too sick or lack of ICU beds	6/15 (40.0)	13/40 (32.5)	-7.5	0.72 (0.21-2.46)
Stelfox *et al*[32]	Canada, medical ICU	2012	Too well/too sick or lack of ICU beds	1106/3245 (34.1)	80/249 (32.1)	-2.0	0.92 (0.69-1.21)
Total				4968/19760 (25.1)	1419/4001 (35.5)	10.3	1.64 (1.52-1.76)

ICU: Intensive care unit.

and included all additional medical interventions such as radiology procedures (CT, MRI, United States), the placement of central venous or dialysis catheters, hemodialysis (HD), peritoneal dialysis, continuous veno-venous HD and other related techniques etc. The variable costs were calculated based on present market values of specific medical interventions[9].

The total ICU-stay cost of all 148 patients was used to calculate the daily unit cost for the ICU. The daily post ICU ward cost was calculated as the average daily cost for standard care on internal medical clinics in the Feredation of Bosnia and Herzegovina. This data was also published by the Federal Health Insurance Institute[9].

The comparator cohort cost was calculated as the product of the average ward daily cost and the hospital length of stay of the real patient cohort. For the purposes of the model, it was assumed that the hypothetical patient cohort would have the same length of stay as real ICU patients that were analyzed.

Incremental hospital costs were then calculated using the following formula: IC hospital = ICU cost - Ward cost = LOS icu × (C icu day - C ward day); LOS-length of stay, C-cost. Future cost for the ICU survivors were approximated using the mean annual health care expenditure per capita for the population of Bosnia and Herzegovina, which was 928 dollar for the year 2011, as reported by the WHO[33]. This approach has been

Model	Citation	Year	Events/total		Statistics each study				Odds ratio and 95%CI
			Word	ICU	Odds ratio	Lower limit	Upper limit	*P*-value	0.10 0.20 0.50 1.00 2.00 5.00 10.00
	Frishmo-Lima *et al*[20]	1994	31/65	7/62	7.164	2.841	18.065	0.000	
	Metcalfe *et al*[21]	1997	75/165	178/480	1.414	0.988	2.023	0.058	
	Sprung *et al*[22]	1999	28/61	51/321	4.492	2.501	8.069	0.000	
	Joynt *et al*[23]	2001	145/236	142/388	2.760	1.977	3.854	0.000	
	Garrouste-Oregas *et al*[24]	2003	38/141	46/189	1.147	0.696	1.889	0.590	
	Garrouste-Oregas *et al*[12]	2005	49/128	120/412	1.509	0.997	2.286	0.052	
	Simchen *et al*[25]	2004	192/349	80/190	1.682	1.177	2.403	0.004	
	Simchen *et al*[27]	2007	44/169	23/97	1.133	0.634	2.024	0.674	
	Thiéry *et al*[26]	2005	39/54	57/105	2.189	1.078	4.447	0.030	
	Lapichino *et al*[28]	2010	197/600	1482/6708	1.724	1.440	2.064	0.000	
	Edbrooke *et al*[29]	2011	375/1137	1389/6312	1.744	1.521	2.001	0.000	
	Stelfox *et al*[32]	2012	80/249	1106/3245	0.916	0.695	1.206	0.530	
	Robert *et al*[30]	2012	58/193	277/1139	1.337	0.955	1.871	0.090	
	Cabrini *et al*[31]	2012	13/40	6/15	0.722	0.212	2.463	0.603	
Fixed					1.648	1.519	1.788	0.000	

Figure 3 Meta-analysis of unadjusted mortality rates from the 14 studies reporting mortality rates in patients admitted to and refused intensive care unit. Based on the reported international data odds ratio for mortality of critically ill patients when treated outside of intensive care unit on standard care wards was calculated, OR = 1.64, 95%CI: 1.51-1.78.

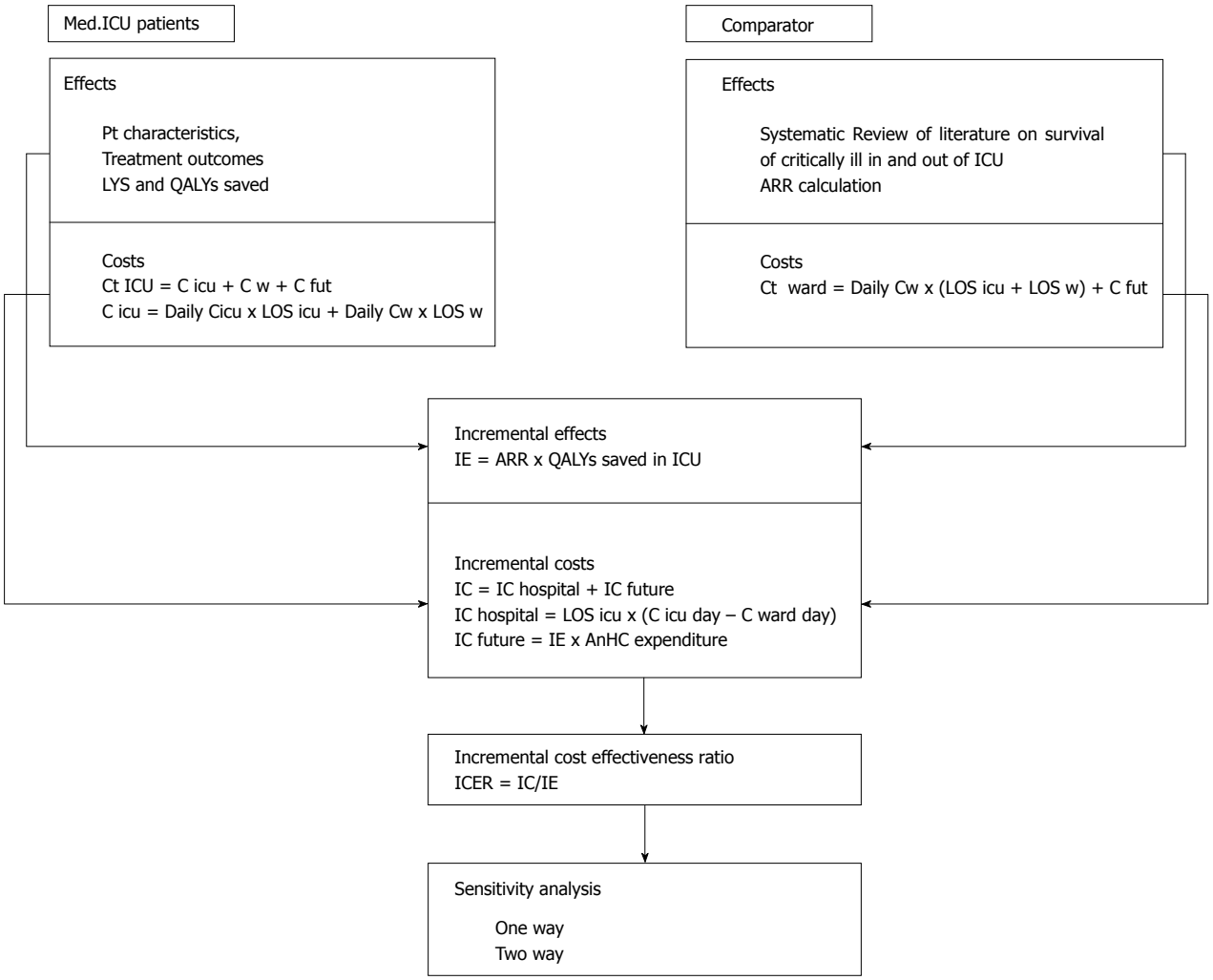


Figure 4 Overview of methodology used in the study. The first phase was data collection for two patient cohorts, observed medical ICU patients and comparator cohort, which was represented by the same number of critically ill patients, with the same characteristics who would be treated on general hospital ward. Costs and treatment outcomes (effects) were recorded and calculated. In the second phase incremental analysis of costs and effects was done. The third phase gave the main incremental cost effectiveness ratio and in fourth a sensitivity analysis of cost effectiveness ratio to key model parameters was performed. Costs and effects were discounted at an annual rate of 3%. LYS: Life years saved; QALY: Quality adjusted life years; ARR: Attributable risk reduction for mortality with treatment of critically ill in ICU; Ct: Total costs; C icu: Costs of ICU treatment; C w: Costs of ward treatment; C fut: Future health care costs, after hospital release; Daily C icu: Average cost per ICU day; Daily C w: Average cost per general hospital ward day in internal medical department; LOS icu/w: Length of stay in the ICU or on general ward; IE: Incremental effects; IC: Incremental costs; AnHC expenditure: Annual health care expenditure per capita for Bosnia and Herzegovina; ICER: Incremental cost-effectiveness ratio. ICU: Intensive care unit.

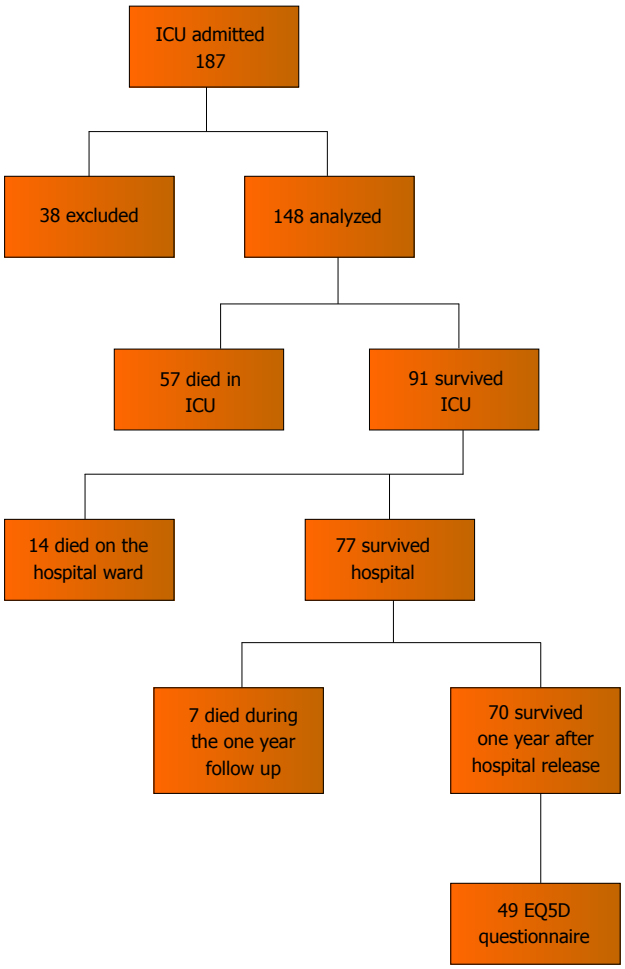


Figure 5 Patient flow diagram. Out of 148 patients that were included in the study, 57 (38.5%) died in the ICU, 14 (9.4%) died on the hospital wards after the ICU, 7 (4.7%) died during one year follow up, 70 (47.2%) survived one year after hospital release and 49 were interviewed for the health related quality of life assessment using the EuroQol-5D questionnaire. ICU: Intensive care unit.

previously used in economic evaluations[8,34].

Costs were reported using a World Health Organization (WHO) suggested currency, the International dollar. This is a theoretical currency, calculated from the WHO published purchasing power parities, and represents what can be bought in a country with one United States dollar. In practice, it corresponds to United States dollar[35].

Incremental future cost was calculated using the following formula: IC future = IE (number of QALYs gained by the treatment in the ICU) × mean annual health care expenditure per capita for the population of Bosnia and Herzegovina and were discounted to present value for the year 2012. The incremental cost was calculated as the sum of incremental hospital and the incremental future costs, or: IC = IC hospital + IC future. IC= [LOS icu × (C icu day - C ward day)] + [IE × mean annual health care expenditure per capita].

Prediction of life time QALYs

For one year survivors a life expectancy was calculated using life tables for the population of Bosnia and Herzegovina for the year 2011, obtained from the WHO[36]. For one year survivors the life expectancy was calculated as expected life duration from a patient's age at admission.

For patients who did not survive one year the exact length of life after hospital release was used. Life time QALYs were calculated by multiplying the predicted life expectancy or real life-time with utility values for HRQOL.

The HRQOL was assessed using the EQ-5D questionnaire[37]. Written permission along with official translation of the questionnaire was granted by the Euro-QOl Group[37]. A HRQOL index was calculated from the resulting five digit EQ-5D profile using reference values for population of Europe and Slovenia. Resulting the HRQOL index was compared to reference values. An adjustment was made for missing data on the quality of life index for patients who did not answer the EQ5D questionnaire and for those who died before one year from the hospital release. For one year survivors who did not answer the questionnaire it was assumed that they had the mean value of the HRQOL index of the age and sex matched respondents. For one year non-survivors it was assumed they had the 75% of the mean HRQOL of respondents. This approach was previously taken in cost effectiveness analysis by Linko *et al*[35]. Life time QALY was calculated as the product of life years saved and HQOL utility value.

Statistical analysis

Discrete data are reported as frequencies and continuous data as means (confidence interval-CI) or medians [interquartile ranges-Interquartile range (IQR)], as appropriate. All hypotheses in the study were two-sided, with the level of significance 0.05. Discrete variables were compared using the χ^2 test. Normally distributed continuous variables were compared using the Student's *t* test, and non-normally distributed variables were compared using the Mann Whitney test. Multiple groups were compared using the Kruskal Wallis test. Comparison of one year survivors EQ-5D index values to the reference values of the age and sex matched population of Slovenia was done using the Wilcoxon signed matched pair test. Statistical analysis was done using SPSS 19 and MS Excel 2010 programs. No funding was received for the conduct of this study.

RESULTS

Patient characteristics

In the period from June 2011 to June 2012 a total of 183 patients were treated in the medical ICU of the Sarajevo University Clinical Center, out of which 148 were included in the study (Figure 5). Overall patient characteristics separated by status one year after hospital release are reported in Table 2. Patients differed in various terms, with patients that survived one year longer, significantly younger (mean 49 years *vs* 63 years, $P < 0.01$), less severely ill (mean SAPS

Table 2 Patient characteristics

		All n = 148	1 yr survivors	Dead after one year	P
Age					
	Mean (SD)	56 (17)	49 (17)	63 (15)	< 0.01[a]
Male (%)			58.6	57.7	1[b]
SAPSII	Mean (SD)	51 (20)	42 (19)	59 (17)	< 0.001[a]
Dg.(%)					
	Cardiac arrest	16.9	18.6	15.4	0.17[b]
	Cardiogenic shock	1.4	0	2.6	
	Coma	12.2	5.7	17.9	
	Status epilepticus.	4.7	2.9	6.4	
	CHF	3.4	4.3	2.6	
	Hypercapnic ARF	10.1	10.0	10.3	
	Hypoxic ARF	12.8	12.9	12.8	
	Intoxication	9.5	15.7	3.8	
	Malignant neurolept.sy	0.7	1.4	0	
	Neuromuscular ARF	2.7	4.3	1.3	
	Other	2	2.9	1.3	
	Renal/metabolic	1.4	1.4	1.3	
	Sepsis (including shock)	22.3	20.0	24.4	
	Other	16.20%	12.90%	1.30%	
ICU LOS					
	Sum	1474			
	Median (IQR)	6 (3-12)	6 (4-16)	5 (3-10)	0.116[c]
28 d ICU free days	Median (IQR)	0 (0-22)	12.5 (0-23)	0 (0-19)	0.002[c]
Ward LOS after ICU					
	Sum	1694			
	Median (IQR)	14 (0-14)	14 (13.75-15.25)	0 (0-1.25)	< 0.001[c]
Mechanical ventilation	%	80	74	87	0.097[b]
Ventilator-free days at 28 d	Median (IQR)	23 (18-25)	23.5 (18-26)	22 (18-25)	0.150[c]

[a]Student's t test; [b]χ^2 test, [c]Mann Whitney U test; Dg: Admission diagnosis; ICU: Intensive care unid; LOS: Length of stay; SAPS Ⅱ: Simplified Acute Physiology Score Ⅱ. IQR: Interquartile range; CHF: Chronic heart failure.

Ⅱ 42 *vs* 59, $P < 0.001$), mainly admitted through the emergency department (44% *vs* 26%, $P = 0.027$), with a shorter hospital stay before the ICU [median 1 IQR (0-4) *vs* 1.5 IQR (0-8), $P = 0.039$] and shorter courses of mechanical ventilation [median 3 IQR (0-9) *vs* 5 IQR (3-9), $P = 0.024$] and vasopressor use (11% *vs* 37%, $P = 0.01$). The most frequent admission diagnoses among one year survivors were: Sepsis (20%), cardiac arrest (18.6%), intoxication (15.7%) and hypoxemic acute respiratory failure (12.9%). Non-survivors were admitted to the ICU mostly due to: Sepsis (24.4%), comma (17.9%), cardiac arrest (15.4%) and hypoxemic acute respiratory failure (12.8%). All critically ill patients had median ICU length of stay of 6 d, IQR (3-12), that did not differ between survivors and non-survivors. Median length of post ICU hospital stay was 14 d, IQR (13.75-15.75) which refers to one year survivors, because non survivors died mostly in the ICU or very shortly after ICU release. One year survivors had significantly higher median 28 d ICU free days [12.5, IQR (0-23)] compared to non-survivors [0, IQR (0-19)]. Ventilator free days at 28 d did not differ significantly between survivors and non survivors, and overall median was 23 d, IQR (18-25).

Patient mortality

Patient flow diagram presents the phases where mortality was recorded (Figure 5). Seventy patients (47.2%) survived one year after hospital discharge, 7 (4.7%) died during the one year follow up, 14 (9.4%) died on the hospital wards after the ICU, and 57 (38.5%) died in the ICU. Hospital mortality was 48%, 30 d mortality was 41.9%, 60 d mortality was 48.6%, and one year mortality was 52.7%.

Follow up surveys

The only statistically significant difference between respondents and non-respondents was that respondents were older (mean age 51 years) than non-respondents (mean 44 years). The respondents were mainly females (79.3%), compared to non-respondents where only 20.7% were females, which was not statistically significant.

The results of interviews are shown in Table 3. Most of the patients did not have problems or had some problems with mobility (95.9%), while severe problems with mobility had 4.1% of the respondents. Most of the patients did not have severe problems with self-care (91.8%). Severe problems with every activites had 20.4%, with pain or discomfort had 10.2% and with anxiety or depression had 6.10% of patients. The patients evaluated their HRQOL lower [0.63 IQR (0.56-0.70)] than the value of the resultant quality of life index calculated from their answers 0.69, IQR (0.49-0.84).

After adjustment for non-respondents and patients

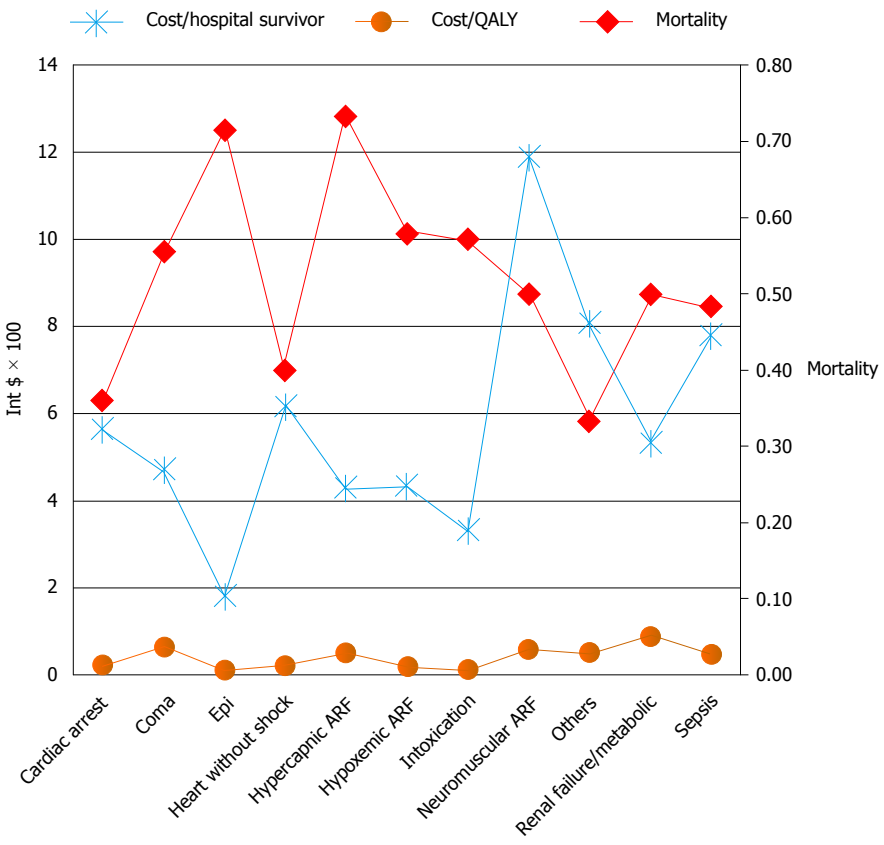


Figure 6 Cost effectiveness measures (costs per hospital survivor, costs per quality adjusted life year saved by the hospital treatment) and hospital mortality, presented depending on the diagnostic category. The highest mortality had patients admitted for the treatment of status epilepticus, hypercapnic acute respiratory failure, acute renal failure and sepsis. The highest costs were with the neuromuscular ARF and the sepsis diagnostic category. ARF: Acute respiratory failure; QALY: Quality adjusted life year.

Table 3 Distribution of responses to EQ-5D modalities at one year

	Problems	*n* = 49	%
Mobility	No	25	51.0
	Some	22	44.9
	Severe	2	4.10
Self-care	No	37	75.5
	Some	8	16.3
	Severe	4	8.2
Usual activities			
	No	13	26.5
	Some	26	53.1
	Severe	10	20.4
Pain/discomfort			
	No	30	61.2
	Some	14	28.6
	Severe	5	10.2
Anxiety/depression			
	No	27	55.1
	Some	19	38.8
	Severe	3	6.10
VAS	0.63 (0.56-0.70)		

VAS: Visual analogue scale. Data are presented as numbers (percentage). EQ-5D-3Lquestionnaire is an instrument developed by the EuroQol group with five health related quality of life dimensions and a visual analogue scale for patients to subjectively evaluate the state of their quality of life.

who died during the one year follow up median HRQOL was 0.64, IQR (0.49-0.76). The value of HRQOL index at one year was significantly lower than the age and sex matched reference value.

Cost analysis

The cost per ICU day was 193 dollar, and the cost per ward day was 73 dollar. The cost of ICU-patient cohort equals the sum of the ICU-stay cost (126312 dollar) and the ward after ICU-stay cost (126312 dollar) resulting in total cost of 410212 dollar, and the mean per patient cost of 2772 dollar (95%CI: 2373-3170 dollar). The minimal hospital cost per patient was 140 dollar and the maximum was 13706 dollar. The highest cost per hospital survivor and the cost per QALY were with neuromuscular acute respiratory failure and sepsis (Figure 6).

The cost of treatment of critically ill patients varied between 1820 dollar and 20109 dollar per hospital survivor and between 100 dollar and 2514 dollar per QALY saved. Mean factors that influenced costs were: Age, diagnostic category, ICU and hospital length of stay and number and type of diagnostic and therapeutic interventions.

The ICER

Results of the systematic review summarizing effectiveness of ICU *vs* non-ICU treatment are presented in

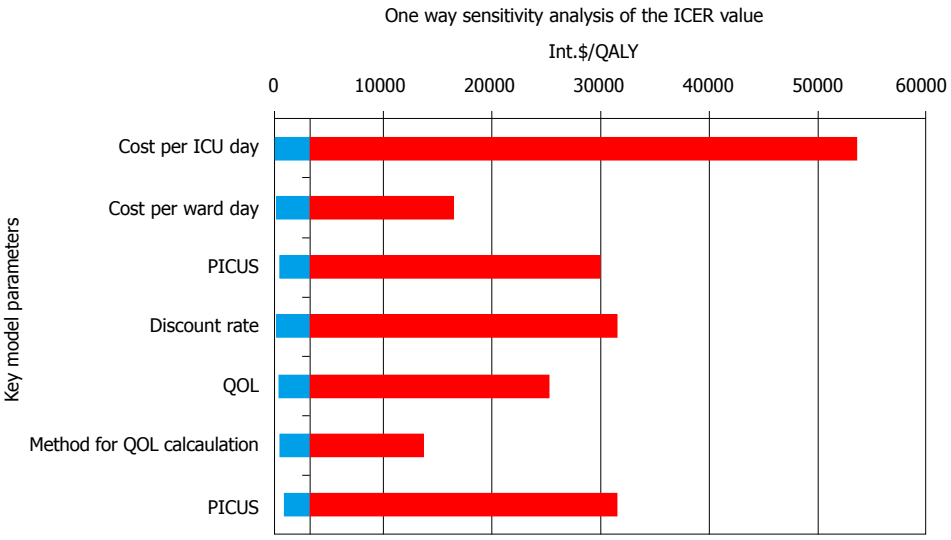


Figure 7 Variations of incremental cost effectiveness ratio values in the one way sensitivity analysis. The values are given in International dollar. The highest variations in ICER values and consequently the impact on ICER values had cost per ICU day, followed with post ICU survival rate and discount rate. ICU: Intensive care unit; PICUS: Post ICU survival; QOL: Quality of life; ICER: Incremental cost effectiveness ratio.

Table 4 Costs, effects, incremental analysis of costs and effects and cost effectiveness ratio

	Hospital treatment costs	Future costs (present value)	Total
Cost-ICU ($)	410212	524432	934644
Cost-ward ($)	234240	454158	688398
Incremental cost ($)	175972	70274	246246
Effects-ICU (QALYs)		567	
Effects-ward (QALYs)		4913	
Incremental effects (QALYs)		757	
ICER ($/QALY)		3254	

Incremental cost represents the difference between the total ICU patient cohort cost and the comparator cohort cost and was calculated based on the decision model assumptions and attributable mortality risk reduction, using the formula presented in detail in the methods section, and after discounting future costs and health effects at an annual rate of 3% to the year 2012. ICU: Intensive care unit; ICER: Incremental cost-effectiveness ratio; QALY: Quality adjusted life year.

Figure 3 and Table 1. With the average ICU refusal rate, of 15% and the odds ratio for mortality of 1.64 (95%CI: 1.51-1.78) on a ward, the attributable mortality risk reduction (ARR) was calculated to be 13.4% for ICU-treated critically ill patients. Details can be found in the electronic data supplement and similar approach was previously applied by Ridley and Morris[8]. In the cohort of one year ICU survivors, a total of 2235 life years and 1455 QALYs were saved, which is 567 QALYs after discounting. The incremental effect was then equal to 75.7 QALYs after applying the attributable risk reduction from the systematic review. The incremental cost was calculated as the sum of the incremental hospital cost and the present value of the incremental future-cost and was equal to 246246 dollar. The ICER for intensive care was 3254 dollar per QALY (Table 4).

Sensitivity analysis

Analysis of sensitivity of the ICER values to key model parameters is presented in Figures 7 and 8.

A tornado plot in the one way sensitivity analysis was constructed to observe the impact of different parameters on ICER values, Figure 7. From the plot it can be seen that the ICU-daily cost had the highest impact on ICER values.

Values of ICER varied between 1026 dollar and 54495 dollar per QALY, with the mean of 4137 dollar (SD 4863 dollar), and the median of 2580 dollar /QALY. The minimal value of ICER was calculated for the case when the cost per ICU day was 50% lower (97 dollar), with the cost of a general ward day constant (74 dollar), the QOL index 0.64, the annual discount rate of 3%, and the ARR of 62%. The ICER would be maximum, if the cost per ICU day were 300% (580 dollar), with the constant ward cost and the ARR of 2.5%, which is only a hypothetical and not real possibility.

If the ARR varied between 13.4 and 62%, the ICER would vary from 1438 dollar to 3286 dollar per QALY (mean 2121 dollar, median 1982 dollar /QALY). As the ARR value rises its impact on the ICER significantly drops, two way sensitivity analysis (Figure 8).

DISCUSSION

The main finding of our study is a favorable ICER for the treatment of critically ill medical patients in an ICU in a resource limited setting. Severity of illness, short and long term mortality, and the quality of life after critical illness were mainly comparable to studies performed in a resource-rich setting.

Our practice before the establishment of this medical ICU showed that we could not provide effective critical care on general hospital wards due to the lack

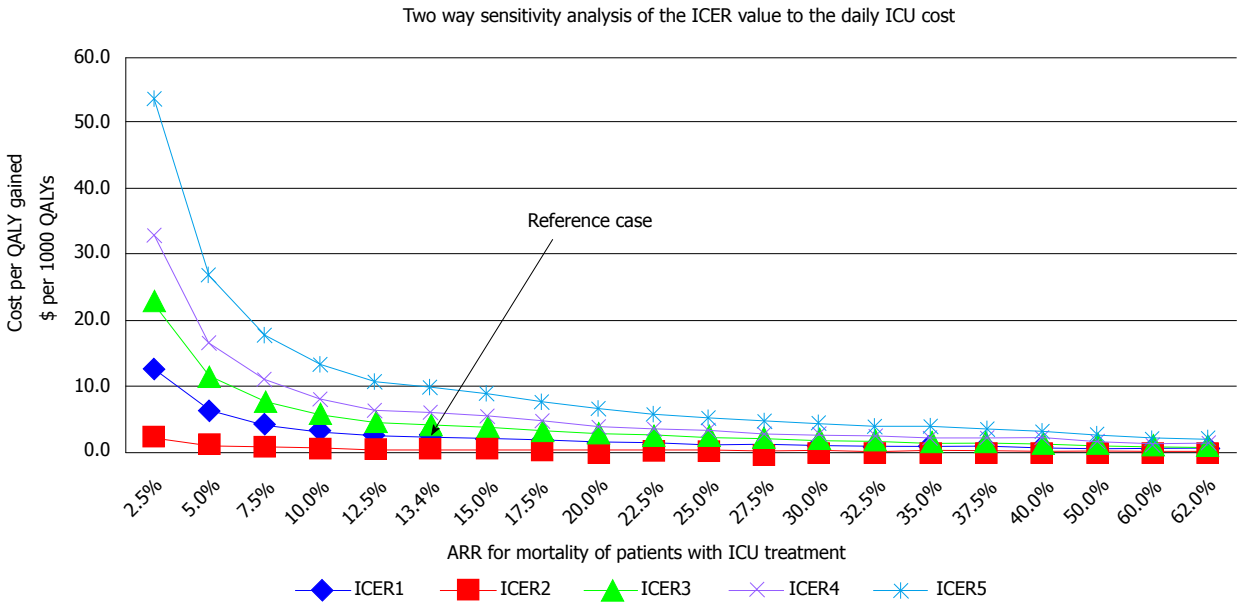


Figure 8 The two way sensitivity analysis. Horizontal axis represents different values of the ARR. Vertical axis-values of ICER when cost per ICU day and ARR change: ICER 1 - daily ICU cost 193 dollar, ICER 2 - daily ICU cost 96.5 dollar (50% of reference cost), ICER 3 - daily ICU cost 289.5 (150% of reference cost), ICER 4 - daily ICU cost 386 dollar (200% of reference cost), ICER 5 - daily ICU cost 579 dollar (300% of reference cost). Reference case, the ICER of 3254 dollar/ QALY when cost per ICU day is 193 dollar and ARR are value of 13.4. ICER: Incremental cost effectiveness ratio; ICU: Intensive care unit; QALY: Quality adjusted life year; ARR: Attributable mortality risk reduction.

of equipment and personnel. Indeed, a decision on ICU establishment should not be made on utilitarian grounds. However, our study proves that in a resource poor setting having an ICU is also cost effective and can compete with other health care priorities for resource allocation. Therefore, investment in critical care facilities even in a resource poor setting can be justified not only by ethical and altruistic reasons but also by very good cost effectiveness.

Similar to previous studies, the health related QOL of patients one year after critical illness was significantly lower than the QOL of the age and sex matched general population[22,23,35,38-42]. Cost effectiveness of critical care in our study might as well be underestimated as we used international data on survival of critically ill patients outside of an ICU as one of the main input parameters in our decision analytic model. The ICU patient cohort had a substantially low fixed cost estimate. Such low fixed cost estimate is a consequence of the fact that, unfortunately, personnel costs in a resources limited setting are much lower than such costs in developed countries. Further, a higher incremental effectiveness of the ICU treatment of the critically ill at the Sarajevo University Clinical Center can be expected, simply because most interventions that are needed for vital function support are not available on general wards in our hospital. Data on patient survival in and out of ICU come from observational studies on treatment outcomes of ward care for the critically ill, when those patients were refused an ICU admission with careful admission triage due to the lack of beds. Ethical issues preclude conduction of randomized control trials on this subject. Therefore, the actual effectiveness of the ICU care can only be roughly estimated. Similarly, ethical and administrative reasons precluded data collection on a comparator patient cohort in our institution. However, any bias can only be in the direction of higher effectiveness of the ICU treatment because hospital floor outcomes in this limited resource setting are far worse.

Another question that could be raised is what was the opportunity cost of an investment in critical care? Opportunity costs depend on an individual situation within the health care system of a country because health care investment priorities differ among countries. Our results indorse the argument that investment in critical care facilities can also fairly compete with other health care priorities.

A number of cost utility analyses in intensive care have been published to date, but none has been done in Bosnia and Herzegovina, south-eastern Europe or any other resource limited setting. Consequently, our results cannot be adequately compared. Cost effectiveness analyses of critical care have been performed in Western Europe, and in the United States. Sznajder *et al*[42], reported the cost of 1150 dollar/year of life preserved, and the cost of 4100 dollar/QALY in France in1996. Graf *et al*[43] in Germany reported the cost of 28354 dollar/ year of life preserved in the year 1998. Linko *et al*[35] reported on a prospective multicenter study conducted in 25 ICUs in Finland. The average life expectancy of survivors was 16.8 years, and 11.3 QALY, with the cost effectiveness ratio of 1391 dollar/QALY. Aforementioned studies did not use a standard comparator for ICU care, assuming that the alternative to the ICU treatment was a theoretical certainty of death. If we had assumed

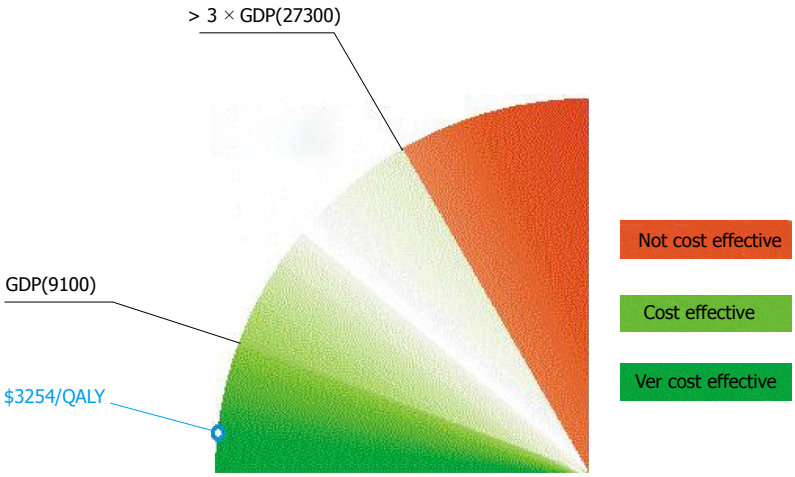


Figure 9 The World Health Organization interpretation of the cost effectiveness of health care interventions. The WHO interprets the cost effectiveness of a health care intervention in relation to the country's economic development represented by the GDP per capita. If the value of ICER is less than country's GDP per capita, then the intervention is very cost effective. If the value of ICER falls between one and three times GDP per capita, then the intervention is cost effective and if the ICER is more than three times GDP per capita, the intervention is considered not cost effective. WHO: World Health Organization; GDP: Gross domestic product; ICER: Incremental cost effectiveness ratio.

100% mortality in our comparator group, medical ICU patients in Sarajevo would have had an even more favorable CEA profile with the hospital cost per patient of 2771 dollar, the cost per hospital survivor 5327 dollar, and the cost per QALY 295 dollar, with the average life expectancy of 32 years. Edbrooke *et al*[29] conducted a large study which analyzed cost effectiveness of ICU treatment on the population of over 7000 patients in 11 medical and surgical units in 7 different countries of the European Union. Results of this study indicate the cost of 103771 dollar/life saved, 7065 dollar/year of life saved, and the average expected length of life of 15 years for survivors. This study did not take future health care costs into account.

Inter-study comparability is generally difficult with respect to different methodological approaches such as the costing, perspective, analytical horizon, and the QOL estimation. Our study is different from other published cost effectiveness studies in critical care because decision analytic modeling was used as an legitimate instrument in economic evaluation studies in order to implement methodological recommendations for cost effectiveness analyses in critical care given by the American Thoracic Society[18,44].

Defining what cost-effective is requires judgment about the social willingness to pay for a QALY or life year saved. Although there is no absolute cutoff, an incremental cost-effectiveness ratio of 50000 dollar to 100000 dollar/year of life gained is generally considered a good value for money in the United States today[45]. Similarly, the National Institute for Clinical Excellence in the United Kingdom accepts technologies with cost effectiveness ratios ranging from £ 5000 to £ 15000 per QALY[46]. The WHO gives a general interpretation of cost effectiveness of health interventions in the context of a country's regional position and economic development[47]. Cost effectiveness of other medical interventions, such as coronary bypass surgery, mitral valve replacement for rheumatic heart disease, medical management for hypertension and tertiary management for lung, liver, esophageal, and stomach cancer was classified by the World Bank as so high that was recommended that public policy should discourage their use in settings where resources are severely constrained[10]. In spite of those recommendations, these interventions are being supported by public health authorities in developing countries. According to the WHO, values of ICER less than Gross Domestic Product (GDP) per capita are highly cost-effective, between one to three times GDP per capita are effective in terms of cost, while the value of ICER over three times GDP are not cost-effective. For Bosnia and Herzegovina, with the GDP per capita of 9100 dollar, the limit of acceptable ICER is approximately 27300 dollar for the year 2011 (Figure 9). Thus critical care in Sarajevo with the ICER less than Bosnian GDP per capita is very cost effective[47]. However, these estimations may not reflect affordability and social willingness to pay.

Like any research, this study has limitations. The study measured life expectancy using life tables for the population of Bosnia and Herzegovina to predict a remaining lifespan of patients. This approach assumes that the life expectancy of survivors will be comparable to the life expectancy of an age-matched and sex-matched general population. ICU patients were followed up for one year after discharge from the hospital. This period appears to be long enough to determine possible additional mortality of patients after critical illness, because it appears that mortality in our patients stabilized five months after critical illness. This is consistent with previously published results[39,48,49]. Besides aforementioned, the post ICU survival rate was one of the key parameters for which we performed the sensitivity analysis. Secondly, the HRQOL was measured

one year after hospital discharge and assumed to be constant over time. However, it is known that the HRQOL declines with age. In our patient sample, there was no statistically significant difference in the quality of life between age groups. Thirdly, patients that died within 24 h in the ICU were excluded from the analysis, which could introduce bias into the analysis. However, the overall number of those patients was small and unlikely to significantly impact on our results. Further, we had only 70% EQ-5D questionnaire respondents among one year survivors, which could also distort our results. For the rest of survivors, an approximation was made according to the methodology previously used[35]. With our questionnaire results we were able to roughly estimate the value of HRQOL one year after critical illness, and gain a sense of the order, which we found satisfactory for the rest of calculations. The fifth potential source of concern is the absence of the concurrent control group of critically ill patients treated on the ward. Since none of the studies came from the countries in development there is also the possibility of the publication bias, which might distort our results. We controlled the uncertainty around this parameter by the sensitivity analysis. The value of ICER for intensive care in Bosnia and Herzegovina would exceed 50000 dollar/QALY only in cases where the attributable risk reduction for mortality was implausibly small. Contrary to that possibility, the highest values of attributable risk reduction are more appropriate for the Sarajevo University Clinical Center and consequently even better cost effectiveness of critical care.

In conclusion, public health authorities should support the development of critical care services in low and middle income countries because the ICU treatment of critically ill medical patients is cost effective.

COMMENTS

Background

Considering the fact that critical care is an expensive specialty, question can be raised whether investment erase - critical care in a resource constrained setting is cost effective. High costs of treatment in the intensive care unit (ICU) have limited access to critical care in low and middle income countries. The authors' objective was to assess the cost effectiveness of the treatment of critically ill patients in medical ICU compared to no ICU treatment in a low-middle income country with limited access to ICU resources.

Research frontiers

The economic evaluation studies of critical care have been extensively performed in developed countries with resource rich health care setting. A search of the literature on the analysis of costs and effectiveness in the field of intensive care medicine found no studies published from the Balkans, South-Eastern Europe or other resource limited settings.

Innovations and breakthroughs

Care for critically ill is considered expensive and is a low priority for public health decision makers in resource limited countries. The authors' results suggest that critical care is and can be cost effective even in the settings of constrained resources.

Applications

This study can serve as an argument for public health authorities to support the development of critical care services in low and middle income countries.

Terminology

Cost effectiveness analysis is a form of the full economic evaluation which incorporates medical and economical aspects of health care programes or interventions. Cost utility analysis is a form of economic evaluation of health care programes which uses quality adjusted life years (QALYs) as a measure of health effects and shows the number of QALYs saved by the intervention at a certain cost expressed in Dollar or international Dollar.

Peer-review

The authors have performed a good study, the manuscript is interesting.

REFERENCES

1 **Russel LB**, Siegel JE, Daniels N, Gold MR, Luce BR, Mandelblatt JS. Cost-effectiveness analysis as a guide to resource allocation in health: roles and limitations. In: Gold MR, Siegel JE, Russel LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. Oxford University Press, 1996: 3-24

2 **Weinstein MC**, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med* 1977; **296**: 716-721 [PMID: 402576 DOI: 10.1056/NEJM197703312961304]

3 Basic types of economic evaluation. In: Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press, 2005: 7-26

4 Cost Effectiveness Analysis: Introduction. CDC Econ Eval Tutorials (E). [updated 2013 Nov 22]. Available from: URL: http//www.cdc.gov/owcd/eet/costeffect2/fixed/1.html

5 **Sukcharoen N**. Basic Principles of Health Economics for Obstetricians and Gynecologists. *Thai J Obstet Gynaecol* 2003; **15**: 3-7

6 **Cuthbertson BH**, Rattray J, Campbell MK, Gager M, Roughton S, Smith A, Hull A, Breeman S, Norrie J, Jenkinson D, Hernández R, Johnston M, Wilson E, Waldmann C. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ* 2009; **339**: b3723 [PMID: 19837741 DOI: 10.1136/bmj.b3723]

7 **Williams TA**, Dobb GJ, Finn JC, Webb SA. Long-term survival from intensive care: a review. *Intensive Care Med* 2005; **31**: 1306-1315 [PMID: 16132895 DOI: 10.1007/s00134-005-2744-8]

8 **Ridley S**, Morris S. Cost effectiveness of adult intensive care in the UK. *Anaesthesia* 2007; **62**: 547-554 [PMID: 17506731 DOI: 10.1111/j.1365-2044.2007.04997.x]

9 Strateski plan razvoja zdravstva u FBiH. [updated 2013 Nov 25]. Available from: URL: http//www.fmoh.gov.ba/index.php/zakoni-i-strategije/strategije-i-politike/53-strateski-plan-razvoja-zdravstva-u-fbih

10 **Jamison DT**, Mosley WH. Disease control priorities in developing countries: health policy responses to epidemiological change. *Am J Public Health* 1991; **81**: 15-22 [PMID: 1983911 DOI: 10.2105/AJPH.81.1.15]

11 **Bank W**. World Development Report 1993: Investing in Health. [updated 2013 Nov 25]. Available from: URL: http//openknowledge.worldbank.org/handle/10986/5976

12 **Garrouste-Orgeas M**, Montuclard L, Timsit JF, Reignier J, Desmettre T, Karoubi P, Moreau D, Montesino L, Duguet A, Boussat S, Ede C, Monseau Y, Paule T, Misset B, Carlet J. Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. *Crit Care Med* 2005; **33**: 750-755 [PMID: 15818100 DOI: 10.1097/01.CCM.0000157752.26180.F1]

13 **Le Gall JR**, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957-2963 [PMID: 8254858 DOI: 10.1001/jama.1993.03510240069035]

14 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**:

818-829 [PMID: 3928249 DOI: 10.1097/00003246-198510000-00009]
15 **Vincent JL**, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239 DOI: 10.1007/BF01709751]
16 **Kümpers P**, Hafer C, Lukasz A, Lichtinghagen R, Brand K, Fliser D, Faulhaber-Walter R, Kielstein JT. Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. *Crit Care* 2010; **14**: R9 [PMID: 20122150 DOI: 10.1186/cc8861]
17 Definitions. [accessed 2015 Sept 15]. Available from: URL: http//research.tufts-nemc.org/cear4/SearchingtheCEARegistry/Definitions.aspx
18 Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *Am J Respir Crit Care Med* 2002; **165**: 540-550 [PMID: 11850349 DOI: 10.1164/ajrccm.165.4.16541]
19 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264-269, W64 [PMID: 19622511 DOI: 10.7326/0003-4819-151-4-200908180-00135]
20 **Frisho-Lima P**, Gurman G, Schapira A, Porath A. Rationing critical care -- what happens to patients who are not admitted? *Theor Surg* 1994; **9**: 208-211 [PMID: 11660442]
21 **Metcalfe MA**, Sloggett A, McPherson K. Mortality among appropriately referred patients refused admission to intensive-care units. *Lancet* 1997; **350**: 7-11 [PMID: 9217712 DOI: 10.1016/S0140-6736(96)10018-0]
22 **Sprung CL**, Geber D, Eidelman LA, Baras M, Pizov R, Nimrod A, Oppenheim A, Epstein L, Cotev S. Evaluation of triage decisions for intensive care admission. *Crit Care Med* 1999; **27**: 1073-1079 [PMID: 10397207 DOI: 10.1097/00003246-199906000-00021]
23 **Joynt GM**, Gomersall CD, Tan P, Lee A, Cheng CA, Wong EL. Prospective evaluation of patients refused admission to an intensive care unit: triage, futility and outcome. *Intensive Care Med* 2001; **27**: 1459-1465 [PMID: 11685338 DOI: 10.1007/s001340101041]
24 **Garrouste-Orgeas M**, Montuclard L, Timsit JF, Misset B, Christias M, Carlet J. Triaging patients to the ICU: a pilot study of factors influencing admission decisions and patient outcomes. *Intensive Care Med* 2003; **29**: 774-781 [PMID: 12677368]
25 **Simchen E**, Sprung CL, Galai N, Zitser-Gurevich Y, Bar-Lavi Y, Gurman G, Klein M, Lev A, Levi L, Zveibil F, Mandel M, Mnatzaganian G. Survival of critically ill patients hospitalized in and out of intensive care units under paucity of intensive care unit beds. *Crit Care Med* 2004; **32**: 1654-1661 [PMID: 15286540 DOI: 10.1097/01.CCM.0000133021.22188.35]
26 **Thiéry G**, Azoulay E, Darmon M, Ciroldi M, De Miranda S, Lévy V, Fieux F, Moreau D, Le Gall JR, Schlemmer B. Outcome of cancer patients considered for intensive care unit admission: a hospital-wide prospective study. *J Clin Oncol* 2005; **23**: 4406-4413 [PMID: 15994150 DOI: 10.1200/JCO.2005.01.487]
27 **Simchen E**, Sprung CL, Galai N, Zitser-Gurevich Y, Bar-Lavi Y, Levi L, Zveibil F, Mandel M, Mnatzaganian G, Goldschmidt N, Ekka-Zohar A, Weiss-Salz I. Survival of critically ill patients hospitalized in and out of intensive care. *Crit Care Med* 2007; **35**: 449-457 [PMID: 17167350 DOI: 10.1097/01.CCM.0000253407.89594.15]
28 **Iapichino G**, Corbella D, Minelli C, Mills GH, Artigas A, Edbooke DL, Pezzi A, Kesecioglu J, Patroniti N, Baras M, Sprung CL. Reasons for refusal of admission to intensive care and impact on mortality. *Intensive Care Med* 2010; **36**: 1772-1779 [PMID: 20533023 DOI: 10.1007/s00134-010-1933-2]
29 **Edbrooke DL**, Minelli C, Mills GH, Iapichino G, Pezzi A, Corbella D, Jacobs P, Lippert A, Wiis J, Pesenti A, Patroniti N, Pirracchio R, Payen D, Gurman G, Bakker J, Kesecioglu J, Hargreaves C, Cohen SL, Baras M, Artigas A, Sprung CL. Implications of ICU triage decisions on patient mortality: a cost-effectiveness analysis. *Crit Care* 2011; **15**: R56 [PMID: 21306645 DOI: 10.1186/cc10029]
30 **Robert R**, Reignier J, Tournoux-Facon C, Boulain T, Lesieur O, Gissot V, Souday V, Hamrouni M, Chapon C, Gouello JP. Refusal of intensive care unit admission due to a full unit: impact on mortality. *Am J Respir Crit Care Med* 2012; **185**: 1081-1087 [PMID: 22345582 DOI: 10.1164/rccm.201104-0729OC]
31 **Cabrini L GM**. Observed versus predicted hospital mortality in general wards patients assisted by a medical emergency team. *Signa Vitae* 2012; **7**: 38-42
32 **Stelfox HT**, Hemmelgarn BR, Bagshaw SM, Gao S, Doig CJ, Nijssen-Jordan C, Manns B. Intensive care unit bed availability and outcomes for hospitalized patients with sudden clinical deterioration. *Arch Intern Med* 2012; **172**: 467-474 [PMID: 22412076 DOI: 10.1001/archinternmed.2011.2315]
33 **WHO**. Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. [updated 2013 Oct 30]. Available from: URL: http//www.who.int/choice/book/en/
34 **Green C**, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, Payne E, Cuthbertson BH. Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris) for the treatment of severe sepsis in adults: a systematic review and economic evaluation. *Health Technol Assess* 2005; **9**: 1-126, iii-iv [PMID: 15774234 DOI: 10.3310/hta9110]
35 **Linko R**, Suojaranta-Ylinen R, Karlsson S, Ruokonen E, Varpula T, Pettilä V. One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. *Crit Care* 2010; **14**: R60 [PMID: 20384998 DOI: 10.1186/cc8957]
36 **Global Health Observatory Data Repository**. Life tables Bosnia and Herzegovina. [updated 2013 Nov 25]. Available from: URL: http//apps.who.int/gho/data/view.main.60200?lang=en
37 **EuroQol**. EQ-5D-3L. [updated 2013 Nov 25]. Available from: URL: http//www.euroqol.org/eq-5d-products/eq-5d-3l.html
38 **Manns BJ**, Lee H, Doig CJ, Johnson D, Donaldson C. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002; **347**: 993-1000 [PMID: 12324556 DOI: 10.1056/NEJMsa020969]
39 **Granja C**, Teixeira-Pinto A, Costa-Pereira A. Quality of life after intensive care--evaluation with EQ-5D questionnaire. *Intensive Care Med* 2002; **28**: 898-907 [PMID: 12122528 DOI: 10.1007/s00134-002-1345-z]
40 **Hurel D**, Loirat P, Saulnier F, Nicolas F, Brivet F. Quality of life 6 months after intensive care: results of a prospective multicenter study using a generic health status scale and a satisfaction scale. *Intensive Care Med* 1997; **23**: 331-337 [PMID: 9083237 DOI: 10.1007/s001340050336]
41 **Gordon AC**, Oakervee HE, Kaya B, Thomas JM, Barnett MJ, Rohatiner AZ, Lister TA, Cavenagh JD, Hinds CJ. Incidence and outcome of critical illness amongst hospitalised patients with haematological malignancy: a prospective observational study of ward and intensive care unit based care. *Anaesthesia* 2005; **60**: 340-347 [PMID: 15766336 DOI: 10.1111/j.1365-2044.2005.04139.x]
42 **Sznajder M**, Aegerter P, Launois R, Merliere Y, Guidet B. A cost-effectiveness analysis of stays in intensive care units. *Intensive Care Med* 2001; **27**: 146-153 [PMID: 11280626 DOI: 10.1007/s001340000760]
43 **Graf J**, Wagner J, Graf C, Koch KC, Janssens U. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients--a cost-utility analysis. *Crit Care Med* 2005; **33**: 547-555 [PMID: 15753746 DOI: 10.1097/01.CCM.0000155990.35290.03]
44 **Weinstein MC**, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA* 1996; **276**: 1253-1258 [PMID: 8849754 DOI: 10.1001/jama.1996.03540150055031]
45 **Talmor D**, Greenberg D, Howell MD, Lisbon A, Novack V, Shapiro N. The costs and cost-effectiveness of an integrated sepsis treatment protocol. *Crit Care Med* 2008; **36**: 1168-1174 [PMID: 18379243 DOI: 10.1097/CCM.0b013e318168f649]
46 Health inequalities and population health. NICE. [updated 2013 Nov

03]. Available from: URL: http//www.nice.org.uk/
47 **WHO**. WHO-CHOICE. WHO. [updated 2013 Oct 14]. Available from: URL: http//www.who.int/choice/en/
48 **Ridley S**, Plenderleith L. Survival after intensive care. Comparison with a matched normal population as an indicator of effectiveness. *Anaesthesia* 1994; **49**: 933-935 [PMID: 7802234 DOI: 10.1111/j.1365-2044.1994.tb04306.x]
49 **Delannoy B**, Floccard B, Thiolliere F, Kaaki M, Badet M, Rosselli S, Ber CE, Saez A, Flandreau G, Guérin C. Six-month outcome in acute kidney injury requiring renal replacement therapy in the ICU: a multicentre prospective study. *Intensive Care Med* 2009; **35**: 1907-1915 [PMID: 19693486 DOI: 10.1007/s00134-009-1588-z]

P- Reviewer: Ewers A, Normadeane A, Robertson-Smith J, Zhang ZH
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i2.165

World J Crit Care Med 2016 May 4; 5(2): 165-170
ISSN 2220-3141 (online)

Automatic quality improvement reports in the intensive care unit: One step closer toward meaningful use

Mikhail A Dziadzko, Charat Thongprayoon, Adil Ahmed, Ing C Tiong, Man Li, Daniel R Brown, Brian W Pickering, Vitaly Herasevich

Mikhail A Dziadzko, Charat Thongprayoon, Adil Ahmed, Ing C Tiong, Man Li, Daniel R Brown, Brian W Pickering, Vitaly Herasevich, Multidisciplinary Epidemiology and Translational Research in Intensive Care, Mayo Clinic, Rochester, MN 55905, United States

Vitaly Herasevich, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose related to this publication.

Data sharing statement: No additional data available.

Correspondence to: Vitaly Herasevich, MD, PhD, Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States. herasevich.vitaly@mayo.edu
Telephone: +1-507-2554055
Fax: +1-507-2554267

Received: July 31, 2015
Peer-review started: July 31, 2015
First decision: October 13, 2015
Revised: October 27, 2015
Accepted: December 17, 2015
Article in press: December 18, 2015
Published online: May 4, 2016

Abstract

AIM: To examine the feasibility and validity of electronic generation of quality metrics in the intensive care unit (ICU).

METHODS: This minimal risk observational study was performed at an academic tertiary hospital. The Critical Care Independent Multidisciplinary Program at Mayo Clinic identified and defined 11 key quality metrics. These metrics were automatically calculated using ICU DataMart, a near-real time copy of all ICU electronic medical record (EMR) data. The automatic report was compared with data from a comprehensive EMR review by a trained investigator. Data was collected for 93 randomly selected patients admitted to the ICU during April 2012 (10% of admitted adult population). This study was approved by the Mayo Clinic Institution Review Board.

RESULTS: All types of variables needed for metric calculations were found to be available for manual and electronic abstraction, except information for availability of free beds for patient-specific time-frames. There was 100% agreement between electronic and manual data abstraction for ICU admission source, admission service, and discharge disposition. The agreement between electronic and manual data abstraction of the time of ICU admission and discharge were 99% and 89%. The time of hospital admission and discharge were similar for both the electronically and manually abstracted datasets. The specificity of the electronically-generated report was 93% and 94% for invasive and non-invasive ventilation use in the ICU. One false-positive result for each type of ventilation was present. The specificity for ICU and in-hospital mortality was 100%. Sensitivity was 100% for all metrics.

CONCLUSION: Our study demonstrates excellent accuracy of electronically-generated key ICU quality metrics. This validates the feasibility of automatic metric generation.

Key words: Electronic medical record; Quality indicators; Critical care; Information processing; Datamart; Automatic;

Intensive care; Health care

Core tip: Meaningful use of electronic healthcare records (EHRs) requires quality measures. Many administrative reporting tools provided by current EHRs are based on insufficiently accurate data and thus of limited use. We examine the feasibility and the validity of electronic generation of institutional key intensive care unit (ICU) quality metrics using ICU DataMart, a near-real time relational database.

Dziadzko MA, Thongprayoon C, Ahmed A, Tiong IC, Li M, Brown DR, Pickering BW, Herasevich V. Automatic quality improvement reports in the intensive care unit: One step closer toward meaningful use. *World J Crit Care Med* 2016; 5(2): 165-170 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i2/165.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i2.165

INTRODUCTION

Up to 6 million adult patients are admitted annually to intensive care units (ICU) across the United States[1,2]. This environment is influenced by factors such as intense cognitive demands, multiple communication channels, interruptions, multitasking, and complex organ support devices[3,4]. The distinctive workflow and time sensitive nature of critical illness management are predisposing factors for medical errors[5,6].

According to an Institute of Medicine (IOM) report, health information technology (HIT) must play a central role in the quality improvement process of healthcare[7,8]. Quality measures are required for meaningful use of electronic health records (EHRs)[9]. ICU quality metrics focus on care processes such as adherence to best practices[10,11]. In comparison to these care processes, there are structural measures incorporated in the National Quality Forum (NQF) as quality measures. Metrics can be a valuable tool to evaluate the quality of care delivered to the patient and serve as an indicator to assess whether a patient received recommended steps of care[11,12]. The reporting of valuable quality measures drives clinical process improvements and is largely accepted by clinicians[13].

HIT offers the opportunity to conduct large scale quality improvement projects that were previously limited in scope due to the reliance on manual data abstraction. Manual generation of quality improvement metrics causes dissatisfaction and consumes time and human resources[14,15]. Current clinical information systems do not routinely support the generation of practice management reports. However, the federal Electronic Health Record Incentive Program expects embedded electronic reporting of Quality Metrics directly from EHRs[16]. Automated quality reporting saves 5 to 14 min per case for different metrics[17]. This translates to a theoretical savings of $1 million annually, assuming 100% accuracy of data extraction.

Most high level administrative reporting is based on flawed data and thus of limited clinical use[18,19]. Most of the elements known to be important indicators of processes of care are either not captured, or are captured with insufficient accuracy[18]. The EMR, on the other hand, is a rich source of pertinent information. We recently developed and successfully tested fully automatic APACHE and SWIFT score calculator[20,21]. These study examines the feasibility and the validity of electronic generation of key ICU quality metrics.

MATERIALS AND METHODS

The Critical Care Independent Multidisciplinary Program (CC-IMP) team at Mayo Clinic defined 11 key ICU metrics for electronic reporting. Multiple variables required for electronic data abstractions were identified (Table 1).

Patient population

Adult patients (age ⩾ 18 years) admitted to the medical or surgical ICUs from 04/01/2012 through 04/30/2012 were included. Patients without research authorization were excluded. Out of 925 eligible patients, 93 (10%) were randomly selected for validation purposes. The Mayo Clinic Institution Review Board approved this minimal risk study.

Manual data extraction

All data necessary to calculate quality metrics was collected manually from the EMR by a trained researcher. Standard operating procedures were created to insure uniformity of data collection. Whenever a value was missing or unavailable it was assumed to be normal. The investigator involved in manual data extraction was blinded to the results of the electronic data extraction. Manually collected data was considered as the reference standard.

Electronic data extraction

Information required for quality reports was abstracted from Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) ICU DataMart, a near-real time relational database with open-schema data feeds imported from the EHR[22]. Data domains included physiologic monitoring, laboratory and radiologic investigations, medication orders, and provider notes. An automatic algorithm was used to identify the components required for each of the 11 metrics in the quality reports.

Statistical analysis

Descriptive data are presented as median with inter-quartile range (IQR) for continuous variables or count with percentage for categorical variables. Paired *t*-test and McNemar's tests were used to compare continuous and categorical variable between electronic and manual data. Sensitivity and specificity for electronic data abstraction

Table 1 Critical Care Independent Multidisciplinary Program defined metrics

Metric		Description	Variables needed
M1	Hospital length of stay for ICU graduates - unadjusted	Hospital length of stay is based on all patients discharged from the hospital during the specified time-frame. A patient may have multiple admissions to the ICU	Hospital Admission Hospital Discharge ICU admission ICU discharge
M2	ICU length of stay - unadjusted	ICU length of stay is based on all patients discharged from the ICU during the specified time-frame	ICU admission ICU discharge
M3	ICU length of stay - adjusted	Adjusted ICU length of stay is based on all patients discharged from the ICU during the specified time-frame. Expected ICU length of stay is the APACHE IV predicted ICU length of stay. Adjusted length of stay is observed ICU length of stay divided by expected ICU length of stay	ICU admission ICU discharge APACHE IV bundle (demographic, vitals, labs, Glasgow coma score, health conditions, time stamps and geolocations, procedures and diagnosis)
M4	ICU readmission rate	Readmission summary is based on all patients admitted to the ICU during the specified time-frame. An admission is counted as a readmission if it is not the patient's first admission to the ICU during that hospital stay. Readmissions to the same ICU and readmissions within 24 h are summarized	ICU admission ICU discharge Admission source (location)
M5	ICU admissions	Admission summary is based on all patients admitted to the ICU during the specified time-frame	ICU admission ICU discharge
M6	ICU admission source and admission service	Admission source summary is based on all patients admitted to the ICU during the specified time-frame	ICU admission ICU discharge Admission source (location)
M7	Duration of mechanical ventilation	Ventilation summary is based on all patients discharged from the ICU during the specified time- frame. Use of invasive and non-invasive ventilation is summarized as well as the median duration. Numbers for invasive and non-invasive ventilation will not sum to the numbers for ventilation because patients may have both types	ICU admission ICU discharge Duration invasive or non-invasive ventilation for each day of ICU stay
M8	ICU mortality rate - unadjusted	Mortality rate summary is based on all patients discharged from the ICU during the specified time frame. Multiple discharges per patient are allowed	ICU admission ICU discharge Patient status
M9	ICU mortality rate - adjusted	Mortality summary is based on all patients discharged from the ICU during the specified time-frame. Multiple discharges per patient are allowed. Expected ICU mortality is based on each patient's APACHE IV predicted probability of hospital death. Standard mortality ratio is calculated by dividing observed ICU mortality by expected APACHE IV hospital mortality	ICU admission ICU discharge Patient status APACHE III/IV bundle (demographic, vitals, labs, Glasgow coma score, health conditions, time stamps and geolocations, procedures and diagnosis)
M10	ICU admissions for low-risk monitoring	Low-risk monitoring summary is based on all patients admitted to the ICU during the specified time-frame. Low risk monitoring calculation based on the TISS-28 score[27]. Patients with score 0-13 are considered low-risk monitoring	ICU admission ICU discharge TISS-28 score bundle (vitals, labs, orders, procedures)
M11	ICU census - hourly utilization	Unit utilization summarizes the average hourly unit utilization for each specified time-frame on the hourly ending census	ICU admission ICU discharge Number of bed per unit

ICU: Intensive care unit.

were calculated based on comparison of the test results and the reference standard (manually created report). All statistical analysis was performed in JMP (SAS, Cary, NC, United States). These statistical methods were reviewed by a statistician from the Division of Biomedical Statistics & Informatics at Mayo Clinic in Rochester, MN.

RESULTS

All types of variables needed for metric calculations were found to be available for manual and electronic abstraction, except information for availability of free beds for patient-specific time-frame (Table 2).

There was excellent agreement for admission, discharge, and transfer information, with the exception of ICU discharge time, which differed by more than 1 h in 10.7% of admissions. ICU and hospital mortality were reported identically in both cohorts, with absolute sensitivity and specificity (Table 3).

No statistically significant difference was found between manual and electronic cohorts comparing the use of invasive and non-invasive mechanical ventilation. One hundred percent of sensitivity was found for both variables. One false-positive result was returned from each type of ventilation usage, which produced decreased specificity (Table 4).

DISCUSSION

The Mayo Clinic EHR contains all necessary data for

Table 2 Clinical characteristics of baseline cohort

Number	Characteristic[1]	Overall (n = 93)
1	Age (yr)	73 (62, 83)
2	Male sex	53 (57%)
3	APACHE Ⅲ score	60 (46.5, 72)
4	SOFA score	3 (2, 5)
5	ICU type	
	Medical	51 (56%)
	Surgical	29 (30%)
	Mixed	13 (14%)
	Ventilator use	
6	Invasive	18 (19.4%)
7	Non-invasive	22 (23.7%)
8	ICU length of stay (d)	1.1 (0.9, 2.1)
9	ICU mortality	1 (1%)
10	Hospital length of stay (d)	5.4 (3.6, 11.1)
11	Hospital mortality	10 (10.7%)

[1]Values are n (%) for categorical variables and median (IQR) for continuous variables. ICU: Intensive care unit.

Table 3 Agreement of admission, discharge, and transfer information

Component	Agreement
Admit/discharge times[1]	
ICU admission	99%
ICU discharge	89%
Hospital admission	100%
Hospital discharge	100%
Pre-ICU location	100%
Admission ICU	100%
ICU discharge location	100%

[1]Agreement was considered to be within ± 1 h. ICU: Intensive care unit.

automatic abstraction and calculation of key quality metrics for ICU practice except availability of free beds and APACHE Ⅲ admission diagnosis. Demographic information, time stamps for admission and discharge, point-of-care related events, vital signs, laboratory findings, procedures, and outcomes were successfully extracted.

If integrated systems like METRIC ICU DataMart are not used, it is challenging to extract data for automated calculations of quality metrics. Dykes *et al*[22] reported 41% of variables available from "draft documentation" and an additional 30% available from specific applications, resulting in only 71% of data needed for automated calculation of their custom quality metrics. Kaiser Permanente reports partial or full automation of 6 of 13 quality metrics defined by the Joint Commission with 35% to 61% of data availability[17]. More specific automated quality metric calculation has been reported for SCIP-VTE-2 (deep venous thrombosis) with an accuracy of 96.3%[23]. Measurement concepts have been proposed for automated calculation of American College of Emergency Physicians Quality Metrics basing on availability of variables[24]. EHR-based automated calculation of 12 "meaningful use" quality metrics for more than 100 patients resulted in variable sensitivity (from 46% to 98%) and specificity (62% to 97%). Positive and negative predictive value ranged from 32% to 99%[25].

Table 4 Analysis of sensitivity and specificity

Variables and their usage for metrics	Sensitivity	Specificity	True positive	False positive	True negative	False negative
MV use (from M7)	100%	94.40%	75	1	17	0
NIV use (from M7)	100%	95.50%	71	1	21	0
ICU mortality (M8, M9)	100%	100%	0	0	93	0
In-hospital mortality	100%	100%	10	0	83	0

M7, M8, M9 are quality metrics 7, 8 and 9 respectively. ICU: Intensive care unit.

We used a different approach to provide metrics. Data, organized specifically for analytical purposes in ICU DataMart, provided accurate information about time-specific events during hospitalization[3,4,26]. Using data independent from the clinical practice EHR infrastructure is more flexible. This allows for creation of specific rules and datasets generating algorithms for automated calculation of custom or externally reportable quality metrics. Once data are extracted, they are organized in specific tables in ICU DataMart.

Attempts to analyze the agreement between manual and automated data revealed some sources of data discrepancy. Disagreement for the time of ICU discharge was 11%. This discrepancy resulted from a technical issue: Discharge time for automated data collection was initially defined when monitoring was discontinued, while in manual data abstraction, discharge was defined as the time discharge orders were written. These metrics have been useful for planning purposes as well.

Specific real time metrics were obtained and stored in ICU DataMart tables for retrospective analysis. For example, the current practice relies on this data for bed allocation as service line practices change over time. As a practice grows and requires more beds, our hourly bed utilization guides these changes.

These results demonstrate the feasibility of automated calculation of quality metrics with good accuracy, specificity, and sensitivity. ICU DataMart-based automated calculations can be utilized as a stand-alone tool for practice improvement, administrative purposes, or to provide externally reportable metrics if the institutional EHR does not support such activities.

This retrospective study has several limitations. It was performed in a single center. A custom, institution-specific ICU DataMart for data abstraction and specially developed quality metrics were used.

Automated Quality Metric calculations are feasible using a near-real time EHR infrastructure with data

storage capabilities. Electronic data extraction provided accurate (≥ 90%), sensitive (100%), and specific (≥ 93%) results. No user interaction was required to obtain ICU quality metrics.

ACKNOWLEDGMENTS

Authors are grateful to Andrew C Hanson for his assistance and suggestions on preparing the manuscript for publication.

COMMENTS

Background

In the United States millions of adult patients are admitted to intensive care units annually. Health information technology plays a central role in the quality improvement process of healthcare. Intensive care unit (ICU) quality metrics focus on care processes such as adherence to best practices. These metrics can be a valuable tool to evaluate the quality of care delivered to the patient. The reporting of valuable quality measures drives clinical process improvements. Manual generation of quality improvement metrics causes dissatisfaction and consumes time and human resources. The current generation of clinical information systems does not routinely support the generation of practice management reports.

Research frontiers

Most of the high level administrative reporting is of limited use due to outdated, corrupted, and/or incomplete data. There is no universal approach to build automated quality metric reports with direct abstraction from electronic medical records.

Innovations and breakthroughs

A near-real time electronic healthcare record (EHR) infrastructure with data storage capabilities was used for automated quality metric calculations without user interaction. Electronic data extraction provided accurate, sensitive, and specific results.

Applications

This approach can be used for automated quality metric calculation at any institution, regardless of the current EHR system.

Peer-review

Meaningful use of electronic healthcare systems allows immediate data information for both quality-performance and risk management successful processes. Quality metric measures incorporated by official regulatory offices as National Quality Forum enable a high quality course to improve effective choices for an adequate administration in ICU assistance. This study of Mayo Clinic quality-performance protocols supports an optimal use of both human and technical resources, leading us to improved management results as in top-ranked health institutions.

REFERENCES

1 **Barnato AE**, Kahn JM, Rubenfeld GD, McCauley K, Fontaine D, Frassica JJ, Hubmayr R, Jacobi J, Brower RG, Chalfin D, Sibbald W, Asch DA, Kelley M, Angus DC. Prioritizing the organization and management of intensive care services in the United States: the PrOMIS Conference. *Crit Care Med* 2007; **35**: 1003-1011 [PMID: 17334242 DOI: 10.1097/01.CCM.0000259535.06205.B4]

2 **Barrett ML**, Smith MW, Elixhauser A, Honigman LS, Pines JM. Utilization of Intensive Care Services, 2011: Statistical Brief #185. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Health Care Policy and Research (US), 2006 [PMID: 25654157]

3 **Pickering BW**, Herasevich V, Ahmed A, Gajic O. Novel Representation of Clinical Information in the ICU: Developing User Interfaces which Reduce Information Overload. *Appl Clin Inform* 2010; **1**: 116-131 [PMID: 23616831 DOI: 10.4338/ACI-2009-12-CR-0027]

4 **Pickering BW**, Hurley K, Marsh B. Identification of patient information corruption in the intensive care unit: using a scoring tool to direct quality improvements in handover. *Crit Care Med* 2009; **37**: 2905-2912 [PMID: 19770735 DOI: 10.1097/CCM.0b013e3181a96267]

5 **Ahmed A**, Chandra S, Herasevich V, Gajic O, Pickering BW. The effect of two different electronic health record user interfaces on intensive care provider task load, errors of cognition, and performance. *Crit Care Med* 2011; **39**: 1626-1634 [PMID: 21478739 DOI: 10.1097/CCM.0b013e31821858a0]

6 **Malhotra S**, Jordan D, Patel VL. Workflow modeling in critical care: piecing your own puzzle. *AMIA Annu Symp Proc* 2005: 480-484 [PMID: 16779086]

7 **Building a Safer Health System**. To Err Is Human. Committee on Quality of Health Care in America. In: Kohn LT, Corrigan JM, Donaldson MS, editors. Washington, D.C.: The National Academies Press, 2000. Available from: URL: http://www.nap.edu/read/9728/chapter/1

8 **Kohn L**. To err is human: an interview with the Institute of Medicine's Linda Kohn. *Jt Comm J Qual Improv* 2000; **26**: 227-234 [PMID: 10749007]

9 **Centers for Medicare & Medicaid Services (CMS)**, HHS. Medicare and Medicaid programs; electronic health record incentive program. Final rule. *Fed Regist* 2010; **75**: 44313-44588 [PMID: 20677415]

10 **Morris AC**, Hay AW, Swann DG, Everingham K, McCulloch C, McNulty J, Brooks O, Laurenson IF, Cook B, Walsh TS. Reducing ventilator-associated pneumonia in intensive care: impact of implementing a care bundle. *Crit Care Med* 2011; **39**: 2218-2224 [PMID: 21666444 DOI: 10.1097/CCM.0b013e3182227d52]

11 **Scales DC**, Dainty K, Hales B, Pinto R, Fowler RA, Adhikari NK, Zwarenstein M. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA* 2011; **305**: 363-372 [PMID: 21248161 DOI: 10.1001/jama.2010.2000]

12 **Netzer G**, Liu X, Shanholtz C, Harris A, Verceles A, Iwashyna TJ. Decreased mortality resulting from a multicomponent intervention in a tertiary care medical intensive care unit. *Crit Care Med* 2011; **39**: 284-293 [PMID: 21076286 DOI: 10.1097/CCM.0b013e3181ffdd2f]

13 **Chassin MR**, Loeb JM, Schmaltz SP, Wachter RM. Accountability measures--using measurement to promote quality improvement. *N Engl J Med* 2010; **363**: 683-688 [PMID: 20573915 DOI: 10.1056/NEJMsb1002320]

14 **Cleary R**, Beard R, Coles J, Devlin B, Hopkins A, Schumacher D, Wickings I. Comparative hospital databases: value for management and quality. *Qual Health Care* 1994; **3**: 3-10 [PMID: 10136257]

15 **Nolan T**, Berwick DM. All-or-none measurement raises the bar on performance. *JAMA* 2006; **295**: 1168-1170 [PMID: 16522838 DOI: 10.1001/jama.295.10.1168]

16 **Centers for Medicare & Medicaid Services (CMS)**, HHS. Medicare and Medicaid programs; electronic health record incentive program-stage 2. Final rule. *Fed Regist* 2012; **77**: 53967-54162 [PMID: 22946138]

17 **Garrido T**, Kumar S, Lekas J, Lindberg M, Kadiyala D, Whippy A, Crawford B, Weissberg J. e-Measures: insight into the challenges and opportunities of automating publicly reported quality measures. *J Am Med Inform Assoc* 2014; **21**: 181-184 [PMID: 23831833 DOI: 10.1136/amiajnl-2013-001789]

18 **Clemmer TP**. Computers in the ICU: where we started and where we are now. *J Crit Care* 2004; **19**: 201-207 [PMID: 15648035 DOI: 10.1016/j.jcrc.2004.08.005]

19 **Rubenfeld GD**. Using computerized medical databases to measure and to improve the quality of intensive care. *J Crit Care* 2004; **19**: 248-256 [PMID: 15648042 DOI: 10.1016/j.jcrc.2004.08.004]

20 **Chandra S**, Agarwal D, Hanson A, Farmer JC, Pickering BW, Gajic O, Herasevich V. The use of an electronic medical record

based automatic calculation tool to quantify risk of unplanned readmission to the intensive care unit: a validation study. *J Crit Care* 2011; **26**: 634.e9-634.e15 [PMID: 21715140 DOI: 10.1016/j.jcrc.2011.05.003]

21 **Ofoma UR**, Chandra S, Kashyap R, Herasevich V, Ahmed A, Gajic O, Pickering BW, Farmer CJ. Findings from the implementation of a validated readmission predictive tool in the discharge workflow of a medical intensive care unit. *Ann Am Thorac Soc* 2014; **11**: 737-743 [PMID: 24724964 DOI: 10.1513/AnnalsATS.201312-436OC]

22 **Dykes PC**, Caligtan C, Novack A, Thomas D, Winfield L, Zuccotti G, Rocha RA. Development of automated quality reporting: aligning local efforts with national standards. *AMIA Annu Symp Proc* 2010; **2010**: 187-191 [PMID: 21346966]

23 **Kukhareva PV**, Kawamoto K, Shields DE, Barfuss DT, Halley AM, Tippetts TJ, Warner PB, Bray BE, Staes CJ. Clinical Decision Support-based Quality Measurement (CDS-QM) Framework: Prototype Implementation, Evaluation, and Future Directions. *AMIA Annu Symp Proc* 2014; **2014**: 825-834 [PMID: 25954389]

24 **Griffey RT**, Pines JM, Farley HL, Phelan MP, Beach C, Schuur JD, Venkatesh AK. Chief complaint-based performance measures: a new focus for acute care quality measurement. *Ann Emerg Med* 2015; **65**: 387-395 [PMID: 25443989 DOI: 10.1016/j.annemergmed.2014.07.453]

25 **Kern LM**, Malhotra S, Barrón Y, Quaresimo J, Dhopeshwarkar R, Pichardo M, Edwards AM, Kaushal R. Accuracy of electronically reported "meaningful use" clinical quality measures: a cross-sectional study. *Ann Intern Med* 2013; **158**: 77-83 [PMID: 23318309 DOI: 10.7326/0003-4819-158-2-201301150-00001]

26 **Herasevich V**, Kor DJ, Li M, Pickering BW. ICU data mart: a non-iT approach. A team of clinicians, researchers and informatics personnel at the Mayo Clinic have taken a homegrown approach to building an ICU data mart. *Healthc Inform* 2011; **28**: 42, 44-45 [PMID: 22121570]

27 **Miranda DR**, de Rijk A, Schaufeli W. Simplified Therapeutic Intervention Scoring System: the TISS-28 items--results from a multicenter study. *Crit Care Med* 1996; **24**: 64-73 [PMID: 8565541]

P- Reviewer: Inchauspe A
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2016 August 4; 5(3): 171-200

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

A peer-reviewed, online, open-access journal of critical care medicine

Editorial Board

2016-2019

The *World Journal of Critical Care Medicine* Editorial Board consists of 235 members, representing a team of worldwide experts in critical care medicine. They are from 44 countries, including Argentina (2), Australia (7), Austria (2), Bangladesh (1), Belgium (4), Brazil (4), Canada (6), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (6), Germany (9), Greece (9), Hungary (1), India (10), Iran (2), Israel (6), Italy (13), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (2), Singapore (2), Slovenia (1), South Africa (1), Spain (6), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (7), United States (70), and Uruguay (1).

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 5 Number 3 August 4, 2016

World Journal of Critical Care Medicine
Volume 5 Number 3 August 4, 2016

Contents

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
August 4, 2016

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i3.171

World J Crit Care Med 2016 August 4; 5(3): 171-179
ISSN 2220-3141 (online)

REVIEW

Ethical publishing in intensive care medicine: A narrative review

Christian J Wiedermann

Christian J Wiedermann, Department of Internal Medicine, Central Hospital of Bolzano, 39100 Bolzano, Italy

Author contributions: Wiedermann CJ is the sole author of this manuscript and responsible for conception and design, data collection, analysis and interpretation, and writing of the review.

Conflict-of-interest statement: The author declares no conflict of interest for this article.

Manuscript source: Invited manuscript

Correspondence to: Christian J Wiedermann, MD, Department of Internal Medicine, Central Hospital of Bolzano, Lorenz-Böhler-Street 5, 39100 Bolzano, Italy. christian.wiedermann@sabes.it
Telephone: +39-0471-908190
Fax: +39-0471-908504

Received: February 9, 2016
Peer-review started: February 14, 2016
First decision: May 19, 2016
Revised: July 4, 2016
Accepted: July 14, 2016
Article in press: July 18, 2016
Published online: August 4, 2016

Abstract

Ethical standards in the context of scientific publications are increasingly gaining attention. A narrative review of the literature concerning publication ethics was conducted as found in PubMed, Google Scholar, relevant news articles, position papers, websites and other sources. The Committee on Publication Ethics has produced guidelines and schedules for the handling of problem situations that have been adopted by professional journals and publishers worldwide as guidelines to authors. The defined requirements go beyond the disclosure of conflicts of interest or the prior registration of clinical trials. Recommendations to authors, editors and publishers of journals and research institutions were formulated with regard to issues of authorship, double publications, plagiarism, and conflicts of interest, with special attention being paid to unethical research behavior and data falsification. This narrative review focusses on ethical publishing in intensive care medicine. As scientific misconduct with data falsification damage patients and society, especially if fraudulent studies are considered important or favor certain therapies and downplay their side effects, it is important to ensure that only studies are published that have been carried out with highest integrity according to predefined criteria. For that also the peer review process has to be conducted in accordance with the highest possible scientific standards and making use of available modern information technology. The review provides the current state of recommendations that are considered to be most relevant particularly in the field of intensive care medicine.

Key words: Peer review; Duplicate publication; Plagiarism; Scientific misconduct; Publication retractions; Boldt fraud; Fujii fraud

Core tip: Ethical standards in the context of scientific publications are increasingly gaining attention. Recommendations to authors, editors and publishers of journals and research institutions were formulated by The Committee on Publication Ethics with regard to

issues of authorship, double publications, plagiarism, and conflicts of interest, with special attention being paid to unethical research behavior and data falsification. As scientific misconduct with data falsification damage patients and society, it is important to ensure that only studies are published that have been carried out with highest integrity according to predefined criteria and that also the peer review process has to be conducted in accordance with the highest possible scientific standards.

Wiedermann CJ. Ethical publishing in intensive care medicine: A narrative review. *World J Crit Care Med* 2016; 5(3): 171-179 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/171.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.171

INTRODUCTION

Clinicians and researchers must be able to rely on the integrity and fair presentation of biomedical publications. They have, after all, a vested interest in it[1]. In recent years, the traditional relationship of trust between authors of publications of clinical studies, editors of medical journals, and their readers has come to falter because of numerous examples of open scientific misconduct[2-7]. Numerous journals in intensive care medicine have been affected by the increased number of published articles that they have had to retract. Measures to preserve scientific integrity are therefore becoming increasingly important. These include recommendations how to perform and present clinical studies. What publishers of scientific journals undertake to ensure the integrity of the scientific literature has become a recognized performance criterion[8]. The integrity of a biomedical journal depends on the ethical conduct of those who carry the greatest responsibility for the research publications, namely the authors, on the one hand, and the publishers, on the other, who need to understand that honest mistakes are inevitable, and are able to distinguish them from deliberate wrongdoing.

The editors need to ensure that all articles published in their journals fulfill the highest standards of scientific integrity[9]. Previously, when confronted with integrity problems, editors behaved as though unethical behavior of authors was not in their area of responsibility. Today, most of them have recognized that time and energy need to be invested in the investigation of allegations of scientific misconduct in order to ensure the scientific integrity of the journal. According to a recent survey of 200 leading journals, only two-thirds have fixed rules on withdrawal of publications, and in 95% they would be allowed to opt for such a move even against the will of the authors[10].

Usually, accusations of wrongdoing are raised by referees or readers. Publishers may and can assume that the whistleblower is acting in good faith and that their anonymity must be protected. Accused authors again must be considered as innocent until the suspected misconduct has undergone careful examination and proven to be such. The principles underlying such an investigative procedure are the subject of this review paper. In this context, collaboration between journals and research institutions is of key importance[11]. Based on the experiences of the recent past, the relevant issues include questions about misrepresentation of study designs, faulty statistics, double publications, data falsification, withdrawal of unreliable publications, and assessment of submitted manuscripts, including peer review, authorship issues and conflicts of interest. This review describes the principles of ethical publishing. It gives an overview on the subject. Statements are based on the available literature and the recommendations of the Committee on Publication Ethics (COPE) (http://publicationethics.org). The problems addressed relate to allegation or evidence of various types of reporting bias, plagiarism, double publications, multiple submissions, fragmented multiple publications of research findings of individual studies, and selective reporting; authorship; falsification and fabrication of data; and withdrawal of published articles.

METHODOLOGY

This narrative review has been made to address the problems of publication ethics in intensive care medicine. Author reviewed available literature, reports and surveys on the integrity of publications on critical care medicine as found in PubMed, Google Scholar, relevant news articles, position papers, websites and other sources.

UNETHICAL PUBLISHING IN INTENSIVE CARE MEDICINE

Retractions of publications are a sign that a journal takes seriously its responsibility for the integrity of its publications. Erroneous, unethical or fraudulent studies must be indicated to be such by using the possible formats "Expression of Concern", "Erratum", "Corrigendum" and "Notice of Retraction" or "Retraction Note" in order to ensure the scientific community that the publications in question have been assessed correctly and can be quickly identified as such in the literature databases.

Until a few years ago, relatively few retracted publications in the field of intensive care medicine were made public (Table 1). Recently, there has been an exponential growth in publication retractions both in biomedical literature and in the field of intensive care (Figure 1). This has as much to do with the capabilities of modern information technology and their impact on academic medicine and medical research as with changes in career opportunities for researchers and the

Table 1 Retracted publications arising from 28 critical care journals

Journal	Retractions (*n*)	Retracted Fujii papers (*n*)	Retracted Boldt papers (*n*)
American Journal of Critical Care	-	-	-
American Journal of Respiratory and Critical Care Medicine	7	-	-
Anaesthesia and Intensive Care	6	6	-
Anästhesiologie Intensivmedizin Notfallmedizin Schmerztherapie	6	-	6
Annals of Intensive Care	-	-	-
Burns	-	-	-
Chest	5	-	-
Critical Care	-	-	-
Critical Care and Resuscitation	-	-	-
Critical Care Clinics	-	-	-
Critical Care Medicine	5	-	2
Critical Care Nurse	-	-	-
Current Opinion in Critical Care	1	-	-
Injury	2	-	-
Intensive Care Medicine	7	-	6
Journal of Critical Care	-	-	-
Journal of Intensive Care Medicine	-	-	-
Journal of Neurotrauma	1	-	-
Journal of Trauma and Acute Care Surgery	-	-	-
Journal of Trauma Nursing	-	-	-
Medicina Intensiva	-	-	-
Minerva Anestesiologica	2	1	1
Neurocritical Care	-	-	-
Pediatric Critical Care Medicine	-	-	-
Respiratory Care	1	-	-
Resuscitation	3	-	-
Seminars in Respiratory and Critical Care Medicine	-	-	-
Shock	2	-	-
Total	48	7	15

Results of a PubMed search (available from: URL: http//www.ncbi.nlm.nih.gov/pubmed) on 05/04/2015. Search term "retraction of publication[publication type" and "american journal of critical care" (journal) or "american journal of respiratory and critical care medicine" (journal) or "anaesthesia and intensive care" (journal) or "anasthesiologie intensivmedizin notfallmedizin schmerztherapie" (journal) or "annals of intensive care" (journal) or "burns" (journal) or "chest" (journal) or "critical care" (journal) or "critical care and resuscitation" (journal) or "critical care clinics" (journal) or "critical care medicine" (journal) or "critical care nurse" (journal) or "current opinion in critical care" (journal) or "injury" (journal) or "intensive care medicine" (journal) or "journal of critical care (journal) or "journal of intensive care medicine" (journal) or "journal of neurotrauma" (journal) or "journal of trauma and acute care surgery" (journal) or "medicina intensiva" (journal) or "minerva anestesiologica" (journal) or "neurocritical care" (journal) or "pediatric critical care medicine" (journal) or "respiratory care" (journal) or "resuscitation" (journal) or "seminars in respiratory and critical care medicine" (journal) or "shock" (journal).

changing financial environment for research. And the number of publications retracted can be expected to rise in the future[12].

Two cases of research fraud in critical care medicine and anaesthesia

In the field of intensive care medicine, the majority of article withdrawals were made by leading international

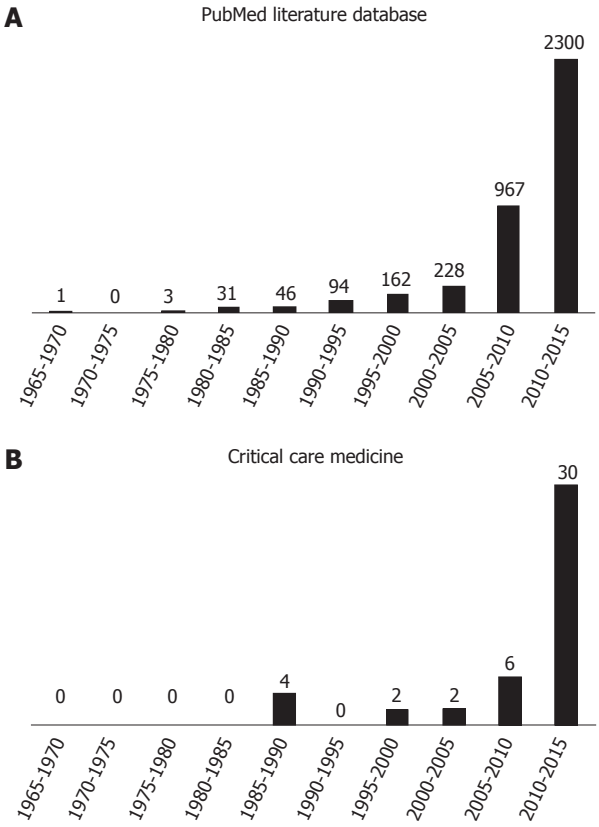


Figure 1 Retracted publications in biomedical literature and those arising from 28 critical care journals in the last five decades. Results of a PubMed search (available from: URL: http//www.ncbi.nlm.nih.gov/pubmed) on 05/04/2015 with the search term (A) "retraction of publication (publication type)" for the biomedical literature and (B) that of Table 1 for the critical care medicine literature (search terms described in Table 1).

scientific journals of the United States and Europe (*Am J Resp Crit Care Med*, *Chest*, *Crit Care Med*, *Intensive Care Med*). These are rather high-impact and not low-impact journals[13]. It is interesting to note that out of 28 involved journals, two national journals, namely "*Anaesthesia and Intensive Care*" and "*Anaesthesiology Intensive Care Emergency Medicine Pain Therapy*" from Australia and Germany, respectively are responsible for a quarter of all withdrawals in the field of intensive care (Table 1): All six articles retracted by "*Anesthesia and Intensive Care*" were articles of the Japanese author Fujii and all six withdrawals by the journal "*Anaesthesiology Intensive Care Emergency Medicine Pain Therapy*" were publications of Boldt in Germany. These two cases of scientific misconduct represent almost half (22/48) of all publication retractions in this area of medical research and therefore need further scrutiny. In seven of the 48 retracted articles in the area of intensive care, "*Intensive Care Medicine*" was involved and six of them were publications of Boldt. The exact scope of his fraud has neither been clearly determined, nor fully investigated. What is clear is that Joachim Boldt as an author of more than 215 publications on clinical trials had no authorization from the relevant ethics committees at both places where

Table 2 Cooperation between research institutions and journals on research integrity cases: Guidance from the committee on publication ethics

Who should	Do what
Institutions	Have a representative or an office for research integrity with highly visible contact details
	Inform magazines about cases of misconduct, in which the reliability of published data is doubtful
	Respond to journals when requested for information on issues such as disputed authorship, questionable data quality, existing conflict of interest or other issues that could affect the reliability of the published works, including honest errors
Journals	Initiate investigations into allegations of scientific misconduct or unacceptable publication
	Have guidelines to support responsible research and provisions for implementation of investigative procedures in cases of suspected scientific misconduct
	Give the contact details of the publisher responsible for questions of research and publication integrity
	Inform institutions if they suspect that wrongdoing by their researchers and submit evidence which support these concerns
	Cooperate with the institutions in question and in investigations suspected misconduct
	Be ready to announce retraction or correction of publications according to the guidelines on COPE if investigations confirm misconduct
	Have guidelines for responding to institutions and other organizations that investigate suspected cases of scientific misconduct

COPE: Committee on publication ethics (available from: URL: http//publicationethics.org/resources/guidelines).

he worked (University Hospital of Giessen and Klinikum Ludwigshafen) for carrying out research on patients. Therefore, a total of 88 of his publications were retracted in March 2011 for the time being.

The Fujii fraud: In 2000, a letter to the editor was published in "*Anesthesia and Analgesia*" that questioned the credibility of information on adverse drug reactions, because they were almost always identical in the 47 articles of the Japanese author Dr. Yoshitaka Fujii[2]. Against this background of suspicion of falsifying data, many years later, when the author submitted a manuscript to another journal, the matter was thoroughly investigated in cooperation with the publisher and the author's research institution with the result that it was found that no ethics committee approval had been obtained for the study, and furthermore, data manipulation was detected[3]. At the same time, the British anesthesiologist Dr. John Carlisle checked the integrity of the data of a total of 168 randomized controlled trials that Dr. Fujii had published over the years. He gave overwhelming statistical evidence that it was highly unlikely that the statistical distributions of continuous and categorical variables described in the publications are what could be expected to occur by chance[4]. After further examination of several Japanese universities where Dr. Fujii had worked continuously only for a few years each, the suspicion of falsification could not be discounted. Finally, a hitherto unprecedented number of 189 publications in anesthesia and intensive care medicine journals were recommended for retraction by the Japanese Society for Anesthesia.

In the case of the Japanese anesthesiologist Dr. Yoshitaka Fujii, who had worked in six Japanese universities and falsified a large number of publications, the involved academic institutions, in collaboration with the Japanese Society of Anesthesiology, quickly analyzed 300 articles after a group of editors and researchers suspected fundamental problems in many of his publications[2-4].

Although the fraudulent publications were discovered to be such only years later, recommendations to have these retracted were made to the responsible editors in a relatively short time, because the involved Japanese institutions and journals worked together constructively. Although research scandals are rated negatively by the public, in the end, particularly research institutions can benefit from this kind lively professionalism.

The Boldt fraud: In announcing the retraction of an article by Dr. Joachim Boldt, a group of editors declared that lack of ethics committee approval of a study does "not (...) mean that the research results per se are fraudulent"[5]. Data fraud was found in 10 of the publications[14]. The Klinikum Ludwigshafen could not find study documents on 92% of patients recruited for studies[14]. Suspicious homogeneity in the mortality data was seen in five publications[15]. Six publications on cardiac and major abdominal surgery showed suspiciously low interleukin-6 measurement variability[16-21]. For two of the six articles[17,19] data for comparative analysis were available in a thesis[22]. The dissertation showed that the articles misrepresented a single study as two separate studies, and that data had been manipulated to conceal the double publication.

Dissertations as a data source for fraudulent publications were found in two other retractions, one of which had already been withdrawn due to lack of ethics committee approval[23-25]. As of today, 89 publications have been retracted because they had failed to obtain ethics committee approval[5]; there are additional articles that have been retracted because of data falsification and double publications: two because of proven fabrication of data[26,27], and two because of proven data manipulation[28,29].

In 2012, the Klinikum Ludwigshafen pointed out that only those publications of Dr. Boldt had been examined that had appeared after 1999[14]. Because nearly 40% of clinical trials were carried out at the University Hospital Giessen, and articles based on these trials were published prior to 1999 and because thesis data were

falsified in publications[17,19,22-25], it can be assumed that falsification occurred prior to 1999.

In the meantime, comparative analysis of theses and publications are being carried out at the University of Giessen. Initial results have led to a series of further retractions, all of which are explained by systematic data falsification and partly with simultaneous dual publication[30-33] and trial design change[34]. From a confidential communication from the University of Giessen to the editors of the journals involved, from which "Retraction Watch"[35] was permitted to quote, it can be assumed that there are still large numbers of other publications of clinical studies of Boldt that will be retracted because of scientific misconduct going beyond lack of approval from ethics committee[34]. Among the most important issues that arise from the fraudulent series of Boldt is: How was it possible for Boldt to publish over a period of 25 years, working at two research facilities only, at least 217 articles on clinical trials involving thousands of patients with more than 180 co-authors (Christian J Wiedermann, unpublished survey) without arousing any suspicion of misconduct in institutions where he worked and the co-authors?

CORRECTING UNETHICAL LITERATURE

Research-based institutions as well as scientific journals are obliged to fulfill their different responsibilities. Institutions are responsible for the conduct of research and the promotion of a healthy research environment. Journals are responsible for assuring that their editors uphold the high scientific quality of all their publications. On issues of integrity of the research, it is important for both sides to communicate and to cooperate with each other effectively. To achieve this, COPE has issued recommendations[36], according to which the obligations are defined (Table 2).

Data falsification, plagiarism, double publications and irregularities in the authorship are the most common reasons for journal editors for having to deal with the question whether published articles should be retracted. Other problems are those of patients' rights and whether they were taken into consideration and whether permission was obtained from ethics committees. The retraction of publications should not be confused with "errata" or "corrigenda" - these are necessary when journals make some mistakes during production or when authors seek to retrospectively correct honest mistakes.

Identification of plagiarism and data falsification

With word processors, it has become easy to copy data and texts when writing scientific articles and exchange texts between documents and thus inadvertently or intentionally produce plagiarized texts. It is therefore important that citations and paraphrasing are properly done. It must be clear that the copying of existing documents is only permitted if the copied sections are clearly labeled as such, for example, by the text being enclosed in quotation marks and by correctly specifying the sources. Many institutions and scientific journal, particularly in English-speaking countries, now check submitted texts with commercial plagiarism software. One such text-comparative software is "iThenticate", which, in conjunction with a large database of published scientific documents called "Crosscheck" provided by publishers, detects plagiarism and redundant publication. One disadvantage of these systems is that analysis is limited to determining the number of copied words, and the number of copied words that is acceptable is defined by the institutions themselves and the journals[37]. Another disadvantage is that figures cannot be compared. The publishers of journals must themselves specify their evaluation criteria for text and picture similarities.

In surveys made, on average 2% of scientists admitted to having falsified research data at least once, and up to 34% admitted to having used other questionable research practices[38]. The actual frequency is likely to be even higher.

The approach to statistically identify potentially fraudulent data in publications of randomized clinical trials (RCTs) was developed and refined by Carlisle *et al*[39] so that "improbability" in the distribution of data in RCTs can be determined with increasing accuracy. It is conceivable that, in the foreseeable future, such statistical methods will be introduced in the publication routine - analogous to the use of software for detection of plagiarism to check plausibility of data integrity[40], which should become possible at least for prolific authors.

Retraction

Retractions of unreliable publications are important for scientific but also for economic reasons. After an investigation for misconduct, retracted publications of research projects that were funded by the "National Institutes of Health" in the United States lost about $58 million in direct financing in 1992-2012, representing on average US$ 392.582 per article). Researchers affected by withdrawal of one of their articles suffered a 90% decline in their publication output and large losses in the further financing of their projects[41]. Coauthors are not privy enough in publications also suffer from being under suspicion of participation in falsification and often without their knowledge. Their interest in correct publication practice can be used in strategies against unethical publishing[42].

Editorial efforts necessary for retracting a fraudulent publication are often enormous. Not least, the public loss of confidence arising from the misconduct and retraction of publications causes harm to scientific research itself. Although retracted publications represent only a small percentage of the total literature[43,44], it can be assumed that the number of unreported cases of falsified research reports is much higher than

is currently known. Only a fraction of the cases of scientific misconduct is actually uncovered and made public[38,45]. Worse still, the results of the retracted article continue to be cited[46-48]. Only in a fifth of the cases of announced retraction of scientific publications is research or publication misconduct cited as a reason by the journals for the retraction; in two-fifths of the cases, merely loss of credibility of data or their interpretation is cited as a reason[48].

From the fact of a journal withdrawing an article, is it permitted to conclude that the reason for retraction was scientific misconduct on the part of the authors? There are demands that this should not be done since there are several reasons why journals retract an article. This, however, is not a justifiable demand because authors identified as having falsified their data in one publication appear as authors in numerous retracted publications and thus distort the interpretation of the situation. Thus, although numerous articles of the anesthesiologist Dr. Joachim Boldt were retracted only for lack of ethics committee approval, suspicions of falsification were not investigated[49,50]. This shows how important the involvement of universities and research institutions in the review of falsification suspicion is, mainly because they have the ability to prove fraudulent intent and scientific fraud. This is underlined by the recent observation that even if regulatory authorities such as the American "Food and Drug Administration" (FDA) detects significant deviations from good clinical practice in clinical trials, they are seldom reflected in the clinical literature, and this happens even when there was clear evidence of data manipulation and other forms of scientific fraud[51,52]. As an example of misconduct in publication ethics, the FDA study for approval of the infusion solution Voluven® in United Sates can also be cited in this context: The nephrotoxic potential of this drug was indeed reported to the authorities, but was not been included in the publication, and this situation continues to this day without any relevant note of caution related to selective outcome reporting being added[53]. Another example is the FIRST trial[54], where the trial design has been published beforehand, but the final publication was different from the stated parameters[55].

Erratum, corrigendum and expression-of-concern

COPE guidelines explain when articles should be retracted, when corrections should be made and when only the "expression of concern" might be more appropriately used. Decisions that editors of journals must make still remain difficult. Thus, an analysis of the response of individual journals to a recent series of unethical publications of the German anesthesiologist Dr. Joachim Boldt that would need to be retracted according to the research institutions involved shows that only a small percentage of these have been dealt according to the COPE criteria[56].

For the researchers themselves and for the public, withdrawal of publications and the reasons for it[44,57-59], are of increasing interest. Both the absolute and relative number of retracted articles has increased dramatically. To what extent this represents an increase of scientific misconduct is unclear because journals also have better ways to detect especially plagiarism and multiple publications. Undoubtedly, researchers are under great pressure to publish and be "cited"[60].

Editors and publishers have the important duty to draw the attention of readers to scientific misconduct when publications have proven to be unreliable. In times of the conventional printing and traditional library catalogs, it was difficult to make any necessary corrections and any retractions of publications known in such a way that they could be brought into relation with the original articles. Today, the electronic publishing and cataloging system has simplified this task enormously. Readers are referred to corrections or retractions of texts at the very beginning of their electronic search. In this respect, supplementary information is already added to the table of contents and the article itself. Corrections and retractions are built directly into the affected article in this way. CrossMark (http://www.crossref.org/crossmark/) provides additional opportunities for cross-reference to refer the reader to comments and modifications of scientific publications. Thus, publishers can meet their responsibilities, so that retracted publications do not continue to be cited.

In case serious misconduct is suspected, the investigation of which takes more time to complete than expected, editors can warn readers of potential problems with an individual article even before completion of the investigations. In such cases, the publication of an "expression of concern" is advised by COPE.

DEGREES OF SEVERITY OF FRAUDULENT PUBLICATIONS

Even when intentional fraud seems obvious, ethical problems in publication may not be intentional and may arise out of ignorance or carelessness. This must be considered while investigating scientific misconduct. In the transparent description of such investigations, scientific journals as well as research institutions must handle the issue appropriately in accordance with the severity of misconduct involved. When plagiarism is suspected, there are differences in responsibility between senior researchers and young scientists in manuscript preparation, which should be reflected in the response of the journal to the submitted article, as well as the disciplinary measures taken by the institutions. The COPE algorithms describe in as differentiated a way as possible, how the publisher can respond to different types of ethical publication problems. Of course, not all aspects could be anticipated and some had to be left open and left to the co-operation between publishers, publishing houses and research institutions. One such issue is how to react to an anonymous informant.

CONCLUSION

Steps that need to be carried out by journal editors when confronted with unethical publishing include notifying the affected authors and research institutions, and investigation of the incident and publishing a report on it. It is important to be vigilant in order to detect breaches of publication ethics whenever they take place.

All authors must adhere to the principles of ethical publishing and agree with and conform to the policy of the journal in this regard. The corresponding author has obtained the consent of all the listed co-authors for the submission and publication of all versions of the manuscript. This is confirmed by all authors. All of the authors make their email address available, over which they are kept informed about all the steps up to the final step of publication or rejection.

All individuals have been added to the group of authors that have made a significant independent contribution to the manuscript.

The submitted manuscript is original and not already published elsewhere, except as oral presentation or poster with an abstract of no more than one page. In addition, the integrity of submitted articles is assured by the obligatory peer review process using all possible information technology and statistical tools.

The data of the manuscript have been obtained according to modern ethical standards taking into consideration the guideline recommendations such as those of PRISMA and free of decidedly non-authorized texts or data copies from other sources. All contents derived from previously published sources, either their own or those of others, are properly cited. Should any of the above-mentioned conditions be unmet, the authors are obliged to notify the journal as soon as possible about it. Correct statistics are important.

Editors, authors and reviewers must follow the basic rules of ethical publishing when submitting articles for publication, do peer reviewing or when they identify potential integrity problems when reading the articles. Most published articles are free of unethical behavior. Articles that, despite careful review process, violate good publication ethics, must be identified, analyzed and corrected or, where appropriate, retracted. In the work-up of problem cases, the methods formulated in the recommendations of COPE (http://publicationethics.org/resources/guidelines) can be put into use. "*Intensive Care Medicine*" makes full use of these recommendations. Rapid and close cooperation between authors, research institutions, the publisher of the journal and the publishing house is of the highest importance. It is emphasized that the critical reader plays an important role in the identification of irregularities and possible violation of good publication ethics. While respecting the reader anonymity, all concerned are encouraged to report suspected misconduct to the publication editor of the magazine.

REFERENCES

1 **Caelleigh AS**. Role of the journal editor in sustaining integrity in research. *Acad Med* 1993; **68**: S23-S29 [PMID: 8373488 DOI: 10.1097/00001888-199309000-00030]

2 **Kranke P**, Apfel CC, Roewer N, Fujii Y. Reported data on granisetron and postoperative nausea and vomiting by Fujii et al. Are incredibly nice! *Anesth Analg* 2000; **90**: 1004-1007 [PMID: 10735823 DOI: 10.1097/00000539-200004000-00054]

3 **Miller DR**. Retraction of articles written by Dr. Yoshitaka Fujii. *Can J Anaesth* 2012; **59**: 1081-1088 [PMID: 23055039 DOI: 10.1007/s12630-012-9802-9]

4 **Carlisle JB**. The analysis of 168 randomised controlled trials to test data integrity. *Anaesthesia* 2012; **67**: 521-537 [PMID: 22404311 DOI: 10.1111/j.1365-2044.2012.07128.x]

5 Editors-in-Chief statement regarding published clinical trials conducted without IRB approval by Joachim Boldt. *Minerva Anestesiol* 2011; **77**: 562-563 [PMID: 21540815]

6 **Shafer SL**. Shadow of doubt. *Anesth Analg* 2011; **112**: 498-500 [PMID: 21296856 DOI: 10.1213/ANE.0b013e31820ad3b7]

7 China's medical research integrity questioned. *Lancet* 2015; **385**: 1365 [PMID: 25890401 DOI: 10.1016/S0140-6736(15)60700-0]

8 **Tobin MJ**. Assessing the performance of a medical journal. *Am J Respir Crit Care Med* 2004; **169**: 1268-1272 [PMID: 15187009 DOI: 10.1164/rccm.2404006]

9 **Bailar JI**, Angell M, Boots S, Myers E, N Palmer, Shipley M, Woolf P. Ethics and Policy in scientific publication. Council of Biology Editors, Bethesda (MD), 1990

10 **Resnik DB**, Wager E, Kissling GE. Retraction policies of top scientific journals ranked by impact factor. *J Med Libr Assoc* 2015; **103**: 136-139 [PMID: 26213505 DOI: 10.3163/1536-5050.103.3.006]

11 **Wager E**, Kleinert S. Cooperation between research institutions and journals in research integrity cases: guidance from the Committee on Publication Ethics. London: Committee on Publication Ethics. [accessed 2015 Oct 12]. Available from: URL: http//publicationethics.org

12 **Marcus A**, Oransky I. What studies of retractions tell us. *J Microbiol Biol Educ* 2014; **15**: 151-154 [PMID: 25574267 DOI: 10.1128/jmbe.v15i2.855]

13 **Fang FC**, Casadevall A. Retracted science and the retraction index. *Infect Immun* 2011; **79**: 3855-3859 [PMID: 21825063 DOI: 10.1128/IAI.05661-11]

14 Hospital presents results of final report: committee completes investigation in the case of Dr Boldt. [accessed 2015 Oct 13]. Available from: URL: http//www.klilu.de/content/veranstaltungen___presse/pressearchiv/2012/hospital_presents_results_of_final_report_committee_completes_investigation_in_the_case_of_dr_boldt/index_ger.html

15 **Ioannidis JP**, Trikalinos TA, Zintzaras E. Extreme between-study homogeneity in meta-analyses could offer useful insights. *J Clin Epidemiol* 2006; **59**: 1023-1032 [PMID: 16980141 DOI: 10.1016/j.jclinepi.2006.02.013]

16 **Lang K**, Suttner S, Boldt J, Kumle B, Nagel D. Volume replacement with HES 130/0.4 may reduce the inflammatory response in patients undergoing major abdominal surgery. *Can J Anaesth* 2003; **50**: 1009-1016 [PMID: 14656778 DOI: 10.1007/bf03018364]

17 **Boldt J**, Ducke M, Kumle B, Papsdorf M, Zurmeyer EL. Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery. *Intensive Care Med* 2004; **30**: 416-422 [PMID: 14712346 DOI: 10.1007/s00134-003-2110-7]

18 **Boldt J**, Schölhorn T, Mayer J, Piper S, Suttner S. The value of an albumin-based intravascular volume replacement strategy in elderly patients undergoing major abdominal surgery. *Anesth Analg* 2006; **103**: 191-199, table of contents [PMID: 16790652 DOI: 10.1213/01.ane.0000221179.07006.06]

19 **Boldt J**, Brosch Ch, Röhm K, Papsdorf M, Mengistu A. Comparison of the effects of gelatin and a modern hydroxyethyl starch solution on renal function and inflammatory response in elderly cardiac surgery patients. *Br J Anaesth* 2008; **100**: 457-464

[PMID: 18305082 DOI: 10.1093/bja/aen016]
20 **Boldt J**, Suttner S, Brosch C, Lehmann A, Röhm K, Mengistu A. The influence of a balanced volume replacement concept on inflammation, endothelial activation, and kidney integrity in elderly cardiac surgery patients. *Intensive Care Med* 2009; **35**: 462-470 [PMID: 18807007 DOI: 10.1007/s00134-008-1287-1]
21 **Boldt J**, Mayer J, Brosch C, Lehmann A, Mengistu A. Volume replacement with a balanced hydroxyethyl starch (HES) preparation in cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2010; **24**: 399-407 [PMID: 20510247 DOI: 10.1053/j.jvca.2010.03.001]
22 **Papsdorf M**. Auswirkungen einer Volumenersatztherapie auf Makro- und Mikrozirkulation und deren Regulatoren: Ein Vergleich von Hydroxyethylstärke und Humanalbumin beim kritisch kranken Patienten. Dissertation, Justus-Liebig-Universität Gießen, 2004
23 **Schellhaaß A**. Untersuchungen über den Einfluss von Volumenersatzmitteln auf die Blutgerinnung in der Abdominalchirurgie - Vergleich zweier kristalloider und zweier kolloidaler Volumenersatzmittel. Dissertation, Justus-Liebig-Universität Gießen, 2003
24 **Boldt J**, Haisch G, Suttner S, Kumle B, Schellhaass A. Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend) on measures of coagulation. *Br J Anaesth* 2002; **89**: 722-728 [PMID: 12393770 DOI: 10.1093/bja/aef242]
25 Are lactated Ringer's solution and normal saline solution equal with regard to coagulation?: Retraction. *Anesth Analg* 2011; **112**: 1178 [PMID: 21451081 DOI: 10.1213/ANE.0b013e31821a9566]
26 Retraction note: Volume therapy in the critically ill: is there a difference? *Intensive Care Med* 2014; **40**: 145 [PMID: 24271030 DOI: 10.1007/s00134-013-3164-9]
27 **Boldt J**, Suttner S, Brosch C, Lehmann A, Röhm K, Mengistu A. Cardiopulmonary bypass priming using a high dose of a balanced hydroxyethyl starch versus an albumin-based priming strategy. *Anesth Analg* 2009; **109**: 1752-1762 [PMID: 19923501 DOI: 10.1213/ANE.0b013e3181b5a24b]
28 Notice of formal retraction of an article by Dr Joachim Boldt. *Br J Anaesth* 2014; **112**: 397 [PMID: 24431372 DOI: 10.1093/bja/aet488]
29 **Shafer SL**. Editor's note: notice of retraction. *Anesth Analg* 2014; **119**: 1225 [PMID: 25329035 DOI: 10.1213/ANE.0000000000000417]
30 Blood Conservation Techniques and Platelet Function in Cardiac Surgery: Retraction. *Anesthesiology* 2015; **123**: 492 [PMID: 26196884 DOI: 10.1097/01.anes.0000466953.80399.76]
31 **Boldt J**, Zickmann B, Rapin J, Hammermann H, Dapper F, Hempelmann G. Influence of volume replacement with different HES-solutions on microcirculatory blood flow in cardiac surgery. *Acta Anaesthesiol Scand* 1994; **38**: 432-438 [PMID: 7524255 DOI: 10.1111/aas.12585]
32 **Boldt J**, von Bormann B, Kling D, Börner U, Mulch J, Hempelmann G. Volume replacement with a new hydroxyethyl starch preparation (3 percent HES 200/0.5) in heart surgery. *Infusionsther Klin Ernahr* 1986; **13**: 145-151 [PMID: 2427448]
33 **Boldt J**, von Bormann B, Kling D, Börner U, Mulch J, Hempelmann G. Retraction Statement. *Transfus Med Hemother* 2015; **42**: 266 [PMID: 26557818 DOI: 10.1159/000436984]
34 **Chaudry IH**, Lang CH. Expression of concern. *Shock* 2015; **43**: 620 [PMID: 25978810 DOI: 10.1097/SHK.0000000000000393]
35 **Palus S**. Three more retractions for former record-holder Boldt, maybe more to come. [accessed 2015 Sept 30]. Available from: URL: http//retractionwatch.com/2015/08/13/three-more-retractions-for-former-record-holder-boldt-maybe-more-to-come
36 **Wager E**, Kleinert S. Cooperation between research institutions and journals on research integrity cases: guidance from the Committee on Publication Ethics (COPE). *Maturitas* 2012; **72**: 165-169 [PMID: 22541357 DOI: 10.1016/j.maturitas.2012.03.011]
37 **Wager E**. Defining and responding to plagiarism. *Learn Publ* 2014; **27**: 33-42 [DOI: 10.1087/20140105]
38 **Fanelli D**. How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. *PLoS One* 2009; **4**: e5738 [PMID: 19478950 DOI: 10.1371/journal.pone.0005738]
39 **Carlisle JB**, Dexter F, Pandit JJ, Shafer SL, Yentis SM. Calculating the probability of random sampling for continuous variables in submitted or published randomised controlled trials. *Anaesthesia* 2015; **70**: 848-858 [PMID: 26032950 DOI: 10.1111/anae.13126]
40 **Miller DR**. Probability screening in manuscripts submitted to biomedical journals--an effective tool or a statistical quagmire? *Anaesthesia* 2015; **70**: 765-768 [PMID: 26033111 DOI: 10.1111/anae.13165]
41 **Stern AM**, Casadevall A, Steen RG, Fang FC. Financial costs and personal consequences of research misconduct resulting in retracted publications. *Elife* 2014; **3**: e02956 [PMID: 25124673 DOI: 10.7554/eLife.02956]
42 **Foo JY**, Tan XJ. Analysis and implications of retraction period and coauthorship of fraudulent publications. *Account Res* 2014; **21**: 198-210 [PMID: 24325213 DOI: 10.1080/08989621.2013.848799]
43 **Cokol M**, Iossifov I, Rodriguez-Esteban R, Rzhetsky A. How many scientific papers should be retracted? *EMBO Rep* 2007; **8**: 422-423 [PMID: 17471252 DOI: 10.1038/sj.embor.7400970]
44 **Steen RG**. Retractions in the medical literature: Who is responsible for scientific integrity? *Am Med Writers Ass J* 2011; **26**: 2-7
45 **Titus SL**, Wells JA, Rhoades LJ. Repairing research integrity. *Nature* 2008; **453**: 980-982 [PMID: 18563131 DOI: 10.1038/453980]
46 **Budd JM**, Sievert M, Schultz TR, Scoville C. Effects of article retraction on citation and practice in medicine. *Bull Med Libr Assoc* 1999; **87**: 437-443 [PMID: 10550028]
47 **Wiedermann CJ**. Hydroxyethyl starch effects on tissue perfusion and oxygenation in patients undergoing liver surgery. *Int J Clin Exp Med* 2014; **7**: 1623 [PMID: 25035791]
48 **Bornemann-Cimenti H**, Szilagyi IS, Sandner-Kiesling A. Perpetuation of Retracted Publications Using the Example of the Scott S. Reuben Case: Incidences, Reasons and Possible Improvements. *Sci Eng Ethics* 2015 Jul 7; Epub ahead of print [PMID: 26150092 DOI: 10.1007/s11948-015-9680-y]
49 **Wilkes MM**, Navickis RJ. The Boldt affair: a quandary for meta-analysts. *Anesthesiol News* 2013; **39**: 8-9
50 **Grieneisen ML**, Zhang M. A comprehensive survey of retracted articles from the scholarly literature. *PLoS One* 2012; **7**: e44118 [PMID: 23115617 DOI: 10.1371/journal.pone.0044118]
51 **Hamrell MR**. Raising suspicions with the Food and Drug Administration: detecting misconduct. *Sci Eng Ethics* 2010; **16**: 697-704 [PMID: 20842536 DOI: 10.1007/s11948-010-9232-4]
52 **Seife C**. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. *JAMA Intern Med* 2015; **175**: 567-577 [PMID: 25664866 DOI: 10.1001/jamainternmed.2014.7774]
53 **Hartog CS**, Reinhart K. CRYSTMAS study adds to concerns about renal safety and increased mortality in sepsis patients. *Crit Care* 2012; **16**: 454; author reply 454 [PMID: 23134688 DOI: 10.1186/cc11673]
54 **James MF**, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). *Br J Anaesth* 2011; **107**: 693-702 [PMID: 21857015 DOI: 10.1093/bja/aer229]
55 **Finfer S**. Hydroxyethyl starch in patients with trauma. *Br J Anaesth* 2012; **108**: 159-160; author reply 160-161 [PMID: 22157448 DOI: 10.1093/bja/aer424]
56 **Elia N**, Wager E, Tramèr MR. Fate of articles that warranted retraction due to ethical concerns: a descriptive cross-sectional study. *PLoS One* 2014; **9**: e85846 [PMID: 24465744 DOI: 10.1371/journal.pone.0085846]
57 **Wager E**, Williams P. Why and how do journals retract articles? An analysis of Medline retractions 1988-2008. *J Med Ethics* 2011; **37**: 567-570 [PMID: 21486985 DOI: 10.1136/jme.2010.040964]
58 **Williams P**, Wager E. Exploring why and how journal editors retract articles: findings from a qualitative study. *Sci Eng Ethics* 2013; **19**: 1-11 [PMID: 21761244 DOI: 10.1007/s11948-011-9292-0]
59 **Steen RG**. Retractions in the scientific literature: is the incidence of research fraud increasing? *J Med Ethics* 2011; **37**: 249-253 [PMID: 21186208 DOI: 10.1136/jme.2010.040923]

60 **Kornhaber RA**, McLean LM, Baber RJ. Ongoing ethical issues concerning authorship in biomedical journals: an integrative review. *Int J Nanomedicine* 2015; **10**: 4837-4846 [PMID: 26257520 DOI: 10.2147/IJN.S87585]

P- Reviewer: Cattermole GN, Delgado MCM, den Uil CA, Llompart-Pou JA **S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i3.180

World J Crit Care Med 2016 August 4; 5(3): 180-186
ISSN 2220-3141 (online)

BRIEF ARTICLE

Retrospective Study

Enteral nutrition administration in a surgical intensive care unit: Achieving goals with better strategies

Sara Wilson, Nagendra Y Madisi, Adel Bassily-Marcus, Anthony Manasia, John Oropello, Roopa Kohli-Seth

Sara Wilson, Department of Clinical Nutrition, Mount Sinai Hospital, New York, NY 10129, United States

Nagendra Y Madisi, Adel Bassily-Marcus, Anthony Manasia, John Oropello, Roopa Kohli-Seth, Division of Surgical Critical Care Medicine, Department of Surgery, Icahn School of Medicine at Mount Sinai, New York, NY 10129, United States

Author contributions: Wilson S, Madisi NY and Kohli-Seth R contributed equally to this work; Wilson S helped in the acquisition of the data; Wilson S, Madisi NY and Kohli-Seth R analyzed, interpreted the data and drafted the manuscript; Bassily-Marcus A, Manasia A and Oropello J provided analytical oversight, revised the manuscript and material support; Kohli-Seth R contributed to the conception and design of the study, supervised the study and provided administrative support; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by Icahn School of Medicine at Mt Sinai Institutional Review Board.

Informed consent statement: Waiver of informed consent was provided by Icahn School of Medicine at Mt Sinai Institutional Review Board.

Conflict-of-interest statement: All the authors involved in the study have no conflict of interest to declare.

Data sharing statement: Data is available from the corresponding author - nagendra.madisi@mountsinai.org.

Manuscript source: Unsolicited manuscript

Correspondence to: Nagendra Y Madisi, MD, Critical Care Fellow, Division of Surgical Critical Care Medicine, Department of Surgery, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1264, New York, NY 10029, United States. nagendra.madisi@mountsinai.org
Telephone: +1-443-2207373

Received: February 24, 2016
Peer-review started: February 27, 2016
First decision: April 15, 2016
Revised: May 2, 2016
Accepted: June 1, 2016
Article in press: June 3, 2016
Published online: August 4, 2016

Abstract

AIM: To evaluate the impact of an enteral feeding protocol on administration of nutrition to surgical intensive care unit (SICU) patients.

METHODS: A retrospective chart review was conducted on patients initiated on enteral nutrition (EN) support during their stay in a 14 bed SICU. Data collected over a seven-day period included date of tube feed initiation, rate initiated, subsequent hourly rates, volume provided daily, and the nature and length of interruptions. The six months prior to implementation of the feeding protocol (pre-intervention) and six months after implementation (post-intervention) were compared. One hundred and four patients met criteria for inclusion; 53 were pre-intervention and 51 post-intervention.

RESULTS: Of the 624 patients who received nutrition support during the review period, 104 met the criteria for inclusion in the study. Of the 104 patients who met criteria outlined for inclusion, 64 reached the calculated goal rate (pre = 28 and post = 36). The median time to achieve the goal rate was significantly shorter in the post-intervention phase (3 d *vs* 6 d; $P = 0.01$). The time to achieve the total recommended daily volume showed

a non-significant decline in the post-intervention phase (P = 0.24) and the overall volume administered daily was higher in the post-intervention phase (61.6% *vs* 53.5%; P = 0.07). While the overall interruptions data did not reach statistical significance, undocumented interruptions (interruptions for unknown reasons) were lower in the post-intervention phase (pre = 23/124, post = 9/96; P = 0.06).

CONCLUSION: A protocol delineating the initiation and advancement of EN support coupled with ongoing education can improve administration of nutrition to SICU patients.

Key words: Enteral nutrition; Surgical critical care; Protocol; Critical care; Nutrition support

Core tip: Surgical critical care patients are more prone to frequent feeding interruptions for unavoidable reasons. In this study we validated that implementation of a feeding protocol in a surgical intensive care unit (SICU) decreased time to achieve goal rate and increased the total volume administered daily, despite frequent interruptions. It also increased detailed documentation by unit staff of interruptions allowing us to identify a trend with regard to feeding interruptions to better understand which practices/procedures require further review. The median time to achieve the goal rate was significantly shorter in the post-intervention phase. The time to achieve the total recommended daily volume showed a non-significant decline in the post-intervention phase and the overall volume administered daily was higher in the post-intervention phase. While the overall interruptions data did not reach statistical significance, undocumented interruptions (interruptions for unknown reasons) were lower in the post-intervention phase. To our knowledge, we are the second largest single center study supporting the benefit of implementing a feeding protocol in a SICU.

Wilson S, Madisi NY, Bassily-Marcus A, Manasia A, Oropello J, Kohli-Seth R. Enteral nutrition administration in a surgical intensive care unit: Achieving goals with better strategies. *World J Crit Care Med* 2016; 5(3): 180-186 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/180.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.180

INTRODUCTION

Nutrition support is an important element of managing surgical critical care patients. Perioperative malnourishment and prolonged catabolism can lead to multiple deleterious effects, including delayed or abnormal wound healing, secondary infections, muscle atrophy, and increased length of stay[1,2]. Providing early enteral nutrition (EN) helps meet the metabolic demands during the acute phase of surgery-associated critical illness, rebuilds nutritional stores during recovery, and reduces hospital mortality[3-6]. When oral feeding is not possible it is more physiologic to deliver nutrients through the gut to preserve its barrier role. EN is therefore preferred over parenteral nutrition (PN) as it has been shown to maintain gastrointestinal (GI) integrity and function and improve blood flow and peristalsis. It also prevents bacterial translocation, thereby decreasing the risk for systemic infections[7]. Existing literature shows that surgical patients are less likely to receive EN and more likely to receive PN compared to medical patients. Tube feeding is often delayed and patients are less likely to achieve nutritional adequacy following both elective and urgent surgery[8]. Patients undergoing gastrointestinal and cardiovascular surgeries receive the least amount of EN with no clear explanation[8]. Despite the known benefits, providing adequate nutrition early is challenging in the surgical intensive care unit (SICU) setting due to frequent interruptions from the scheduling of procedures and tests, perceived intolerance of tube feeding, ventilator weaning trials and routine nursing care. These lengthy and sometimes unnecessary interruptions lead to the inadequate administration of nutrition. Additionally, specific guidelines for controversial practices like checking gastric residual volume (GRV) can also lead to frequent and prolonged interruptions in feeding. Current literature on routine monitoring of GRV refutes the correlation between GRV and a patient's risk for ventilator associated pneumonia, ICU-acquired infections, mechanical ventilation duration, ICU length of stay, or mortality rates[9] however, complete abandonment of this long-standing practice remains a challenge. Given the obstacles to optimal EN support for SICU patients, it is evident that there is a need for more structured processes that guide practitioners and standardize practice.

MATERIALS AND METHODS

A quality improvement project was conducted in the SICU to determine whether patients were being adequately fed. Results indicated that 65% of patients did not achieve goal rate during the seven-day period, and 65% of patients received less than half of the total volume recommended daily. The results of this quality review coupled with the frequency and duration of tube feed interruptions led to the development of an EN feeding protocol. The protocol outlined instructions for more timely advancement of tube feeding to goal rate and incorporated guidelines intended to decrease unnecessary feeding interruptions.

The aim of this study was to evaluate whether the EN feeding protocol improved the ability to meet nutritional goals in a timely fashion and increased overall administration of nutrition during SICU stay.

Patients and settings

This study was conducted in the SICU of a 1171-bed

Table 1 Exclusion criteria

Exclusion criteria	*n*	Pre-intervention phase	Post-intervention phase
Enteral nutrition not initiated	10	8	2
Intestinal transplant	1	1	0
Tube fed < 48 h	30	13	17
Tube feed initiated before ICU admission	1	1	0
Patient to or for GI surgery	2	2	0
Not tolerating	1	1	0
Withdrawal of care	0	0	0
Total	45	26	19

Exclusion criteria with counts for pre-intervention, post-intervention and the total number of patients who met each criterion. ICU: Intensive care unit; GI: Gastrointestinal.

tertiary care teaching hospital. The SICU is a closed 14-bed unit that admits approximately 900 patients annually with an average length of stay of five days. Most SICU patients are post-operative from a variety of surgical specialties, including general surgery, surgical oncology, and liver and intestinal transplant. The charts of 624 adult patients over 18 years of age who received EN support for a one-year period were screened for inclusion in the study. Due to the retrospective nature of this study, the Institutional Review Board waived consent.

The pre-intervention phase was defined as the six months before the EN feeding protocol implementation and the post-intervention phase was the six months post implementation (Table 1).

The primary hospital admission date, SICU admission date, formula name, date of initiation, rate initiated, subsequent hourly rates, and volume provided daily were recorded over a seven-day period. The nature and length of interruptions were noted for all patients included in the study.

Intervention

The EN protocol delineated steps for initiating, advancing and maintaining nutrition support in these patients. Following implementation of the protocol, EN was started at half the goal rate. Gastric residual volumes were checked 6 h after initiation. If GRV were less than 250 mL, EN feeds were advanced to goal rate with GRV and signs and symptoms of intolerance monitored every 6 h, for the first 24 h, or until confirmation of tolerance of tube feeding at the goal rate. In the event that GRV was more than 250 mL, the bedside nurse would inform the physician on call for further assessment of symptoms such as abdominal pain, distention, tenderness, vomiting or high GRV ($\geqslant$ 500 mL). In the presence of any of these symptoms, EN feeding was held for 3 h with reevaluation thereafter. With implementation of the protocol, if symptoms were absent, the ICU team could start promotility agents, if not otherwise contraindicated. Promotility agents used included metoclopramide and erythromycin. The GRV was then rechecked after six hours and feeds advanced as indicated above. If EN was held due to intolerance or inability to advance to goal rate, PN support was considered. Stop rules for procedures were also developed to guide practitioners on the appropriate timing for holding EN support. For emergent procedures feeds would be held and NGT placed to suction to decompress the stomach. For non-emergent procedures, including planned surgery and elective tracheostomy, holding feeds 6 to 8 h prior to procedure was suggested, and for pressure support or weaning trials, holding feeds one hour prior to trial was advised. It was recommended that feeds be restarted upon return from procedure; pending confirmation from the primary team or upon determination that extubation was not possible (Figure 1). Nurses and physicians were educated on the protocol. The importance of clear and accurate documentation, including reason and duration of feeding interruptions was emphasized.

Statistical analysis

The Kaplan-Meier method was used to calculate the time to achieve goal rate and total recommended daily volume over the seven-day period. The Log-Rank test was used to compare the time to both of those events between the pre- and post-intervention phases. An aggregated average percent goal was calculated for each patient and compared. In addition, the percentage of patients who reached goal rate by day seven was compared. Interruptions were categorized by type into avoidable and unavoidable. Gastrointestinal surgeries, interventional radiology (procedures, access), tracheostomy/PEG tube placement, extubation/re-intubation, ventilator weaning trials, high GRV (> 500 mL), and abdominal imaging were considered unavoidable causes. Avoidable interruptions included imaging studies where the radiologist did not request fasting and GRV < 500 mL. The average length of interruptions by type in the pre- and post-intervention phases were also calculated and compared. The Statistical methods of this study were reviewed by John Doucette, Associate professor, preventive medicine at Icahn School of Medicine at Mt Sinai, New York.

RESULTS

Of the 624 patients who had nutrition support during the review period, 104 met criteria for inclusion in the study. Of the 104 who met criteria, 53 were pre- and 51 were post-intervention (Table 2).

The largest admitting service was GI surgery followed by transplant, vascular surgery, surgical oncology, orthopedics and medicine.

Of the 104 patients monitored during the seven-day period, 40 did not reach goal rate (pre = 25, post = 15). Among those who did not reach goal rate, 22 stopped enteral feeding before the seventh day due to extubation, transfer from ICU or hemodynamic instability (pre = 16/25, post = 6/15; P = 0.14). The remaining 18 patients continued on tube feeds for

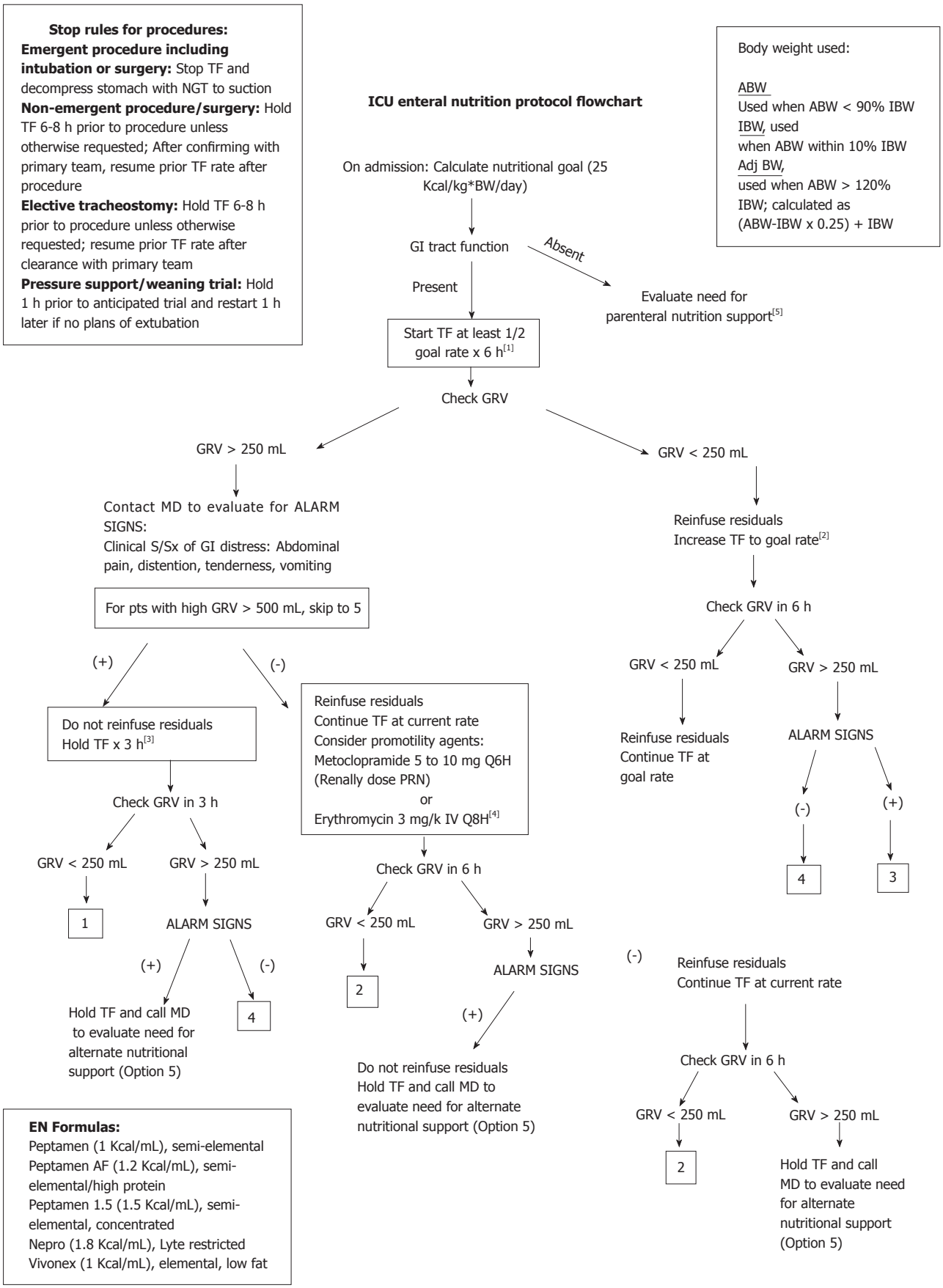


Figure 1 Intensive care unit enteral nutrition protocol flowchart. TF: Tube feeds; NGT: Nasogastric tube; GI: Gastrointestinal; PN: Parenteral nutrition; S/Sx: Symptoms and signs; pts: Patients; GRV: Gastric residual volume; ABW: Actual body weight; IBW: Ideal body weight; Adj BW: Adjusted body weight.

Table 2 Baseline characteristics and study cohort

Patient demographics	Pre-intervention phase	Post-intervention phase	All patients
Age (yr)	67 ± 16	66 ± 16	67 ± 16
Male	31 (58%)	26 (51%)	57 (55%)
Height (cm)	166.79 ± 11.59	167.09 ± 12.37	166.93 ± 11.91
Weight (kg)	76.7 ± 22.8	81.7 ± 25.5	79.1 ± 24.2
GI surgery	18 (34%)	27 (53%)	45 (43%)
Vascular surgery	8 (15%)	3 (6%)	11 (11%)
Transplant	14 (26%)	11 (22%)	25 (24%)
Medicine	3 (6%)	5 (9%)	8 (7.5%)
Surgical oncology	7 (13%)	1 (2%)	8 (7.5%)
Other (ENT, HIV medicine, orthopedics, orthopedic surgery, oral and maxillofacial surgery)	3 (6%)	4 (8%)	7 (7%)
Total	53	51	104

Data are reported as mean ± SD or *n* (%). Patient demographics (average age, gender, average height and average admission weight) and primary service caring for patient upon admission to ICU. ICU: Intensive care unit; GI: Gastrointestinal; HIV: Human immunodeficiency virus.

Table 3 Hold time (hours) median hold time and interquartile ranges by interruption type

Interruption	Pre-intervention phase	Post-intervention phase
Procedures	17.4 (9-19)	20 (7-24)
Residuals	17.5 (7-22)	21.5 (4-29)
Weaning	13.6 (4-15)	12.6 (7-14)
Other[1]	22.9 (10-48)	11.3 (3-15)
Undocumented	5.7 (3-4)	6.9 (4-10)
All interruptions	14.6 (4-17.25)	16.6 (5-22.5)

Data are reported as median and interquartile range. Length of interruptions by type during the pre- and post-intervention phases. [1]Nursing care, change in status, *etc*.

seven days without reaching goal rate.

The distribution of patients who reached goal rate was 55% (28/53) during the pre-intervention phase, and 71% (36/51) during the post-intervention phase. The median time to achieve goal was significantly shorter in the post-intervention phase (3 d *vs* 6 d; *P* = 0.01) (Figure 2). The overall time to achieve total recommended daily volume showed a non-significant decline in the post-intervention phase (*P* = 0.24) (Figure 3). The overall volume administered daily was higher in the post-intervention phase (61.6% *vs* 53.5%; *P* = 0.07).

There were 124 instances of TF interruptions in the pre-intervention phase and 96 in the post-intervention phase. The most common reason was tests and procedures (pre = 42/124, post = 49/96) followed by ventilator weaning (pre= 31/124, post = 19/96), GRV (pre = 22/124, post = 10/96), and "other" (which included nursing care, change in status and other miscellaneous reasons) (pre = 6/124, post = 9/96). Interruptions were categorized as "undocumented"

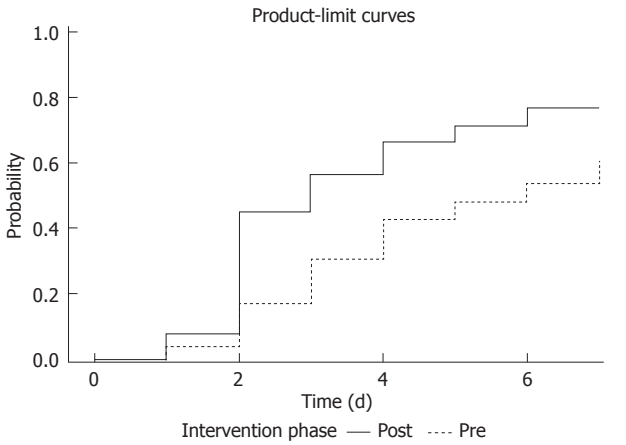


Figure 2 Days to achieve goal rate by intervention phase. The Kaplan-Meier method was used to calculate the time to achieve goal rate over the seven-day period. The log-rank test was used to compare the time to both of those events between the pre- and post-intervention phases.

when the reason could not be found in either the flow sheets or medical record. The overall interruption data did not reach statistical significance. However, undocumented interruptions were lower in the post-intervention phase (pre = 23/124, post = 9/96; *P* = 0.06) (Table 3).

DISCUSSION

To our knowledge, our study is the second largest single center study supporting the benefit of the EN protocol in a SICU[10]. We compared the timeliness to achieve goal rate, the amount of EN received, frequency of nutrition interruptions, and accuracy of documentation in critically ill surgical patients before and after implementation of the EN protocol. Guidelines recommend initiating enteral feeds within 24-48 h of ICU admission, yet up to 50% of patients do not even receive EN during their ICU stay[11,12]. Furthermore, EN interruption occurs more frequently in SICUs than their counterparts for multiple unavoidable reasons, including surgical procedures and imaging studies. Hence, these patients are at higher risk of iatrogenic malnutrition[13,14]. There is an overall lack of consensus on the duration of time to hold EN in preparation for a procedure among various specialists, including anesthesiologists, surgeons and intensivists[15]. Physicians are often reluctant to start EN in hemodynamically unstable patients, despite the overwhelming data showing improved outcomes[16]. Establishing criteria for when to interrupt tube feeding, and more importantly, when to restart feeding, may improve overall administration of nutrition support[17]. After conducting the QI project on enteral feeding in our SICU, we determined that 65% of patients on EN support did not achieve goal rate by the seventh day of administration and received less than 50% of the daily-recommended volume. The literature on developing protocols for EN administration suggests that outlining criteria for the initiation and advancement

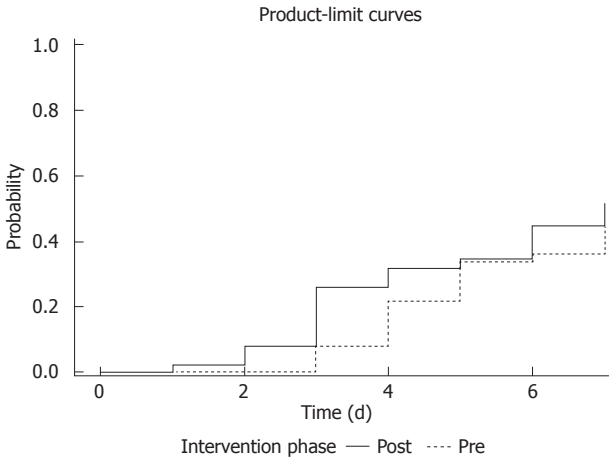


Figure 3 Days to achieve total recommended volume by intervention phase. The Kaplan-Meier method was used to calculate the time to achieve total recommended daily volume over the seven-day period. The log-rank test was used to compare the time to both of those events between the pre- and post-intervention phases.

of EN support may improve nutrient delivery[17,18]. Moreover protocols also serve as an effective tool for the physicians in-training, registered nurses and other support staff. Multiple protocols have been introduced over the past years in different aspects of critical care medicine (ventilator weaning, spontaneous breathing and awakening trails, sedation and analgesia) leading to better outcomes[19].

Despite prolonged hold times our data supports the use of an EN protocol to decrease time to achieve goal rate and increase the volume of tube feeding delivered daily. Though data on interruptions varied between the pre- and post-intervention phases, it highlighted the extensive duration of interruptions for various reasons. During the post-intervention phase one of the greatest challenges faced when executing the feeding protocol was overcoming existing nursing and physician practices regarding holding tube feeding and inconsistent documentation. Creating awareness among physician and nursing staff of enteral feeding practices led to an increase in accurate documentation.

Future research should focus on patient outcomes and quality indicators to promote the use of protocols for EN administration in the SICU, and further extended to other ICUs throughout the hospital. Optimizing the EN protocol by providing distinct instructions for how to minimize feeding interruptions could improve the parameters where significant progress was lacking between the pre and post intervention phases. Guidelines and strategies for moving the location of the tip of the feeding tube more distal in the jejunum could also assist in reducing length of hold times for feeding intolerance. Incorporating volume-based practices that summarize how to adjust tube-feeding rates in order to "catch-up" may also assist in optimizing the protocol, and increasing the overall administration of nutrition daily. By developing standards of practice and guidelines for when to hold and restart enteral feeds, we improved the overall administration of nutrition provided.

Given the retrospective nature of our study, we are unable to establish cause and effect. The study does not draw solid conclusions, however the data can be used to provide descriptive characteristics, and add to the limited literature available.

In conclusion, this study suggests a user friendly EN protocol in conjunction with extensive ongoing education may lead to shorter time to achieve goal rate, and enhance overall administration of nutrition to surgical critical care patients.

ACKNOWLEDGMENTS

To John T Doucette, Associate Professor, Preventive Medicine at Icahn School of Medicine at Mount Sinai for his contribution to the manuscript by helping with the data analysis.

COMMENTS

Background

The benefits of enteral nutrition (EN) to critically ill patients are well cited in the reducing length of stay and hospital mortality. Clinical protocols serve as effective tools for guiding clinical practice and improving patient outcomes (*e.g.*, ventilator weaning, spontaneous breathing and awakening).

Research frontiers

EN is preferred over parenteral nutrition, as it has been shown to maintain gastrointestinal integrity and function, and increase peristalsis and blood flow. Discrepancies between prescribed nutrition goal and actual nutrition delivered in critically ill patients are not uncommon; this is especially the case in the surgical population. Prior studies have established that feeding protocols can increase administration of nutrition to patients. The current research hotspot is to implement a feeding protocol in a surgical intensive care unit (ICU) setting where the number of interruptions are frequent and goal rates are often not achieved.

Innovations and breakthroughs

Few studies to date have been conducted on the use of feeding protocols in surgical ICU patients. Existing literature suggests patients are less likely to get EN compared to medical ICU patients due to concern of postoperative ileus, anastomotic leak, diagnostic testing and operative procedures. To our knowledge, this study is the second largest single center study supporting the benefit of implementing a feeding protocol in surgical ICU. The feeding protocol was introduced and data collected on the rate initiated and total volume provided daily. The authors monitored time to achieve goal rate and the total volume provided six months prior to and following implementation of the protocol. Overall time to achieve goal rate decreased, while the total volume administered daily increased. The protocol also led to an increase in detailed documentation of interruptions by the unit staff.

Applications

The study results suggest feeding protocols can lead to improved nutrient administration during the acute phase. Improved documentation may allow them to identify and trend with regard to feeding interruptions to better understand which practices or procedures require further review.

Terminology

EN is any method of feeding that utilizes the gastrointestinal tract to deliver nutrients. Parenteral nutrition, also referred to as intravenous feeding, is a method of providing nutrition into the body *via* the veins.

Peer-review

This is a well-written paper, focused on an interesting topic.

REFERENCES

1 **McClave SA**, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract* 2009; **24**: 305-315 [PMID: 19483060 DOI: 10.1177/0884533609335176]

2 **Singer P**, Anbar R, Cohen J, Shapiro H, Shalita-Chesner M, Lev S, Grozovski E, Theilla M, Frishman S, Madar Z. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med* 2011; **37**: 601-609 [PMID: 21340655 DOI: 10.1007/s00134-011-2146-z]

3 **Heyland DK**, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! *Crit Care Med* 2011; **39**: 2619-2626 [PMID: 21705881 DOI: 10.1097/CCM.0b013e318226641d]

4 **Heyland DK**, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003; **27**: 355-373 [PMID: 12971736]

5 **Heyland DK**, Stephens KE, Day AG, McClave SA. The success of enteral nutrition and ICU-acquired infections: a multicenter observational study. *Clin Nutr* 2011; **30**: 148-155 [PMID: 20971534 DOI: 10.1016/j.clnu.2010.09.011]

6 **Kreymann KG**, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C. ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; **25**: 210-223 [PMID: 16697087]

7 **Btaiche IF**, Chan LN, Pleva M, Kraft MD. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. *Nutr Clin Pract* 2010; **25**: 32-49 [PMID: 20130156 DOI: 10.1177/0884533609357565]

8 **Drover JW**, Cahill NE, Kutsogiannis J, Pagliarello G, Wischmeyer P, Wang M, Day AG, Heyland DK. Nutrition therapy for the critically ill surgical patient: we need to do better! *JPEN J Parenter Enteral Nutr* 2010; **34**: 644-652 [PMID: 21097764 DOI: 10.1177/0148607110372391]

9 **Poulard F**, Dimet J, Martin-Lefevre L, Bontemps F, Fiancette M, Clementi E, Lebert C, Renard B, Reignier J. Impact of not measuring residual gastric volume in mechanically ventilated patients receiving early enteral feeding: a prospective before-after study. *JPEN J Parenter Enteral Nutr* 2010; **34**: 125-130 [PMID: 19861528 DOI: 10.1177/0148607109344745]

10 **Taylor B**, Brody R, Denmark R, Southard R, Byham-Gray L. Improving enteral delivery through the adoption of the "Feed Early Enteral Diet adequately for Maximum Effect (FEED ME)" protocol in a surgical trauma ICU: a quality improvement review. *Nutr Clin Pract* 2014; **29**: 639-648 [PMID: 25155862]

11 **Yeh DD**, Fuentes E, Quraishi SA, Cropano C, Kaafarani H, Lee J, King DR, DeMoya M, Fagenholz P, Butler K, Chang Y, Velmahos G. Adequate Nutrition May Get You Home: Effect of Caloric/Protein Deficits on the Discharge Destination of Critically Ill Surgical Patients. *JPEN J Parenter Enteral Nutr* 2016; **40**: 37-44 [PMID: 25926426 DOI: 10.1177/0148607115585142]

12 **Heyland DK**, Schroter-Noppe D, Drover JW, Jain M, Keefe L, Dhaliwal R, Day A. Nutrition support in the critical care setting: current practice in canadian ICUs--opportunities for improvement? *JPEN J Parenter Enteral Nutr* 2003; **27**: 74-83 [PMID: 12549603]

13 **Passier RH**, Davies AR, Ridley E, McClure J, Murphy D, Scheinkestel CD. Periprocedural cessation of nutrition in the intensive care unit: opportunities for improvement. *Intensive Care Med* 2013; **39**: 1221-1226 [PMID: 23636828 DOI: 10.1007/s00134-013-2934-8]

14 **Peev MP**, Yeh DD, Quraishi SA, Osler P, Chang Y, Gillis E, Albano CE, Darak S, Velmahos GC. Causes and consequences of interrupted enteral nutrition: a prospective observational study in critically ill surgical patients. *JPEN J Parenter Enteral Nutr* 2015; **39**: 21-27 [PMID: 24714361 DOI: 10.1177/0148607114526887]

15 **Schneider JA**, Lee YJ, Grubb WR, Denny J, Hunter C. Institutional practices of withholding enteral feeding from intubated patients. *Crit Care Med* 2009; **37**: 2299-2302 [PMID: 19455023 DOI: 10.1097/CCM.0b013e3181a007eb]

16 **Khalid I**, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care* 2010; **19**: 261-268 [PMID: 20436064 DOI: 10.4037/ajcc2010197]

17 **Heyland DK**, Cahill NE, Dhaliwal R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: results of a multicenter observational study. *JPEN J Parenter Enteral Nutr* 2010; **34**: 675-684 [PMID: 21097768 DOI: 10.1177/0148607110364843]

18 **Stewart ML**. Interruptions in enteral nutrition delivery in critically ill patients and recommendations for clinical practice. *Crit Care Nurse* 2014; **34**: 14-21; quiz 22 [PMID: 25086090 DOI: 10.4037/ccn2014243]

19 **Helwig A**, Bower D, Wolff M, Guse C. Residents find clinical practice guidelines valuable as educational and clinical tools. *Fam Med* 1998; **30**: 431-435 [PMID: 9624522]

P- Reviewer: Rossi RE, Willms DC **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i3.187

World J Crit Care Med 2016 August 4; 5(3): 187-200
ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Predictive value of cytokines for developing complications after polytrauma

Anne-Britt E Dekker, Pieta Krijnen, Inger B Schipper

Anne-Britt E Dekker, Pieta Krijnen, Inger B Schipper, Department of Trauma Surgery, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands

Author contributions: This study represents a great deal of effort, resources and dedication on the part of the authors in reviewing the literature and performing statistical analyses; all authors have participated in a material way to at least three of the following elements: Study design, gathered data, analysed data, initial draft, ensured accuracy of data; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: The technical appendix including the full search strategy for this systematic review is available from the corresponding author at A.E.Dekker@lumc.nl. Since this study did not involve any biostatistics, no statistical code and dataset are available.

Manuscript source: Invited manuscript

Correspondence to: Anne-Britt E Dekker, MD, Department of Trauma Surgery, Leiden University Medical Center, Postal Zone K6-R, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. a.e.dekker@lumc.nl
Telephone: +31-71-5261065
Fax: +31-71-5266750

Received: February 23, 2016
Peer-review started: February 25, 2016
First decision: March 24, 2016
Revised: April 8, 2016
Accepted: April 21, 2016
Article in press: April 22, 2016

Published online: August 4, 2016

Abstract

AIM: To investigate posttraumatic cytokine alterations and their value for predicting complications and mortality in polytraumatized patients.

METHODS: Studies on the use of specific cytokines to predict the development of complications and mortality were identified in MEDLINE, EMBASE, Web of Science and the Cochrane Library. Of included studies, relevant data were extracted and study quality was scored.

RESULTS: Forty-two studies published between 1988 and 2015 were identified, including 28 cohort studies and 14 "nested" case-control studies. Most studies investigated the cytokines interleukin (IL)-6, IL-8, IL-10 and tumor necrosis factor (TNF-α). IL-6 seems related to muliorgan dysfunction syndrome, multiorgan failure (MOF) and mortality; IL-8 appears altered in acute respiratory distress syndrome, MOF and mortality; IL-10 alterations seem to precede sepsis and MOF; and TNF-α seems related to MOF.

CONCLUSION: Cytokine secretion patterns appear to be different for patients developing complications when compared to patients with uneventful posttraumatic course. More research is needed to strengthen the evidence for clinical relevance of these cytokines.

Key words: Multiple trauma; Cytokine; Acute respiratory distress syndrome; Sepsis; Muli-organ dysfunction syndrome; Multi-organ failure

Core tip: Early identification of patients at risk for

developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and multiorgan failure. This article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death.

Dekker ABE, Krijnen P, Schipper IB. Predictive value of cytokines for developing complications after polytrauma. *World J Crit Care Med* 2016; 5(3): 187-200 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i3/187.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i3.187

INTRODUCTION

The term polytrauma is used to describe a combination of serious injuries in at least two different anatomical regions. Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Trauma initiates a local pro-inflammatory response, encompassing the activation of effector cells, complement cascade, coagulation system, cytokines, acute phase proteins and neuroendocrine mediators[1,2]. This sequence of events is part of the physiologic response to trauma, as it serves to initiate the healing process, prevents the host from additional injury and acts as a barrier against infection[3]. Yet extensive trauma can arouse a comprehensive systemic inflammatory state known as the systemic inflammatory response syndrome (SIRS). An overactivated pro-inflammatory reaction leads to progressive sequestration of leukocytes in vital organs, predisposing patients to the development of organ failure. In an attempt to mediate these deleterious effects, immunesuppressive mediators are released. This counter regulatory response syndrome (CARS) becomes active almost immediately after the onset of SIRS[4]. Despite dampening inflammation, CARS itself may have unfavorable effects as well, as it can induce an increased susceptibility to infections and sepsis[2]. The posttraumatic immunologic alterations of combined SIRS and CARS have been termed CHAOS (cardiovascular shock, homeostasis, apoptosis, organ dysfunctions and immune suppression)[5]. With an overwhelming initial traumatic insult, an overstimulated SIRS response initiates the chaos that results in early multiorgan failure (MOF), present within 72 h after injury[2,6]. A less severe initial insult may prime immune cells while eliciting a moderate inflammatory reaction. In this setting, a second insult ("hit") may strengthen the inflammatory reaction towards immune suppression, predisposing the patient to sepsis[7,8].

Cytokines play a pivotal role in both the pro-inflammatory and the anti-inflammatory reaction to trauma[9,10]. The pro-inflammatory cytokine interleukin-6 (IL-6) is secreted by a wide range of cells including neutrophils, T- and B-lymphocytes and endothelial cells[8,11]. Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β), and liberated after tissue damage and infection. The biologic activity of IL-6 includes increased T- and B-cell activation and proliferation, differentiation of cytotoxic T cells and enhanced activity of natural killer (NK) cells[12]. In addition, IL-6 mediates the induction of the acute phase response and reduces apoptosis in neutrophil granulocytes[4,11]. Combined actions lead to an effective SIRS response early after trauma. The pro-inflammatory cytokine IL-8 is an endogenous chemoattractant. Monocytes, macrophages, neutrophils and endothelial cells secrete IL-8, and its release is enhanced after stimulation with IL-1, TNF-α, C5a and LPS[9,13]. After activation, IL-8 induces expression of adhesion molecules on neutrophils and endothelial cells, which enables the migration of neutrophils to the site of production[4,9]. The anti-inflammatory cytokine IL-10 is primarily synthesized by CD4+ T_H2 lymphocytes and, to a lesser extent, by B lymphocytes, monocytes and macrophages[8]. Activated IL-10 decreases the cytokine production of T_H1 cells, reduces antigen presentation of macrophages and subsequent proliferation of T-lymphocytes, and suppresses monocyte function[4,14,15]. These actions make IL-10 one of the most important mediators in the anti-inflammatory immune response. The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma. The cytokine is produced by monocytes, macrophages, lymphocytes and T lymphocytes. After secretion, TNF-α increases endothelial cell permeability and adhesion properties, and activates macrophages, NK cells and lymphocytes. TNF-α also induces the secretion of various cytokines [IL-6, -8, -10, interferon (IFN-γ)] and immunoglobulin production[7,12]. Release of excessive TNF-α ultimately leads to accumulation of leukocytes in the injured tissues. Many of these cytokines attributed to the potential development of complications in polytrauma patient. Their exact causal role has not been detected yet.

Early identification of patients at risk for developing complications is one of the most challenging problems in the therapy of multiple injuries. Close monitoring of cytokine secretion patterns could give physicians an impression of the individual risk for development of complications. Further, physicians are directed to the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing "second hits" with subsequent risks of development of sepsis and MOF. Previous studies have acknowledged the correlation between markers of inflammation and clinical condition after polytrauma. The aim of the current review was: (1) to summarize the available

knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome (ARDS), sepsis, multiorgan dysfunction syndrome (MODS), MOF and mortality.

MATERIALS AND METHODS

The systematic review was performed in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[16]. Due to heterogeneity across the studies in terms of patient population, study design and analytical techniques used, and the small amount of studies for each biomarker-complication combination, a meta-analysis was not feasible.

Search strategy

Studies addressing the relation between complications after multiple trauma and cytokine concentrations, were identified in the following databases: MEDLINE (1988 - 18 January 2014), Embase (1988 - 18 January 2014), Web of Science (1988 - 18 January 2014) and the Cochrane Library (to Issue 1, 2014). The search strategy was developed by an information specialist, and carried out using various combinations of the key words "multiple trauma", "cytokines" and the complications "systemic inflammatory response sydrome (SIRS)", "ARDS", "sepsis", "MODS", "MOF" and "mortality". In addition, forward citation searches of selected studies and literature reviews were carried out. The initial search was not limited by language, publication date and type of publication. In February 2016, an additional literature search of the mentioned databases was carried out. One relevant new article was found.

Outcome definitions

Primary outcomes were the development of one or more of the following complications: (1) ARDS, determined in concordance with the American-European Consensus Conference 1994 definitions[17]; (2) sepsis, diagnosed when SIRS (defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992[18]) occurred in combination with a septic focus or positive blood culture; (3) MODS; and (4) MOF, in the included studies diagnosed based on different scoring systems[19-24]. The secondary outcome was mortality during a predetermined follow-up period of individual studies.

Study selection

Studies were scanned for eligibility based on title and abstract. Subsequently, eligibility of selected studies was assessed by retrieving the full text of the article. Inclusion criteria were prospective or retrospective cohort, case-control and cross-sectional studies including at least 10 adult multiple trauma patients (ISS $\geqslant$ 16). Excluded were articles in other language than English or German, animal studies and *ex vivo* studies, studies involving pediatric populations, case reports, review articles and letters/editorials. Studies not elaborating on the primary or secondary outcomes investigated in this review were also excluded. In addition, studies measuring cytokine concentrations in samples other than serum (*e.g.*, wound exsudate, broncho-alveolar lavage fluid) were not eligible for inclusion, as local alterations in concentration may not reflect the systemic changes in the immune reaction.

Data extraction

The following data were extracted from included studies: Title, study design, date of publication, size of study population, patient demographics, incidence of complications and mortality, follow-up period, type of cytokines studied, mean cytokine concentrations measured at specific moments during follow-up, and cut-off points with sensitivity and specificity. Data were extracted from figures when raw data were not available. In the case of duplicate publications, the most relevant or informative article was chosen.

Quality assessment

The quality of included studies was critically evaluated with the strengthening the reporting of observational studies in epidemiology (STROBE) statement[25].

Biostatistics statement

In this review of the literature no biostatistical methods were used. For this reason, no biomedical statistician was involved for statistical review.

RESULTS

Identification of studies

After exclusion of duplicate studies, the literature search yielded 730 potentially relevant articles. One hundred and thirty-eight articles passed the first screening and were retrieved for closer examination. Of the retrieved articles, 40 were eligible for study inclusion. The full text of six potentially relevant studies could not be obtained, which were therefore excluded from the analysis. Seven citations were found assessing reference lists of the included studies. One relevant article was encountered in the additional search carried out in 2016. The study selection procedure is outlined in Figure 1.

Study characteristics

The 42 included articles consisted of 28 cohort studies[3,13,26-51] and 14 "nested" case-control studies[11,14,52-63]. Two studies were retrospective[14,52]; the other 40 studies were prospective in study design. Studies were published between 1988 and 2015, and together included 5756 patients. The development of ARDS in relation to cytokine levels was investigated in seven studies; sixteen studies determined cytokine concentrations in sepsis; MODS development was assessed in ten studies; and eleven studies reported cytokine

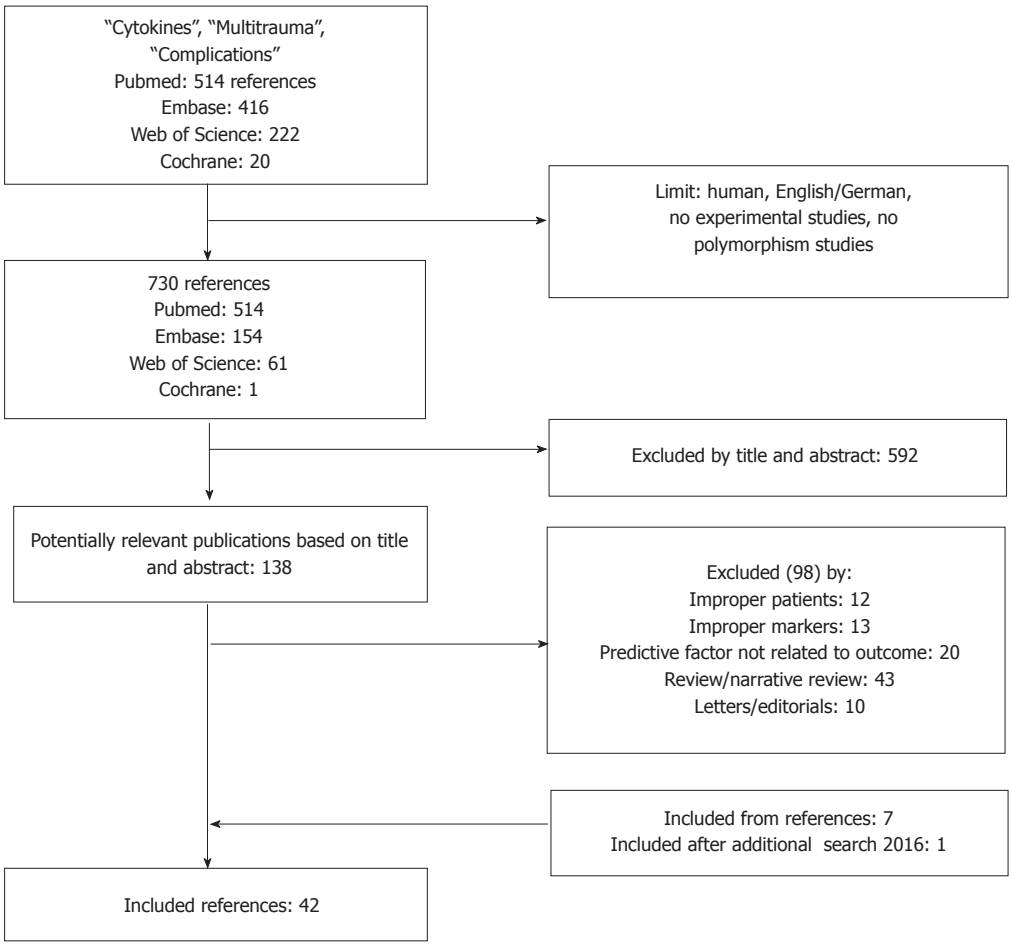


Figure 1 Results of the stepwise literature review procedure.

alterations in MOF. Twenty studies investigated the relation between cytokine concentrations and mortality. Only seven studies reported a cytokine cut-off value for the development of complications, five of which stated sensitivity (and specificity) for the cut-off value. Ten studies reported some kind of prediction value for the investigated cytokines (*i.e.*, odds ratio, area under the curve, sensitivity and specificity, 95%CI and positive/negative predictive value). All included studies are listed in Table 1. The overall study quality according to the STROBE statement was good, with a median total score of 18 points (range 12-24), suggesting a low risk of bias.

Value of main cytokine concentrations for predicting complications

IL-6: (1) ARDS; two studies[37,45] could not relate ARDS to IL-6 concentration alterations, whereas two other studies[48,51] found a positive correlation (Table 2); (2) Sepsis; five studies[35,41,46,47,53] found an increased IL-6 production to be predictive for the development of sepsis, whereas five other studies[28,29,38,39,55] did not (Table 3); (3) MODS; all five prospective cohort studies[3,28,34,46,51] concluded that IL-6 is markedly increased in the early development of MODS (Table 4); and (4) MOF; of the nine prospective studies, six[13,27,32,33,36,56] studies found a positive correlation between increased serum concentrations and development of MOF. Three[11,42,62] investigators demonstrated an elevated IL-6 in MOF patients, which was not predictive according to these studies (Table 5). Also, IL-6 tends to be higher in non-survivors (Table 6).

IL-8: (1) Two prospective cohort studies[37,48] reported a positive correlation between increased serum IL-8 concentrations and development of ARDS, whereas one[45] found no predictive value; (2) Two studies[38,55] reported that IL-8 was not significantly different between patients developing sepsis and those with an uneventful posttraumatic course; (3) One cohort study[3] found a higher IL-8 serum concentration in patients with MODS, which could however not predict the development of multiorgan dysfunction; and (4) Of the six included studies, four prospective studies[27,32,36,56] concluded that IL-8 is significantly higher in MOF. Two prospective studies[11,42] also found a significantly increased serum concentration, but concluded that this could not be translated into a predictive value for adverse outcome. Further, IL-8 concentrations seemed elevated in non-survivors.

Table 1 Overview of included studies, the studied cytokines and the outcome parameters (acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure, mortality)

No.	Ref.	Year	Design	No pts. (control)	Cytokines	ARDS (%)	Sepsis (%)	MODS (%)	MOF (%)	Mortality (%)
1	Billeter *et al*[35]	2009	P-coh	1032	IL-6					10%
2	Bogner *et al*[36]	2009	P-coh	58	IL-6, -8, -10				74%	19%
3	Cook *et al*[58]	2013	P-cc	83 (18)	G-CSF		7%			7%
4	Cuschieri *et al*[34]	2010	P-coh	152	IL-6			37%		5%
5	Donnelly *et al*[37]	1994	P-coh	15	IL-6, -8, -1β; TNF-α	49%				33%
6	Dresing *et al*[26]	2004	P-coh	30	IL-6; TNF-α			13%		19%
7	Egger *et al*[38]	2004	P-coh	26	IL-6, -8		35%			
8	Flores *et al*[39]	2001	P-coh	43	IL-6		49%			16%
9	Frangen *et al*[59]	2008	P-cc	71 (25)	IL-17, -6					22%
10	Frank *et al*[11]	2002	P-cc	77 (15)	IL-6, -8					9%
11	Frink *et al*[3]	2009	P-coh	143	IL-1β, -6, -8, -10; TNF-α		29%	17%		15%
12	Gebhard *et al*[40]	2000	P-coh	94	IL-6					19%
13	Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69 (10)	IL-6, -8; TNF-α, IFN-γ		62%			35%
14	Gouel-Chéron *et al*[53]	2012	P-cc	100 (18)	IL-6, -10		37%			5%
15	Haasper *et al*[28]	2010	P-coh	94	IL-6		16%	22%		13%
16	Hayakawa *et al*[31]	2011	P-coh	45	TNF-α			53%		25%
17	Heizmann *et al*[52]	2008	R-cc	195 (10)	IL-2, -4, -10, -11, -12, -18; IFN-γ					19%
18	Jastrow *et al*[32]	2009	P-coh	48	IL-6, -8, -10, -1β, -2, -4, -12; TNF-α				23%	17%
19	Keel *et al*[41]	2009	P-coh	83	IL-6		40%			12%
20	Lausevic *et al*[33]	2008	P-coh	65	IL-6, -10		62%		55%	51%
21	Lausevic *et al*[29]	2010	P-coh	65	IL-6, -10		63%			51%
22	Law *et al*[42]	1994	P-coh	13	IL-6, -8; TNF-α				46%	23%
23	Lendemans *et al*[13]	2004	P-coh	16	IL-6, -10; TNF-α				56%	
24	Liener *et al*[43]	2002	P-coh	94	IL-8	0%	0%		0%	19%
25	Livingston *et al*[44]	1988	P-coh	20	IFN-γ		30%			15%
26	Maier *et al*[27]	2007	P-coh	251	IL-6, -8, -10				34%	12%
27	Meade *et al*[45]	1994	P-coh	25	IL-6, -8; TNF-α	36%				
28	Menges *et al*[50]	1999	P-coh	68	IL-10, -1; TNF-α		25%		25%	1%
29	Mommsen *et al*[30]	2009	P-coh	55	IL-18		42%	13%		13%
30	Neidhardt *et al*[54]	1997	P-cc	417 (137)	IL-10	5%	11%	22%		22%
31	Oberholzer *et al*[46]	2000	P-coh	1276	IL-6, IL-10		14%	40%		7%
32	Partrick *et al*[56]	1996	P-cc	27 (6)	IL-6, -8				33%	7%
33	Paunel-Görgülü *et al*[47]	2011	P-coh	47 (17)	IL-6		38%			11%
34	Raymondos *et al*[48]	2012	P-coh	24	IL-6, -8, -1β, TNF-α	29%				4%
35	Roetman *et al*[60]	2008	P-cc	229 (110)	IL-18, -4; IFN-γ					16%
36	Schinkel *et al*[61]	2005	P-cc	216 (110)	IL-11				4%	16%
37	Sherry *et al*[14]	1996	R-cc	66 (10)	IL-10	8%	39%			2%
38	Sousa *et al*[51]	2015	P-coh	99	IL-6, -10; TNF-α	19%		34%		28%
38	Spielmann *et al*[57]	2001	P-cc	47 (15)	TNF-α	11%	30%	51%		23%
39	Svoboda *et al*[62]	1994	P-cc	42 (12)	IL-1β, -2, -6; TNF-α				33%	26%
40	Wick *et al*[49]	2000	P-coh	37	IL-12			11%		16%
41	Yagmur *et al*[63]	2005	P-cc	99 (10)	IL-1, -2, -6, -8; TNF-α					17%

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Pts: Patients; Y: Yes; N: No.

IL-10: (1) Three studies, two prospective[54,57] and one retrospective[14], could not relate the serum IL-10 concentrations to the development of ARDS. One study[51] found IL-10 to be significantly higher in patients with ARDS; (2) Of the five reviewed studies, three prospective[29,50,54] and one retrospective study[14] found the IL-10 concentration to be predictive for the development of sepsis, whereas one prospective study[53] did not; (3) Two studies[51,54] reported IL-10 to be significantly elevated in patients with MODS, and two studies[3,57] could not find an association between the cytokine and development of MODS; and (4) According to five studies[13,32,33,36,50] the serum IL-10 concentration was significantly higher in MOF patients. One study showed no significant elevation[27].

TNF-α: (1) Three studies found no relation between TNF-α and development of ARDS[37,45,51]; (2) One study[55] concluded that concentrations were not related to development of sepsis, while one study[50] found significantly increased concentrations in septic patients; (3) Of the four studies reporting on TNF-α concentrations after trauma, two studies[31,51] found TNF-α to be related to the development of MODS, and two studies[3,57] could not relate serum concentrations

Table 2 Value of cytokine concentrations for predicting acute respiratory distress syndrome

Ref.	Year	Design	No pts.	ARDS *n* (%)	Predicts ARDS	Results
IL-6						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-6] is not significantly different in ARDS
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-6] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-6] is significantly higher in patients at high risk for ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-6] is significantly higher at 72 h post injury
IL-8						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	Y	[IL-8] is significantly higher in patients with ARDS, starting at 16 h post injury
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-8] is higher in patients with ARDS after onset of symptoms; does not predict development of ARDS
Raymondos *et al*[48]	2012	P-coh	24	7 (29%)	Y	[IL-8] is significantly higher in patients at high risk for ARDS
IL-10						
Neidhardt *et al*[54]	1997	P-cc	417	19 (5%)	N	[IL-10] is not related to the development of ARDS
Sherry *et al*[14]	1996	R-cc	66	5 (8%)	N	[IL-10] is not related to the development of ARDS
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	Y	[IL-10] is significantly higher in patients with ARDS upon admission, at 24 + 48 + 72 h post injury
Spielmann *et al*[57]	2001	P-cc	47	5 (11%)	N	[IL-10] is not related to the development of ARDS
TNF-αα						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[TNF-α] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[TNF-α] below detection limit
Sousa *et al*[51]	2015	P-coh	99	19 (19%)	N	[TNF-α] is not related to the development of ARDS
IL-1β						
Donnelly *et al*[37]	1994	P-coh	15	7 (49%)	N	[IL-1β] below detection limit
Meade *et al*[45]	1994	P-coh	25	9 (36%)	N	[IL-1β] below detection limit

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; Pts: Patients; Y: Yes; N: No.

Table 3 Value of cytokine concentrations for predicting sepsis

Ref.	Year	Design	No pts.	Sepsis *n* (%)	Diagnostic tests	Predicts sepsis	Results
IL-6							
Billeter *et al*[35]	2009	P-coh	1032			Y	[IL-6] is significantly higher in sepsis between days 3-7
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-6] is significantly higher in sepsis before clinical manifestations; does not predict sepsis
Flores *et al*[39]	2001	P-coh	43	21 (49%)		N	[IL-6] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	ROC AUC 0.500 (95%CI: 0.304-0.696, $P > 0.05$)	N	[IL-6] is not related to the development of sepsis
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)	> 67.1 pg/mL: Sensitivity 85%; specificity 73%	Y	[IL-6] > 67.1 pg/mL is predictive for sepsis on days 1 + 2 (OR = 10.9)
Haasper *et al*[28]	2010	P-coh	94	15 (16%)		N	[IL-6] is not significantly different in sepsis
Keel *et al*[41]	2009	P-coh	83	33 (40%)		Y	[IL-6] is significantly higher in sepsis on days 5 + 14
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		N	[IL-6] is not predictive for sepsis
Oberholzer *et al*[46]	2000	P-coh	1276	179 (14%)		Y	[IL-6] is significantly higher in septic patients
Paunel-Görgülü *et al*[47]	2011	P-coh	47	18 (38%)	AUC ROC 0.79 (day 5 post injury)	Y	[IL-6] is significantly elevated on days 5 + 9 in sepsis
IL-8							
Egger *et al*[38]	2004	P-coh	26	9 (35%)		N	[IL-8] is not significantly altered in sepsis
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.453 (95%CI: 0.254-0.652, $P > 0.05$)	N	[IL-8] is not predictive for sepsis
IL-10							
Gouel-Chéron *et al*[53]	2012	P-cc	100	37 (37%)		N	[IL-10] is not related to the development of sepsis
Lausevic *et al*[33]	2010	P-coh	65	41 (63%)		Y	[IL-10] is significantly lower in sepsis on days 1 + 2
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d

Neidhardt *et al*[54]	1997	P-cc	417	45 (11%)		Y	[IL-10] is significantly higher in sepsis on days 1 + 3 + 5 + 7 + 10 + 14 + 21
Sherry *et al*[14]	1996	R-cc	66	26 (39%)		Y	[IL-10] is significantly higher in sepsis
TNF-αα							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)	AUC ROC 0.466 (95%CI: 0.274-0.657, $P > 0.05$)	N	[TNF-α] is not related to the development of sepsis
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
IFN-γ							
Giamarellos-Bourboulis *et al*[55]	2008	P-cc	69	43 (62%)		N	[IFN-γ] below detection limit
Livingston *et al*[44]	1988	P-coh	20	6 (30%)		Y	[IFN-γ] is markedly lower in sepsis after 14 d
G-CSF							
Cook *et al*[58]	2013	P-cc	83	6 (7%)		Y	[G-CSF] > 500 pg/mL is significantly associated with sepsis
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	23 (42%)		Y	[IL-18] is significantly higher in sepsis on days 3-6 post injury
IL-1							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; Pts: Patients; Y: Yes; N: No.

Table 4 Value of cytokine concentrations for predicting muli-organ dysfunction syndrome

Study	Year	Design	No pts.	MODS *n* (%)	Diagnostic tests	Predicts MODS	Results
IL-6							
Cuschieri *et al*[34]	2010	P-coh	152	29 (37%)	> 350 pg/mL: Sensitivity 79%, specificity 76%; OR = 3.87 (95%CI: 1.13-11.19)	Y	[IL-6] > 350 pg/mL is highly associated with MODS
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.35$; > 761.7 pg/μL: Sensitivity 16.7%, specificity 98.3%	Y	[IL-6] > 76.6 pg/μL is associated with MODS with accuracy of 84.7%
Haasper *et al*[28]	2010	P-coh	94	21 (22%)		Y	[IL-6] is significantly higher in MODS on days 1 + 7
Oberholzer *et al*[46]	2000	P-coh	1276	516 (40%)		Y	[IL-6] is significantly higher in (severe) MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 294 pg/mL: AUC ROC 0.769 (95%CI: 0.414-0.736)	Y	[IL-6] > 294 pg/mL is associated with MODS at 48 + 72 h post injury
IL-8							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.53$; sensitivity 0%	N	[IL-8] is significantly higher in MODS; does not predict development of MODS
IL-10							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.31$; sensitivity 0%	N	[IL-10] is significantly higher in MODS; does not predict development of MODS
Neidhardt *et al*[54]	1997	P-cc	417	92 (22%)		Y	[IL-10] is significantly higher in MODS on days 1 + 3 + 5 + 7 + 10 + 14 + 21 post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[IL-10] is not related to the development of MODS
Sousa *et al*[51]	2015	P-coh	99	34 (34%)	> 4.93 pg/mL: AUC ROC 0.700 (95%CI: 0.506-0.841)	Y	[IL-10] > 4.93 pg/mL is associated with MODS at 24 + 72 h post injury
TNF-αα							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.32$; sensitivity 0%	N	[TNF-α] is significantly higher in MODS; does not predict development of MODS
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[TNF-α] is significantly higher in MODS on days 3 + 5
Sousa *et al*[51]	2015	P-coh	99	34 (34%)		Y	[TNF-α] is associated with MODS at 48 h post injury
Spielmann *et al*[57]	2001	P-cc	47	24 (51%)		N	[TNF-α) is not associated with MODS
IL-1β							
Frink *et al*[3]	2009	P-coh	143	24 (17%)	$r = 0.00$; sensitivity 0%	N	[IL-1β] is not related to development of MODS
IL-12							
Wick *et al*[49]	2000	P-coh	37	4 (11%)		Y	[IL-12] is significantly lower in patients with MODS
IL-18							
Mommsen *et al*[30]	2009	P-coh	55	7 (13%)		Y	[IL-18] is significantly higher in MODS on days 2 + 3 + 6 + 7 + 9 + 10 + 13 + 14
MIF							
Hayakawa *et al*[31]	2010	P-coh	45	24 (53%)		Y	[MIF] is significantly higher in MODS

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MODS; MODS: Muli-organ dysfunction syndrome; Pts: Patients; Y: Yes; N: No.

Table 5 Value of cytokine concentrations for predicting multi-organ failure

Ref.	Year	Design	No pts.	MOF *n* (%)	Diagnostic tests	Predicts MOF	Results
IL-6							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-6] is significantly higher in MOF at 0 - 24 + 72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.25 on day 2	N	[IL-6] is significantly higher in MOF; no reliable predictor due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.816; (IL-6) > 0.861 pg/mL: sensitivity 57%, PPV 100%	Y	[IL-6] > 0.861 pg/mL is highly predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-6] is significantly higher in MOF on all days of hospitalization
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-6] is significantly higher in MOF after two weeks
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-6] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.70 for late-onset MOF	Y	[IL-6] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-6] is significantly higher in MOF at 12 + 36 h
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-6] is higher in MOF at day 1, does not predict MOF
IL-8							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-8] is significantly higher in MOF from 0-72 h
Frank *et al*[11]	2002	P-cc	77		*r* = 0.32 on day 2	N	[IL-8] is significantly higher in MOF; not reliable due to low *r*
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[IL-8] is significantly higher in MOF from 0-24 h
Law *et al*[42]	1994	P-coh	13	6 (46%)		N	[IL-8] is elevated in MOF, does not predict MOF
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.69 for late-onset MOF	Y	[IL-8] is predictive for (late) MOF
Partrick *et al*[56]	1996	P-cc	27	9 (33%)		Y	[IL-8] is significantly higher in MOF at 12 + 36 + 84 h
IL-10							
Bogner *et al*[36]	2009	P-coh	58	43 (74%)		Y	[IL-10] is significantly higher in MOF in early post-injury phase (< 12 h)
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	AUC ROC 0.776; (IL-10) > 38.6 pg/mL: Sensitivity 71%, PPV 77%	Y	[IL-10] > 38.6 pg/mL is predictive for MOF
Lausevic *et al*[33]	2008	P-coh	65	36 (55%)		Y	[IL-10] is significantly higher in MOF in very early post injury phase
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[IL-10] is significantly higher in MOF on days 3 + 4
Maier *et al*[27]	2007	P-coh	251	85 (34%)	AUC ROC 0.60 for late-onset MOF	N	[IL-10) is not predictive for MOF
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-10] is significantly higher in sepsis and MOF after 6 d
TNF-αα							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)		Y	[TNF-α] is significantly higher in MOF from 2 – 6 + 10 – 24 h
Lendemans *et al*[13]	2004	P-coh	16	9 (56%)		Y	[TNF-α] is significantly higher in MOF on days 7 + 8 + 10 + 11
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[TNF-α] is significantly higher in sepsis and MOF after 8 d
Svoboda *et al*[62]	1993	P-cc	42	14 (33%)		Y	[TNF-α] is higher in MOF, but only after onset of symptoms
IL-1(β)							
Menges *et al*[50]	1999	P-coh	68	17 (25%)		Y	[IL-1] is significantly higher in sepsis and MOF on days 3 + 5 + 6 + 9 - 13
Svoboda *et al*[62]	1994	P-xx	42	14 (33%)		N	[IL-1β] is not related to MOF
IL-2							
Svoboda *et al*[62]	1994	P-cc	42	14 (33%)		N	[IL-2] is not related to MOF
IP-10							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 889.9 pg/mL has a sensitivity of 71% and PPV of 100%	Y	[IP-10] is highly predictive for MOF (AUC ROC 0.939)
Eotaxin							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 193.8 pg/mL has a sensitivity of 71% and PPV of 62%	Y	[Eotaxin] is highly predictive for MOF (AUC ROC 0.810)
MIP-1β							
Jastrow *et al*[32]	2009	P-coh	48	11 (23%)	> 248.6 pg/mL has a sensitivity of 71% and PPV of 77%	Y	[MIP-1β] is highly predictive for MOF (AUC ROC 0.871)
IL-11							
Schinkel *et al*[61]	2005	P-cc	216	9 (4%)		N	[IL-11[is not significantly different in MOF

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; ROC: Receiver operating characteristic; AUC: Area under curve; *r*: Correlation coefficient between cytokine and development of MOF; PPV: Positive predictive value; MOF: Multi-organ failure; Pts: Patients; Y: Yes; N: No.

Table 6 Value of cytokine concentrations for predicting mortality

Ref.	Design	No pts.	Mortality *n* (%)	Follow-up	Diagnostic tests	Predicts mortality	Results
IL-6							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-6] is significantly higher in non-survivors at 0 + 6 h
Cuschieri *et al*[34]	P-coh	152	4 (5%)	In-hospital		N	[IL-6] is not significantly higher in non-survivors
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		Y	[IL-6] is significantly higher in non-survivors on days 3 + 5
Frink *et al*[3]	P-coh	143	21 (15%)	In-hospital	> 2176.0 pg/mL: Sensitivity 28.6%, specificity 100% on day 1	Y	[IL-6] is highly predictive for non-survival (AUC ROC 0.858)
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors
Gebhard *et al*[40]	P-coh	94	18 (19%)	In-hospital		Y	[IL-6] is significantly higher in non-survivors at 4 + 6 + 12 h post injury
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.60	N	[IL-6] is not predictive for non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 276 pg/mL: AUC ROC2 0,775 (95%CI: 0.591-0.960)	Y	[IL-6] > 276 pg/mL is significantly correlated with non-survival
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	> 400 pg/mL has a sensitivity of 100%	Y	[IL-6] > 400 pg/mL is significantly correlated with non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-6] is significantly elevated in non-survivors
IL-8							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-8] is significantly higher in non-survivors at 6 + 24 h
Liener *et al*[43]	P-coh	94	18 (19%)	15 d		Y	[IL-8] is significantly higher in non-survivors from 30 min-24 h
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.45	N	[IL-8] is not predictive for non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-8] is significantly elevated in non-survivors
IL-10							
Bogner *et al*[36]	P-coh	58	11 (19%)	90 d		Y	[IL-10] is significantly higher in non-survivors at 72 h post injury
Gouel-Chéron *et al*[53]	P-cc	100	5 (5%)	14 d		Y	[IL-10] is significantly higher in non-survivors when detectable on days 1 + 2
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-10] tends towards lower levels in non-survivors; not significant
Maier *et al*[27]	P-coh	251	29 (12%)	In-hospital	AUC ROC 0.51	N	[IL-10] is not predictive for non-survival
Neidhardt *et al*[54]	P-cc	417	92 (22%)	21 d		Y	[IL-10] is significantly increased in non-survivors on days 1 + 3
Sherry *et al*[14]	R-cc	66	1 (2%)	50 d		N	[IL-10] is not related to non-survival
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h	> 8.24 pg/mL: AUC ROC 0.871 (95%CI: 0.715-1.000)	Y	[IL-10] > 8.24 pg/mL is associated with non-survival at 48 + 72 h post injury
TNF-αα							
Dresing *et al*[26]	P-coh	30	6 (19%)	29 d		N	[TNF-α] is not significantly elevated in non-survivors
Sousa *et al*[51]	P-coh	99	28 (28%)	72 h		N	[TNF-α] is not significantly elevated in non-survivors
Spielmann *et al*[57]	P-cc	47	11 (23%)	6 d		N	[TNF-α] is not significantly elevated in non-survivors
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		Y	[TNF-α] is significantly elevated in non-survivors
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		N	[TNF-α] is not significantly elevated in non-survivors
IL-18							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-18] tends towards lower levels in non-survivors; not significant
Mommsen *et al*[30]	P-coh	55	7 (13%)	14 d		Y	[IL-18] is significantly increased in non-survivors on days 2-7
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d		N	[IL-18] median value is significantly lower in non-survivors
IL-2							
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d		N	[IL-2] tends towards lower levels in non-survivors; not significant
Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital		N	[IL-2] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d		Y	[IL-2] is significantly increased in non-survivors
IL-1							

Svoboda *et al*[62]	P-cc	42	11 (26%)	In-hospital	N	[IL-1] is not related to non-survival
Yagmur *et al*[63]	P-cc	99	17 (17%)	60 d	N	[IL-1] is not related to non-survival
IL-12						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-12] tends towards lower levels in non-survivors; not significant
Wick *et al*[49]	P-coh	37	6 (16%)	In-hospital	Y	[IL-12] is significantly lower in non-survivors
IL-11						
Schinkel *et al*[61]	P-cc	216	34 (16%)	In-hospital	N	[IL-11] is lower in non-survivors, only reaching significance after week 4
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-11] tends towards lower levels in non-survivors; not significant
IL-17						
Frangen *et al*[59]	P-cc	71	16 (22%)	In-hospital	N	[IL-17] is not related to non-survival
IL-4						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IL-4] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IL-4] is not related to mortality
IFN-γ						
Heizmann *et al*[52]	R-cc	195	37 (19%)	42 d	N	[IFN-γ] tends towards lower levels in non-survivors; not significant
Roetman *et al*[60]	P-cc	229	36 (16%)	30 d	N	[IFN-γ] inconsistently detectable

P-coh: Prospective cohort study; P-cc: Prospective case-control study; R-cc: Retrospective case-control study; IL: Interleukin; TNF: Tumor necrosis factor; IFN: Interferon; AUC: Area under the receiver operating characteristic (ROC) curve; Pts: Patients; Y: Yes; N: No.

to MODS; and (4) Four studies[13,32,50,62] showed that patients with MOF had significantly higher TNF-α concentrations compared to patients with uneventful course, although Svoboda *et al*[62] found no predictive value for the cytokine.

DISCUSSION

Polytraumatized patients are at risk for the development of various complications, leading to considerable morbidity and mortality. Early identification of "high risk" patients could improve outcome after accidental injury, because physicians are directed to the appropriate treatment. Further, close monitoring of the immune response could direct physicians to the appropriate timing of surgical interventions, thereby reducing "second hits" with subsequent development of sepsis and organ failure. The aim of the present review was to summarize the knowledge on cytokines predicting the development of ARDS, sepsis, MODS, MOF and mortality. According to the investigated studies, some cytokines seem to predict specific complications: Patients with ARDS seem to have higher IL-8 concentrations; IL-10 secretion seems increased in septic patients; and MODS/MOF development is preceded by an enhanced IL-6, IL-8, IL-10, and TNF-α release. With respect to the other cytokines studied (IFN-γ, G-CSF, IL-1β, -2, -4, -11, -12, -17, -18, MIF, MIP-1β, eotaxin, IP-10), study results are either inconsistent, or the small amount of current evidence makes an objective conclusion for the present study impossible.

IL-6

Release of IL-6 is enhanced after stimulation by micro-organisms and cytokines (TNF-α, IL-1β)[7,8]. It is liberated after tissue damage and infection. The relatively late release and long half-life of IL-6 renders the cytokine a convenient parameter for clinical monitoring of the immune response of individual patients. The conflicting results of the reviewed studies lead to the conclusion that IL-6 cannot be used as a marker for ARDS and sepsis; elevated IL-6 concentrations do appear to precede the development of MODS, MOF and mortality. In future, physicians might therefore use IL-6 as a predictor of MODS, MOF and mortality in polytraumatized patients.

IL-8

IL-8 induces expression of adhesion molecules, thereby enabling migration of neutrophils to the site of production[4,9]. Production of IL-8 takes place early in the inflammatory response and can persist for days or weeks[13]. According to the reviewed studies, IL-8 is higher in patients developing ARDS, MOF and in non-survivors. Of note, when IL-8 is used to investigate the development of ARDS, measuring local concentrations in bronchoalveolar lavage fluid generally leads to earlier identification of patients at risk[64-67]. The causal relation between the chemotaxis IL-8 exerts on PMN's, and subsequent autodestructive changes in remote organs leading to ARDS and MOF[64], likely explains the consistent results of included studies. In line with these results, IL-8 might be used to identify patients prone to develop ARDS and MOF. Such a predictive value could not be demonstrated for the development of sepsis and MODS.

IL-10

IL-10 decreases cytokine production of T_H1 cells and reduces antigen presentation of macrophages and subsequent proliferation of T lymphocytes[14]. Release of high amounts of IL-10 occurs rapidly, generally within 60 min after trauma[54]. According to our study, an

enhanced IL-10 secretion is related to the development of sepsis and MOF. Clearly, a vigorous anti-inflammatory IL-10 release makes the host susceptible to infections with subsequent sepsis and (sepsis-related) MOF. Therefore, IL-10 concentrations might direct physicians to the patients prone to develop sepsis and MOF. Concentrations of IL-10 could not be related to the development of ARDS, MODS and mortality.

TNF-α

The pro-inflammatory cytokine TNF-α is one of the first cytokines to be released after trauma[4]. Peak concentrations of TNF-α can be observed within one to two hours after trauma. Previous studies have demonstrated a positive correlation between elevated TNF-α and poor outcome[68-70]. However, as reported in this review, the elevation of TNF-α could only be related to the development of MOF. This might be explained by the very short half-time of the cytokine (14-18 min), suggesting that peak concentrations early in the posttraumatic course have already returned to baseline by the time a septic event and subsequent organ failure is recognized[2,9,13].

Other cytokines

According to Cook *et al*[58], elevation of G-CSF significantly related to the development of hospital-acquired pneumonia. Wick *et al*[49] demonstrated that all patients with continuous decreased IL-12 levels died from septic MOF; comparable findings were demonstrated by Hensler *et al*[71]. Increased IL-12 production could, however, have unfavorable effects as well[72,73]. According to previous studies, IL-18 release is significantly correlated with sepsis, and its activation might be enhanced after infiltration of micro-organisms[74,75]. This effect could also be demonstrated by Mommsen *et al*[30]. Jastrow *et al*[32] determined a predictive value for several cytokines, among which IP-10, MIP-1β and eotaxin appear to be most accurate. More research has to be done before the value of these cytokines can be reviewed.

Limitations

The principal limitation in this study was the heterogeneity across studies in terms of patient population, study design and statistical techniques used. Hence, meta-analysis of presented data could not be performed. Further, variations between patients in an individual study can result from differences in injury severity or injury pattern, diverse individual immunologic responses (gene polymorphisms), and general confounders such as age, sex, pre-existing diseases, number and amount of administrated therapeutic agents and secondary surgery. These aspects were not clearly outlined in most of the included studies. All these factors may alter the individual inflammatory response, and contribute to a low correlation between investigated cytokine and certain complication. Further, only a small amount of studies for each biomarker-complication combination was selected, due to the very specific research question. This made it difficult to draw clear conclusions from presented results. Also, some studies reported predictive values for the ratio of different cytokines. According to these studies, complications could be predicted more accurately when combining several cytokines in one prediction model. However, we could not include these findings in our results because of the small amount of studies investigating these specific ratios. Additionally, systemic concentrations of cytokines not necessarily reflect concentrations in end-organs. It might therefore be well possible that local concentrations of cytokines can more accurately predict the development of complications. Despite these concerns, the results presented in this review can be useful in the clinical appraisal of critically ill patients. For future studies on cytokines and polytrauma patients, we recommend the development of specific polytrauma protocols. Implementation of such protocols provides the possibility for meta-analysis in the future, as previously mentioned confounding factors would then be handled similarly. Important confounding factors that most studies did not elaborate on, include amount of resuscitation fluids administered, length of mechanical ventilation, need for nutritional support and secondary surgery. Monitoring cytokine secretion patterns without considering these factors, would give an unrealistic representation of posttraumatic immune alterations. Therefore, more research is needed to better understand the specific role of these factors in the individual immune response to trauma.

In conclusion, this article provides an overview of the results from literature concerning posttraumatic immune alterations leading to various complications and death. According to the current review, cytokine secretion patterns are different for patients developing complications, compared to patients with an uneventful posttraumatic course. Some of these cytokines, such as IL-6, IL-8 and IL-10, seem to be of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

COMMENTS

Background

Severe trauma represents the most frequent cause of death in people below the age of 45. Early identification of patients at risk for developing complications is one of the most challenging problems in the treatment of multiple injuries. Close monitoring of cytokine secretion patterns may provide physicians with an impression of the patients' risk for developing complications. Further, cytokine secretion patterns may pose an indication for the appropriate prophylactic treatment, as well as optimal timing of surgical interventions, thereby reducing the risk of sepsis and multiorgan failure. The aim of the current review was: (1) to summarize the available knowledge on specific cytokines that are involved in the posttraumatic immune alterations; and (2) to assess the value of cytokines for predicting the development of acute respiratory distress syndrome, sepsis, muli-organ dysfunction syndrome, multi-organ failure and mortality.

Research frontiers

Polytraumatized patients that survive the initial impact of trauma, are confronted with an enormous host defence reaction, which is associated with morbidity and mortality. Over the past 20-25 years, cytokines have gained attention in the understanding of the posttraumatic pathophysiological immune alterations. Cytokines play a pivotal role in the pro- and anti-inflammatory reaction to trauma, and are essential in the subsequent defence and repair mechanisms. As cytokines serve as messenger molecules in cell-to-cell communication, they are likely to play an important role in the development of posttraumatic complications such as sepsis and multi organ failure.

Innovations and breakthroughs

Previous studies have acknowledged the correlation between cytokine concentrations and patients' clinical condition after polytrauma. Yet, specific predictors for the development of posttraumatic complications have not been identified. The available literature concerning the relation between cytokine concentrations and development of posttraumatic complications was systematically reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that interleukin (IL)-6, IL-8 and IL-10 are of value in the prediction of secondary deleterious effects after trauma. Close monitoring of these cytokines could direct physicians to the appropriate therapy of "high risk" patients, thereby reducing morbidity and mortality after polytrauma.

Terminology

SIRS: Systemic inflammatory response syndrome, defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference 1992; ARDS: Acute respiratory distress syndrome, determined in concordance with the American-European Consensus Conference 1994 definitions; Sepsis: Diagnosed when SIRS occurs in combination with a septic focus or positive blood culture; MODS and MOF: Multi-organ dysfunction syndrome/multi-organ failure, diagnosed based on different scoring systems.

Peer-review

This is an excellent literature analysis on an important issue. The paper was very well-structured and written.

REFERENCES

1 **Flohé S**, Flohé SB, Schade FU, Waydhas C. Immune response of severely injured patients--influence of surgical intervention and therapeutic impact. *Langenbecks Arch Surg* 2007; **392**: 639-648 [PMID: 17605036 DOI: 10.1007/s00423-007-0203-4]

2 **Dewar D**, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. *Injury* 2009; **40**: 912-918 [PMID: 19541301 DOI: 10.1016/j.injury.2009.05.024]

3 **Frink M**, van Griensven M, Kobbe P, Brin T, Zeckey C, Vaske B, Krettek C, Hildebrand F. IL-6 predicts organ dysfunction and mortality in patients with multiple injuries. *Scand J Trauma Resusc Emerg Med* 2009; **17**: 49 [PMID: 19781105 DOI: 10.1186/1757-7241-17-49]

4 **Hietbrink F**, Koenderman L, Rijkers G, Leenen L. Trauma: the role of the innate immune system. *World J Emerg Surg* 2006; **1**: 15 [PMID: 16759367 DOI: 10.1186/1749-7922-1-15]

5 **Keel M**, Trentz O. Pathophysiology of polytrauma. *Injury* 2005; **36**: 691-709 [PMID: 15910820 DOI: 10.1016/j.injury.2004.12.037]

6 **Tschoeke SK**, Ertel W. Immunoparalysis after multiple trauma. *Injury* 2007; **38**: 1346-1357 [PMID: 18048039 DOI: 10.1016/j.injury.2007.08.041]

7 **Ciriello V**, Gudipati S, Stavrou PZ, Kanakaris NK, Bellamy MC, Giannoudis PV. Biomarkers predicting sepsis in polytrauma patients: Current evidence. *Injury* 2013; **44**: 1680-1692 [PMID: 24119650 DOI: 10.1016/j.injury.2013.09.024]

8 **Giannoudis PV**, Hildebrand F, Pape HC. Inflammatory serum markers in patients with multiple trauma. Can they predict outcome? *J Bone Joint Surg Br* 2004; **86**: 313-323 [PMID: 15125116 DOI: 10.1302/0301-620X.86B3.15035]

9 **Hildebrand F**, Pape HC, Krettek C. The importance of cytokines in the posttraumatic inflammatory reaction. *Unfallchirurg* 2005; **108**: 793-794, 796-803 [PMID: 16175346 DOI: 10.1007/s00113-005-1005-1]

10 **Sears BW**, Stover MD, Callaci J. Pathoanatomy and clinical correlates of the immunoinflammatory response following orthopaedic trauma. *J Am Acad Orthop Surg* 2009; **17**: 255-265 [PMID: 19307674 DOI: 10.5435/00124635-200904000-00006]

11 **Frank J**, Maier M, Koenig J, Rose S, Bouma M, Buurman WA, Marzi I. Circulating inflammatory and metabolic parameters to predict organ failure after multiple trauma. *Eur J Trauma* 2002; **28**: 333-339 [DOI: 10.1007/s00068-002-1263-3]

12 **DeLong WG**, Born CT. Cytokines in patients with polytrauma. *Clin Orthop Relat Res* 2004; **(422)**: 57-65 [PMID: 15187834 DOI: 10.1097/01.blo.0000130840.64528.1e]

13 **Lendemans S**, Kreuzfelder E, Waydhas C, Nast-Kolb D, Flohé S. Clinical course and prognostic significance of immunological and functional parameters after severe trauma. *Unfallchirurg* 2004; **107**: 203-210 [PMID: 14999368 DOI: 10.1007/s00113-004-0729-7]

14 **Sherry RM**, Cue JI, Goddard JK, Parramore JB, DiPiro JT. Interleukin-10 is associated with the development of sepsis in trauma patients. *J Trauma* 1996; **40**: 613-666; discussion 616-617 [PMID: 8614042 DOI: 10.1097/00005373-199604000-00016]

15 **Keel M**, Schregenberger N, Steckholzer U, Ungethüm U, Kenney J, Trentz O, Ertel W. Endotoxin tolerance after severe injury and its regulatory mechanisms. *J Trauma* 1996; **41**: 430-47; discussion 430-437; 437-438 [PMID: 8810959 DOI: 10.1097/00005373-199609000-00008]

16 **Moher D**, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535 [PMID: 19622551 DOI: 10.1136/bmj.b2535]

17 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818-824 [PMID: 7509706 DOI: 10.1007/BF01704707]

18 **Bone RC**, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; **101**: 1644-1655 [PMID: 1303622 DOI: 10.1378/chest.101.6.1644]

19 **Marshall JC**, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med* 1995; **23**: 1638-1652 [PMID: 7587228 DOI: 10.1097/00003246-199510000-00007]

20 **Goris RJ**, te Boekhorst TP, Nuytinck JK, Gimbrère JS. Multiple-organ failure. Generalized autodestructive inflammation? *Arch Surg* 1985; **120**: 1109-1115 [PMID: 4038052 DOI: 10.1001/archsurg.1985.01390340007001]

21 **Sauaia A**, Moore FA, Moore EE, Norris JM, Lezotte DC, Hamman RF. Multiple organ failure can be predicted as early as 12 hours after injury. *J Trauma* 1998; **45**: 291-301; discussion 301-303 [PMID: 9715186 DOI: 10.1097/00005373-199808000-00014]

22 **Moore FA**, Moore EE, Poggetti R, McAnena OJ, Peterson VM, Abernathy CM, Parsons PE. Gut bacterial translocation via the portal vein: a clinical perspective with major torso trauma. *J Trauma* 1991; **31**: 629-636; discussion 636-638 [PMID: 2030509 DOI: 10.1097/00005373-199105000-00006]

23 **Lefering R**, Goris RJ, van Nieuwenhoven EJ, Neugebauer E. Revision of the multiple organ failure score. *Langenbecks Arch Surg* 2002; **387**: 14-20 [PMID: 11981679 DOI: 10.1007/s00423-001-0269-3]

24 **Grotz M**, von Griensven M, Stalp M, Kaufmann U, Hildebrand F, Pape HC. Scoring multiple organ failure after severe trauma. Comparison of the Goris, Marshall and Moore scores. *Chirurg* 2001; **72**: 723-730 [PMID: 11469095 DOI: 10.1007/s001040170130]

25 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for

reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344-349 [PMID: 18313558 DOI: 10.1016/j.jclinepi.2007.11.008]

26 **Dresing K**, Armstrong VW, Leip CL, Streit F, Burchardi H, Stürmer KM, Oellerich M. Real-time assessment of hepatic function is related to clinical outcome in critically ill patients after polytrauma. *Clin Biochem* 2007; **40**: 1194-1200 [PMID: 17707362 DOI: 10.1016/j.clinbiochem.2007.06.013]

27 **Maier B**, Lefering R, Lehnert M, Laurer HL, Steudel WI, Neugebauer EA, Marzi I. Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma. *Shock* 2007; **28**: 668-674 [PMID: 18092384 DOI: 10.1097/shk.0b013e318123e64e]

28 **Haasper C**, Kalmbach M, Dikos GD, Meller R, Müller C, Krettek C, Hildebrand F, Frink M. Prognostic value of procalcitonin (PCT) and/or interleukin-6 (IL-6) plasma levels after multiple trauma for the development of multi organ dysfunction syndrome (MODS) or sepsis. *Technol Health Care* 2010; **18**: 89-100 [PMID: 20495248]

29 **Lausević Z**, Vuković G, Stojimirović B, Trbojević-Stanković J, Resanović V, Lausevic M. Kinetics of C-reactive protein, interleukin-6 and -10, and phospholipase A2-II in severely traumatized septic patients. *Vojnosanit Pregl* 2010; **67**: 893-897 [PMID: 21268514 DOI: 10.2298/VSP1011893L]

30 **Mommsen P**, Frink M, Pape HC, van Griensven M, Probst C, Gaulke R, Krettek C, Hildebrand F. Elevated systemic IL-18 and neopterin levels are associated with posttraumatic complications among patients with multiple injuries: a prospective cohort study. *Injury* 2009; **40**: 528-534 [PMID: 19054512 DOI: 10.1016/j.injury.2008.08.007]

31 **Hayakawa M**, Katabami K, Wada T, Minami Y, Sugano M, Shimojima H, Kubota N, Uegaki S, Sawamura A, Gando S. Imbalance between macrophage migration inhibitory factor and cortisol induces multiple organ dysfunction in patients with blunt trauma. *Inflammation* 2011; **34**: 193-197 [PMID: 20499270 DOI: 10.1007/s10753-010-9223-2]

32 **Jastrow KM**, Gonzalez EA, McGuire MF, Suliburk JW, Kozar RA, Iyengar S, Motschall DA, McKinley BA, Moore FA, Mercer DW. Early cytokine production risk stratifies trauma patients for multiple organ failure. *J Am Coll Surg* 2009; **209**: 320-331 [PMID: 19717036 DOI: 10.1016/j.jamcollsurg.2009.05.002]

33 **Lausevic Z**, Lausevic M, Trbojevic-Stankovic J, Krstic S, Stojimirovic B. Predicting multiple organ failure in patients with severe trauma. *Can J Surg* 2008; **51**: 97-102 [PMID: 18377749]

34 **Cuschieri J**, Bulger E, Schaeffer V, Sakr S, Nathens AB, Hennessy L, Minei J, Moore EE, O'Keefe G, Sperry J, Remick D, Tompkins R, Maier RV. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. *Shock* 2010; **34**: 346-351 [PMID: 20844410 DOI: 10.1097/SHK.0b013e3181de687]

35 **Billeter A**, Turina M, Seifert B, Mica L, Stocker R, Keel M. Early serum procalcitonin, interleukin-6, and 24-hour lactate clearance: useful indicators of septic infections in severely traumatized patients. *World J Surg* 2009; **33**: 558-566 [PMID: 19148699 DOI: 10.1007/s00268-008-9896-y]

36 **Bogner V**, Keil L, Kanz KG, Kirchhoff C, Leidel BA, Mutschler W, Biberthaler P. Very early posttraumatic serum alterations are significantly associated to initial massive RBC substitution, injury severity, multiple organ failure and adverse clinical outcome in multiple injured patients. *Eur J Med Res* 2009; **14**: 284-291 [PMID: 19661010 DOI: 10.1186/2047-783X-14-7-284]

37 **Donnelly TJ**, Meade P, Jagels M, Cryer HG, Law MM, Hugli TE, Shoemaker WC, Abraham E. Cytokine, complement, and endotoxin profiles associated with the development of the adult respiratory distress syndrome after severe injury. *Crit Care Med* 1994; **22**: 768-776 [PMID: 8181284 DOI: 10.1097/00003246-199405000-00010]

38 **Egger G**, Aigner R, Glasner A, Hofer HP, Mitterhammer H, Zelzer S. Blood polymorphonuclear leukocyte migration as a predictive marker for infections in severe trauma: comparison with various inflammation parameters. *Intensive Care Med* 2004; **30**: 331-334 [PMID: 14727016 DOI: 10.1007/s00134-003-2111-6]

39 **Flores JM**, Jiménez PI, Rincón MD, Márquez JA, Navarro H, Arteta D, Murillo F. Early risk factors for sepsis in patients with severe blunt trauma. *Injury* 2001; **32**: 5-12 [PMID: 11164394 DOI: 10.1016/S0020-1383(00)00103-0]

40 **Gebhard F**, Pfetsch H, Steinbach G, Strecker W, Kinzl L, Brückner UB. Is interleukin 6 an early marker of injury severity following major trauma in humans? *Arch Surg* 2000; **135**: 291-295 [PMID: 10722030 DOI: 10.1001/archsurg.135.3.291]

41 **Keel M**, Härter L, Reding T, Sun LK, Hersberger M, Seifert B, Bimmler D, Graf R. Pancreatic stone protein is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. *Crit Care Med* 2009; **37**: 1642-1648 [PMID: 19325491 DOI: 10.1097/CCM.0b013e31819da7d6]

42 **Law MM**, Cryer HG, Abraham E. Elevated levels of soluble ICAM-1 correlate with the development of multiple organ failure in severely injured trauma patients. *J Trauma* 1994; **37**: 100-109; discussion 109-110 [PMID: 7913140 DOI: 10.1097/00005373-199407000-00017]

43 **Liener UC**, Brückner UB, Knöferl MW, Steinbach G, Kinzl L, Gebhard F. Chemokine activation within 24 hours after blunt accident trauma. *Shock* 2002; **17**: 169-172 [PMID: 11900333 DOI: 10.1097/00024382-200203000-00002]

44 **Livingston DH**, Appel SH, Wellhausen SR, Sonnenfeld G, Polk HC. Depressed interferon gamma production and monocyte HLA-DR expression after severe injury. *Arch Surg* 1988; **123**: 1309-1312 [PMID: 3140765 DOI: 10.1001/archsurg.1988.01400350023002]

45 **Meade P**, Shoemaker WC, Donnelly TJ, Abraham E, Jagels MA, Cryer HG, Hugli TE, Bishop MH, Wo CC. Temporal patterns of hemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. *J Trauma* 1994; **36**: 651-657 [PMID: 8189465 DOI: 10.1097/00005373-199405000-00009]

46 **Oberholzer A**, Keel M, Zellweger R, Steckholzer U, Trentz O, Ertel W. Incidence of septic complications and multiple organ failure in severely injured patients is sex specific. *J Trauma* 2000; **48**: 932-937 [PMID: 10823539 DOI: 10.1097/00005373-200005000-00019]

47 **Paunel-Görgülü A**, Flohé S, Scholz M, Windolf J, Lögters T. Increased serum soluble Fas after major trauma is associated with delayed neutrophil apoptosis and development of sepsis. *Crit Care* 2011; **15**: R20 [PMID: 21232130 DOI: 10.1186/cc9965]

48 **Raymondos K**, Martin MU, Schmudlach T, Baus S, Weilbach C, Welte T, Krettek C, Frink M, Hildebrand F. Early alveolar and systemic mediator release in patients at different risks for ARDS after multiple trauma. *Injury* 2012; **43**: 189-195 [PMID: 21703617 DOI: 10.1016/j.injury.2011.05.034]

49 **Wick M**, Kollig E, Walz M, Muhr G, Köller M. [Does liberation of interleukin-12 correlate with the clinical course of polytraumatized patients?]. *Chirurg* 2000; **71**: 1126-1131 [PMID: 11043131 DOI: 10.1007/s001040051189]

50 **Menges T**, Engel J, Welters I, Wagner RM, Little S, Ruwoldt R, Wollbrueck M, Hempelmann G. Changes in blood lymphocyte populations after multiple trauma: association with posttraumatic complications. *Crit Care Med* 1999; **27**: 733-740 [PMID: 10321662 DOI: 10.1097/00003246-199904000-00026]

51 **Sousa A**, Raposo F, Fonseca S, Valente L, Duarte F, Gonçalves M, Tuna D, Paiva JA. Measurement of cytokines and adhesion molecules in the first 72 hours after severe trauma: association with severity and outcome. *Dis Markers* 2015; **2015**: 747036 [PMID: 25861153 DOI: 10.1155/2015/747036]

52 **Heizmann O**, Koeller M, Muhr G, Oertli D, Schinkel C. Th1- and Th2-type cytokines in plasma after major trauma. *J Trauma* 2008; **65**: 1374-1378 [PMID: 19077629 DOI: 10.1097/TA.0b013e31818b257d]

53 **Gouel-Chéron A**, Allaouchiche B, Guignant C, Davin F, Floccard B, Monneret G. Early interleukin-6 and slope of monocyte human leukocyte antigen-DR: a powerful association to predict the development of sepsis after major trauma. *PLoS One* 2012; **7**: e33095 [PMID: 22431998 DOI: 10.1371/journal.pone.0033095]

54 **Neidhardt R**, Keel M, Steckholzer U, Safret A, Ungethuem U, Trentz O, Ertel W. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *J Trauma* 1997; **42**: 863-870; discussion 870-871 [PMID: 9191668 DOI: 10.1097/00005373-199705000-00017]

55 **Giamarellos-Bourboulis EJ**, Mouktaroudi M, Tsaganos T, Koutoukas P, Spyridaki E, Pelekanou A, Kotzampassi K. Evidence for the participation of soluble triggering receptor expressed on myeloid cells-1 in the systemic inflammatory response syndrome after multiple trauma. *J Trauma* 2008; **65**: 1385-1390 [PMID: 19077631 DOI: 10.1097/TA.0b013e31814699cc]

56 **Partrick DA**, Moore FA, Moore EE, Biffl WL, Sauaia A, Barnett CC. Jack A. Barney Resident Research Award winner. The inflammatory profile of interleukin-6, interleukin-8, and soluble intercellular adhesion molecule-1 in postinjury multiple organ failure. *Am J Surg* 1996; **172**: 425-429; discussed 429-431 [PMID: 8942538 DOI: 10.1016/S0002-9610(96)00252-8]

57 **Spielmann S**, Kerner T, Ahlers O, Keh D, Gerlach M, Gerlach H. Early detection of increased tumour necrosis factor alpha (TNFalpha) and soluble TNF receptor protein plasma levels after trauma reveals associations with the clinical course. *Acta Anaesthesiol Scand* 2001; **45**: 364-370 [PMID: 11207475 DOI: 10.1034/j.1399-6576.2001.045003364.x]

58 **Cook KM**, Sifri ZC, Baranski GM, Mohr AM, Livingston DH. The role of plasma granulocyte colony stimulating factor and bone marrow dysfunction after severe trauma. *J Am Coll Surg* 2013; **216**: 57-64 [PMID: 23063381 DOI: 10.1016/j.jamcollsurg.2012.08.028]

59 **Frangen TM**, Bogdanski D, Schinkel C, Roetman B, Kälicke T, Muhr G, Köller M. Systemic IL-17 after severe injuries. *Shock* 2008; **29**: 462-467 [PMID: 17909455]

60 **Roetman B**, Schinkel C, Wick M, Frangen T, Muhr G, Köller M. Elevated systemic interleukin-18 in multiple injured patients is not related to clinical outcome. *J Interferon Cytokine Res* 2008; **28**: 741-747 [PMID: 18937548 DOI: 10.1089/jir.2008.0029]

61 **Schinkel C**, Wick M, Muhr G, Köller M. Analysis of systemic interleukin-11 after major trauma. *Shock* 2005; **23**: 30-34 [PMID: 15614128 DOI: 10.1097/01.shk.0000148057.20010.cf]

62 **Svoboda P**, Kantorová I, Ochmann J. Dynamics of interleukin 1, 2, and 6 and tumor necrosis factor alpha in multiple trauma patients. *J Trauma* 1994; **36**: 336-340 [PMID: 8145312 DOI: 10.1097/00005373-199403000-00009]

63 **Yagmur Y**, Ozturk H, Unaldi M, Gedik E. Relation between severity of injury and the early activation of interleukins in multiple-injured patients. *Eur Surg Res* 2005; **37**: 360-364 [PMID: 16465061 DOI: 10.1159/000090337]

64 **Muehlstedt SG**, Lyte M, Rodriguez JL. Increased IL-10 production and HLA-DR suppression in the lungs of injured patients precede the development of nosocomial pneumonia. *Shock* 2002; **17**: 443-450 [PMID: 12069178 DOI: 10.1097/00024382-200206000-00001]

65 **Donnelly SC**, Strieter RM, Kunkel SL, Walz A, Robertson CR, Carter DC, Grant IS, Pollok AJ, Haslett C. Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. *Lancet* 1993; **341**: 643-647 [PMID: 8095568 DOI: 10.1016/0140-6736(93)90416-E]

66 **Aggarwal A**, Baker CS, Evans TW, Haslam PL. G-CSF and IL-8 but not GM-CSF correlate with severity of pulmonary neutrophilia in acute respiratory distress syndrome. *Eur Respir J* 2000; **15**: 895-901 [PMID: 10853855 DOI: 10.1034/j.1399-3003.2000.15e14.x]

67 **Suter PM**, Suter S, Girardin E, Roux-Lombard P, Grau GE, Dayer JM. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. *Am Rev Respir Dis* 1992; **145**: 1016-1022 [PMID: 1586041 DOI: 10.1164/ajrccm/145.5.1016]

68 **Strieter RM**, Kunkel SL, Bone RC. Role of tumor necrosis factor-alpha in disease states and inflammation. *Crit Care Med* 1993; **21**: S447-S463 [PMID: 8403983 DOI: 10.1097/00003246-199310001-00006]

69 **Ozturk H**, Yagmur Y, Ozturk H. The prognostic importance of serum IL-1beta, IL-6, IL-8 and TNF-alpha levels compared to trauma scoring systems for early mortality in children with blunt trauma. *Pediatr Surg Int* 2008; **24**: 235-239 [PMID: 18060414 DOI: 10.1007/s00383-007-2083-7]

70 **Zedler S**, Faist E. The impact of endogenous triggers on trauma-associated inflammation. *Curr Opin Crit Care* 2006; **12**: 595-601 [PMID: 17077693 DOI: 10.1097/MCC.0b013e3280106806]

71 **Hensler T**, Heidecke CD, Hecker H, Heeg K, Bartels H, Zantl N, Wagner H, Siewert JR, Holzmann B. Increased susceptibility to postoperative sepsis in patients with impaired monocyte IL-12 production. *J Immunol* 1998; **161**: 2655-2659 [PMID: 9725269]

72 **Car BD**, Eng VM, Schnyder B, LeHir M, Shakhov AN, Woerly G, Huang S, Aguet M, Anderson TD, Ryffel B. Role of interferon-gamma in interleukin 12-induced pathology in mice. *Am J Pathol* 1995; **147**: 1693-1707 [PMID: 7495294]

73 **Ryffel B**. Interleukin-12: role of interferon-gamma in IL-12 adverse effects. *Clin Immunol Immunopathol* 1997; **83**: 18-20 [PMID: 9073529 DOI: 10.1006/clin.1996.4306]

74 **Emmanuilidis K**, Weighardt H, Matevossian E, Heidecke CD, Ulm K, Bartels H, Siewert JR, Holzmann B. Differential regulation of systemic IL-18 and IL-12 release during postoperative sepsis: high serum IL-18 as an early predictive indicator of lethal outcome. *Shock* 2002; **18**: 301-305 [PMID: 12392271 DOI: 10.1097/00024382-200210000-00002]

75 **Oberholzer A**, Steckholzer U, Kurimoto M, Trentz O, Ertel W. Interleukin-18 plasma levels are increased in patients with sepsis compared to severely injured patients. *Shock* 2001; **16**: 411-414 [PMID: 11770036 DOI: 10.1097/00024382-200116060-00001]

P- Reviewer: Cotogni P, Wang Y **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 2220-3141 (online)

World Journal of *Critical Care Medicine*

World J Crit Care Med 2016 November 4; 5(4): 201-250

Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

A peer-reviewed, online, open-access journal of critical care medicine

Editorial Board

2016-2019

The *World Journal of Critical Care Medicine* Editorial Board consists of 235 members, representing a team of worldwide experts in critical care medicine. They are from 44 countries, including Argentina (2), Australia (7), Austria (2), Bangladesh (1), Belgium (4), Brazil (4), Canada (6), China (23), Croatia (1), Cuba (1), Denmark (1), Egypt (4), Finland (1), France (6), Germany (9), Greece (9), Hungary (1), India (10), Iran (2), Israel (6), Italy (13), Japan (6), Jordan (1), Mexico (1), Morocco (1), Netherlands (4), New Zealand (3), Norway (1), Poland (1), Portugal (4), Russia (1), Saudi Arabia (2), Singapore (2), Slovenia (1), South Africa (1), Spain (6), Sweden (1), Switzerland (3), Thailand (1), Tunisia (1), Turkey (3), United Kingdom (7), United States (70), and Uruguay (1).

WJCCM World Journal of Critical Care Medicine

Contents

Quarterly Volume 5 Number 4 November 4, 2016

Contents

World Journal of Critical Care Medicine
Volume 5 Number 4 November 4, 2016

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
Fang-Fang Ji, Vice Director
World Journal of Critical Care Medicine
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
November 4, 2016

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.201

World J Crit Care Med 2016 November 4; 5(4): 201-203
ISSN 2220-3141 (online)

EDITORIAL

New avenues for reducing intensive care needs in patients with chronic spinal cord injury

Pierre A Guertin

Pierre A Guertin, Department of Psychiatry and Neurosciences, Laval University, Québec City, QC G1V 0A6, Canada

Pierre A Guertin, Laval University Medical Center (CHU de Québec - CHUL), Québec City, QC G1V 4G2, Canada

Author contributions: Guertin PA solely contributed to all aspects of this editorial paper.

Conflict-of-interest statement: The author is also president and chief executive officer of Nordic Life Science Pipeline.

Manuscript source: Invited manuscript

Correspondence to: Pierre A Guertin, PhD, Professor, Laval University Medical Center (CHU de Québec - CHUL), 2705 Laurier Boulevard, RC-9800 (Neuroscience), Québec City, QC G1V 4G2, Canada. pierre.guertin@crchul.ulaval.ca
Telephone: +1-418-5254444
Fax: +1-418-6542753

Received: March 24, 2016
Peer-review started: March 24, 2016
First decision: May 16, 2016
Revised: July 5, 2016
Accepted: August 11, 2016
Article in press: August 15, 2016
Published online: November 4, 2016

Abstract

Relatively soon after their accident, patients suffering a spinal cord injury (SCI) begin generally experiencing the development of significant, often life-threatening secondary complications. Many of which are associated with chronic physical inactivity-related immune function problems and increasing susceptibility to infection that repeatedly requires intensive care treatment. Therapies capable of repairing the spinal cord or restoring ambulation would normally prevent many of these problems but, as of now, there is no cure for SCI. Thus, management strategies and antibiotics remain the standard of care although antimicrobial resistance constitutes a significant challenge for patients with chronic SCI facing recurrent infections of the urinary tract and respiratory systems. Identifying alternative therapies capable of safe and potent actions upon these serious health concerns should therefore be considered a priority. This editorial presents some of the novel approaches currently in development for the prevention of specific infections after SCI. Among them, brain-permeable small molecule therapeutics acting centrally on spinal cord circuits that can augment respiratory capabilities or bladder functions. If eventually approved by regulatory authorities, some of these new avenues may potentially become clinically-relevant therapies capable of indirectly preventing the occurrence and/or severity of these life-threatening complications in people with paraplegic or tetraplegic injuries.

Key words: Prevention of intensive care problems; Quality of care; Temporary recovery of vital functions; Micturition; Spinal networks; Central pattern generators

Core tip: This editorial is one of the first articles to describe clearly the existence of an urgent medical need for new pharmacological products aimed at providing non-invasive solutions for spinal cord injury patients suffering chronically of urinary tract infection or pneumonia. Drugs capable of activating temporarily on demand activity in specific central networks of neurons

that control respiration or micturition are of particular interest.

Guertin PA. New avenues for reducing intensive care needs in patients with chronic spinal cord injury. *World J Crit Care Med* 2016; 5(4): 201-203 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/201.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.201

INTRODUCTION

Spinal cord injury (SCI) of traumatic origin is generally considered an irreversible condition causing, immediately after trauma, both sensory loss and mobility impairment or complete paralysis[1]. Unfortunately it often leads also, within a few weeks to a few months, to serious chronic complications among which immune problems also knows as central nervous system injury-induced immunodepression (CIDS)[2]. In fact, CIDS is probably one of the main factors contributing subsequently to the development of more specific problems such as urinary tract infections (UTIs), bed sores, pneumonia, sepsis[1]. As of now, biologics (*i.e.*, antibiotics) are generally used to treat these infections[3]. However, antibiotics are associated with the increasing problem of antimicrobial resistance and progressive lack of efficacy against infections[4]. When examined closer, different additional factors may contribute to UTIs and pneumonia specifically after SCI. For instance, descending (*i.e.*, brain and brainstem) control over the sacral spinal cord micturition center is generally lost or impaired after SCI leading to urinary retention (UR) problems[5]. When chronic UR is found, the bladder remains full, although leaking may occur (associated also with bladder sphincter dyssynergia), and overgrowth of bacteria is regularly diagnosed, contributing directly to recurrent UTIs[6]. In the case of pneumonia, specifically for those with tetraplegia (but not only), breathing control problems and reduced coughing capabilities have a direct impact upon mucus accumulation and bacterial overgrowth that leads to pneumonia and, sometimes, respiratory failure[7].

INADEQUACY OF CURRENTLY USED APPROACHES

Medical devices for managing bladder problems are probably the most extensively used means to prevent UTIs. Chronic indwelling catheters or intermittent catheters are typically used for regular bladder drainage and, hence, for reducing incidence of bacterial overgrowth. However, the use of catheters also contributes to UTIs. When chronically performed, these devices are associated with multiple problems including pyuria, pericatheter sepsis, haemorrhage, or bladder and kidney damage[8]. Other alternative approaches are occasionally used such as drugs with peripheral actions on bladder contraction, electrostimulation of sacral anterior roots, diapers or condom sheaths although UR remains largely an unmet medical need that is generally life-threatening[8,9]. For respiratory problems and mucus accumulation, mainly mechanical approaches are normally used, *i.e.,* physical therapy, spontaneous or mechanically assisted coughing, suctioning, and mechanical insufflation-exsufflation[10]. These procedures are rather complex, time-consuming and expensive (*i.e.,* both labor and specialized medical devices)[11].

CENTRALLY-ACTING PHARMACOLOGICAL APPROACHES

There is compelling evidence suggesting that lower incidence of pneumonia or UTIs may be found if, respectively, cardiovascular and pulmonary function or bladder function could be stimulated and improved. To investigate that, some researchers are exploring a novel approach essentially based on central (spinal cord) small molecule therapeutics stimulation of neuronal networks known to normally (*i.e.,* in absence of spinal injuries) control either respiration or micturition.

Proof-of-concept data demonstrating the efficacy of restoring corresponding spinal neuronal activity on voiding reflex have been reported in animal models of SCI. Serotonergic drugs such as 5-HT1A and 5-HT7 agonists were shown indeed, following a single intravenous (*i.v.*) administration, to augment acutely micturition reflex and voiding despite the lack of brain control over that same spinal network in paraplegic rats[12,13]. Central actions upon sacral neuronal networks has been clearly shown by Lecci *et al*[14] following intrathecal administration of similar compounds[14]. My own research group in Canada has built upon these findings to show recently that powerful synergistic effects on reflex voiding may be found by co-administration subcutaneously of 5-HT1A and 5-HT7 receptor agonists in paraplegic mice[15]. Comparable voiding-activating has been shown using direct electrical stimulation of corresponding spinal cord areas in anesthetized chronic paraplegic cats[16].

For breathing problems, the role of another set of neurons has been explored using a comparable approach. It is the crossed phrenic pathway in the spinal cord, also known as CPP, that exhibit significant control of phrenic motoneurons and nerves for diaphragm contraction. It had been found originally by the French researchers Aubier and Pariente, that *i.v.* infusion of aminophylline, an adenosine receptor antagonist, can improve ventilation in dogs *via* stronger diaphragmatic contraction[17]. However, Nantwi *et al*[18] more recently showed that adenosine antagonists aminophylline or theophylline can augment respiration by acting centrally although some additional peripheral actions upon the diaphragm cannot be excluded. Theophylline and aminophylline have both been considered as relatively safe

since approved already by FDA as treatment against chronic obstructive pulmonary disease. Other drugs such as 5-HT1A agonist administered *i.p.* to chronic paraplegic rats have been shown also to stabilize ventilator abnormalities[19]. However, clinical efficacy against respiratory problems and related consequences on mucus accumulation and pneumonia with adenosine antagonists or 5-HT1A agonists remains to be shown.

CONCLUSION

No safe or acceptable treatments have yet been found against the occurrence or severity of significant health concerns such as UTIs and pneumonia in chronic SCI patients. Non-invasive and user-friendly pharmacological acting centrally upon specific spinal command centers involved in controlling micturition and breathing may eventually constitute safe and potent treatments against recurrent infections associated with chronic UR and breathing insufficiency after SCI.

REFERENCES

1 **Rouleau P**, Ayoub E, Guertin PA. Traumatic and non-traumatic spinal cord-injured patients in Quebec, Canada: Part 1 - Epidemiological, clinical and functional characteristics. *Open Epidemiol J* 2011; **4**: 131-137 [DOI: 10.2174/1874297101104101 33]

2 **Meisel C**, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci* 2005; **6**: 775-786 [PMID: 16163382 DOI: 10.1038/nrn1765]

3 **Rouleau P**, Guertin PA. Traumatic and nontraumatic spinal-cord-injured patients in Quebec, Canada. Part 3: pharmacological characteristics. *Spinal Cord* 2011; **49**: 186-195 [PMID: 20548322 DOI: 10.1038/sc.2010.70]

4 **Laxminarayan R**, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, Vlieghe E, Hara GL, Gould IM, Goossens H, Greko C, So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ, Qamar FN, Mir F, Kariuki S, Bhutta ZA, Coates A, Bergstrom R, Wright GD, Brown ED, Cars O. Antibiotic resistance-the need for global solutions. *Lancet Infect Dis* 2013; **13**: 1057-1098 [PMID: 24252483 DOI: 10.1016/S1473-3099(13)70318-9]

5 **Beckel JM**, Holstege G. Neurophysiology of the lower urinary tract. *Handb Exp Pharmacol* 2011; **(202)**: 149-169 [PMID: 21290226 DOI: 10.1007/978-3-642-16499-6_8]

6 **Nash MS**. Known and plausible modulators of depressed immune functions following spinal cord injuries. *J Spinal Cord Med* 2000; **23**: 111-120 [PMID: 10914352]

7 **Mutton DL**, Scremin AM, Barstow TJ, Scott MD, Kunkel CF, Cagle TG. Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. *Arch Phys Med Rehabil* 1997; **78**: 712-718 [PMID: 9228873 DOI: 10.1016/S0003-9993(97)90078-2]

8 **Hernández Hernández D**, Tesouro RB, Castro-Diaz D. Urinary retention. *Urologia* 2013; **80**: 257-264 [PMID: 24419919 DOI: 10.5301/RU.2013.11688]

9 **Miyazato M**, Yoshimura N, Chancellor MB. The other bladder syndrome: underactive bladder. *Rev Urol* 2013; **15**: 11-22 [PMID: 23671401 DOI: 10.1095/biolreprod37.1.117]

10 **Berlly M**, Shem K. Respiratory management during the first five days after spinal cord injury. *J Spinal Cord Med* 2007; **30**: 309-318 [PMID: 17853652 DOI: 10.1155/2013/168757]

11 **Zimmer MB**, Nantwi K, Goshgarian HG. Effect of spinal cord injury on the respiratory system: basic research and current clinical treatment options. *J Spinal Cord Med* 2007; **30**: 319-330 [PMID: 17853653 DOI: 10.1016/j.resp.2014.08.005]

12 **Gang W**, Hongjian T, Jasheng C, Jiemin S, Zhong C, Yuemin X, Baojun G, Andersson KE. The effect of the 5-HT7 serotonin receptor agonist, LP44, on micturition in rats with chronic spinal cord injury. *Neurourol Urodyn* 2014; **33**: 1165-1170 [PMID: 23861341 DOI: 10.1002/nau.22463]

13 **Dolber PC**, Gu B, Zhang X, Fraser MO, Thor KB, Reiter JP. Activation of the external urethral sphincter central pattern generator by a 5-HT(1A) receptor agonist in rats with chronic spinal cord injury. *Am J Physiol Regul Integr Comp Physiol* 2007; **292**: R1699-R1706 [PMID: 17204596 DOI: 10.1152/ajpregu.00142.2006]

14 **Lecci A**, Giuliani S, Santicioli P, Maggi CA. Involvement of 5-hydroxytryptamine1A receptors in the modulation of micturition reflexes in the anesthetized rat. *J Pharmacol Exp Ther* 1992; **262**: 181-189 [PMID: 1352548 DOI: 10.1002/nau.22435]

15 **Guertin PA**. Methods and uses for inducing or facilitating micturition in a patient in need thereof. USPTO patent WO 2015/127558 01. 2015

16 **Pikov V**, Bullara L, McCreery DB. Intraspinal stimulation for bladder voiding in cats before and after chronic spinal cord injury. *J Neural Eng* 2007; **4**: 356-368 [PMID: 18057503 DOI: 10.1088/1741-2]

17 **Aubier M**, Murciano D, Viires N, Lecocguic Y, Palacios S, Pariente R. Increased ventilation caused by improved diaphragmatic efficiency during aminophylline infusion. *Am Rev Respir Dis* 1983; **127**: 148-154 [PMID: 6830028 DOI: 10.1164/arrd.1983.127.5.655a]

18 **Nantwi KD**, Goshgarian HG. Alkylxanthine-induced recovery of respiratory function following cervical spinal cord injury in adult rats. *Exp Neurol* 2001; **168**: 123-134 [PMID: 11170727 DOI: 10.1006/exnr.2000.7581]

19 **Teng YD**, Bingaman M, Taveira-DaSilva AM, Pace PP, Gillis RA, Wrathall JR. Serotonin 1A receptor agonists reverse respiratory abnormalities in spinal cord-injured rats. *J Neurosci* 2003; **23**: 4182-4189 [PMID: 12764106 DOI: 10.1371/journal.pone.0130255]

P- Reviewer: Inchauspe AA, Weng CF **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.204

World J Crit Care Med 2016 November 4; 5(4): 204-211
ISSN 2220-3141 (online)

MINIREVIEWS

Clinical decision support for drug related events: Moving towards better prevention

Sandra L Kane-Gill, Archita Achanta, John A Kellum, Steven M Handler

Sandra L Kane-Gill, Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261, United States

Sandra L Kane-Gill, Department of Pharmacy, UPMC, Pittsburgh, PA 15213, United States

Archita Achanta, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261, United States

John A Kellum, Center for Critical Care Nephrology, UPMC and University of Pittsburgh, Pittsburgh, PA 15213, United States

John A Kellum, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States

Steven M Handler, Division of Geriatric Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA 15213, United States

Author contributions: Kane-Gill SL and Achanta A wrote the manuscript; Kellum JA and Handler SM provided intellectual contribution to the content and made critical revisions; all authors reviewed and approved the final version of the manuscript.

Supported by The Agency for Healthcare Research and Quality, No. R18HS02420-01.

Conflict-of-interest statement: Sandra L Kane-Gill and Archita Achanta has no conflicts of interest to disclose; John A Kellum has received consulting fees and/or grant support from Astute Medical and Premier; Steven M Handler receives support as the Chief Medical and Scientific Officer for Curavi Health Inc.

Manuscript source: Invited manuscript

Correspondence to: Sandra L Kane-Gill, PharmD, MSc, FCCM, FCCP, Associate Professor, Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, 918 Salk Hall, 3501 Terrace St., Pittsburgh, PA 15261, United States. slk54@pitt.edu
Telephone: +1-412-6245150
Fax: +1-412-6241850

Received: July 19, 2016
Peer-review started: July 21, 2016
First decision: September 5, 2016
Revised: September 17, 2016
Accepted: October 17, 2016
Article in press: October 18, 2016
Published online: November 4, 2016

Abstract

Clinical decision support (CDS) systems with automated alerts integrated into electronic medical records demonstrate efficacy for detecting medication errors (ME) and adverse drug events (ADEs). Critically ill patients are at increased risk for ME, ADEs and serious negative outcomes related to these events. Capitalizing on CDS to detect ME and prevent adverse drug related events has the potential to improve patient outcomes. The key to an effective medication safety surveillance system incorporating CDS is advancing the signals for alerts by using trajectory analyses to predict clinical events, instead of waiting for these events to occur. Additionally, incorporating cutting-edge biomarkers into alert knowledge in an effort to identify the need to adjust medication therapy portending harm will advance the current state of CDS. CDS can be taken a step further to identify drug related physiological events, which are less commonly included in surveillance systems. Predictive models for adverse events that combine patient factors with laboratory values and biomarkers are being established and these models can be the foundation for individualized CDS alerts to prevent impending ADEs.

Key words: Drug-related side effects and adverse reactions; Decision support systems; Clinical; Medication errors; Patient safety; Clinical pharmacy information systems; Intensive care units; Critical care; Adverse drug event; Clinical decision support systems

Core tip: Drug related events in the intensive care unit are associated with higher medical costs and dire patient outcomes. Clinical decision support (CDS) systems are the most important component to aid in adverse drug event (ADE) surveillance and improve in medication safety. Institutions are increasing the use of CDS systems for event detection and CDS systems that combine patient factors with laboratory values, drug information and biomarkers are key to effective ADE prevention.

Kane-Gill SL, Achanta A, Kellum JA, Handler SM. Clinical decision support for drug related events: Moving towards better prevention. *World J Crit Care Med* 2016; 5(4): 204-211 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/204.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.204

INTRODUCTION

Medication errors (ME) occur at median rate of 106 per 1000 patient days in adult intensive care unit (ICU) patients[1]. ME are concerning because of the prospect of impending injury, known as a preventable adverse drug event (ADE). Table 1 provides definitions of drug related events[2-6]. Approximately one-third of ME result in ADEs[7,8]. Examples of ME resulting in ADEs include missed doses, wrong administration technique, duplicate therapies, drug interactions, equipment failure, inadequate monitoring and preparation errors[9].

Critically ill patients are at greater risk for MEs and ADEs compared to non-ICU patients because of the complexity of their drug regimens, sheer volume of medications that they receive, in particular, the volume of intravenous drugs received and acute changes in organ function that can alter the pharmacokinetics[8,10,11]. Prevention of ME and ADEs is important and the significance can resonate to a greater degree in critically ill patients because the severity of ADEs and related outcomes are worse compared to patients in other settings[8,12-14].

Institutions need to commit to an active medication safety surveillance system to detect and prevent drug related events and ensure the safest care possible[15]. Active medication safety surveillance systems use methods that can be categorized as: (1) retrospective approaches that are conducted after drug related events occur and often after the patient is discharged from the hospital; or (2) prospective approaches that capture events in real-time or as close to real-time as possible allowing for interventions to prevent the event from progressing to harm[16]. Voluntary reporting or incident reporting is the most commonly used retrospective surveillance method[17]. Retrospective methods also include non-targeted and targeted medical record reviews. While non-targeted medical record reviews encompass a detailed look at all patient data, a targeted medical record review such as one using a trigger tool focuses on a review of a particular set of patients[18]. Alternatively a targeted medical record review can focus on a particular section of the chart such as the discharge summary[19]. Prospective methods frequently rely on automated systems using clinical decision support (CDS).

CDS systems improve treatment outcomes and patient care by providing clinicians with patient-specific information that is intelligently filtered and presented at relevant times[20]. CDS is defined as "computer software employing a knowledgebase designed for use by a clinician involved in patient care, as a direct aid to clinical decision-making"[21,22]. CDS is typically incorporated as part of a computerized prescriber order entry (CPOE) system and is used to facilitate prevention of ME and ADEs. This system is used to provide feedback to clinicians through alerts and reminders when triggered by certain information available in electronic format[23]. CDS is more effective than voluntary reporting at identifying ADEs with only 1% of those events identified with CDS provided as incident reports[24]. Although overlap between voluntary reporting and automated CDS for ADE detection is reported as high as 13%[25]. Jha *et al*[24] demonstrated that CDS is more efficient than non-targeted medical record review requiring one-fifth less time to complete ADE surveillance: 11 h/wk *vs* 55 h/wk, respectively. It was also noted that while CDS identified slightly fewer events, the ADEs identified were different between methods, asserting that CDS is a necessary adjunct to medical record review. Overall, CDS is faster, less expensive and can identify ADEs not typically detected by clinicians when compared with voluntary reporting[26-31].

Many hospital systems are moving towards adopting electronic health records with meaningful use guidelines and incentives provided by the Center for Medicare and Medicaid Services, and this is enhancing the incorporation of CDS in patient care[32]. A 2015 survey[33] indicated 94.1% of hospitals adopted an electronic health record. This is important because collecting patient data electronically and applying systems to screen these data for ADEs are the initial steps to develop effective safety surveillance[29]. The same survey reports 80.9% of hospitals employ an inpatient CPOE system with CDS, a remarkable 78.2% increase since 2003[33]. In this article, we discuss the effective use of CDS for detecting ME and ADEs, then we will propose ways to use CDS for the prevention of ADEs to further enhance the safety of patients.

Table 1 Definitions of drug related events

Term	Definition
Medication error[2]	"Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. This may include errors in prescribing, distribution, administration and monitoring"
Adverse drug reaction[3]	"Any undesired, unexpected, or unintended outcome associated with drug use"
Drug-related hazardous condition[3,4]	"Is the antecedent to injury or the temporal gap between the identification of an adverse drug reaction and the drug induced injury". It occurs in the presence or absence of a medication error
ADE[5]	"Injury associated with the use of a drug"
Preventable ADEs[6]	"Injury associated with a medication error"
Potential ADEs[5]	"Medication errors with the potential to cause harm, but harm does not actually occur. Potential ADEs can be further described as intercepted and non-intercepted"
Trigger[6]	"Signals or clues used to identify adverse events"

ADE: Adverse drug event.

DETECTION OF ME AND ADES USING CDS

CDS systems are effective at detecting potential ME and alerting prescribers so that appropriate evaluation and action can be taken. Healthcare providers are inconsistent in the identification of ME because of personal knowledge, previous experience and timing of the medication order review; therefore, it is essential to have a reliable surveillance system to aid in identification[34]. Raschke *et al*[35] reported that 44% of ME would have been missed without the use of CDS. Further, a systematic review of studies evaluating CDS alerts generated in response to drug dose selection for patients with acute kidney injury (AKI) demonstrated that 17 out of 19 studies effectively detected ME allowing for intervention with the implementation of CDS[36]. The thought is that detection of ME with CDS due to scenarios such as inappropriate dosing based on age, weight, underlying condition and renal function will allow for intervention and prevention of potential ADEs.

An effective tool to assist with adverse event identification is the Institute for Healthcare Improvement Trigger Tool that contains a specific module focused on ADEs[6]. The trigger tool demonstrates utility as it was used to detect 230 ADEs in 1009 ICU patient days in 79 patients[14]. Interestingly in this study, only the three triggers were responsible for detecting 78% of ADEs. While the trigger tool was evaluated manually, the triggers can be used as the knowledge or signals for the development of automated alerts using CDS.

Classen *et al*[25] developed a clinical event monitor allowing for detection of ADEs using automated trigger or alert. An alert was sent to the physician when there was a potential for an ADE, upon confirmation of the ADE, the medication(s) were stopped, substituted or an antidote was given if needed. In this 18-mo study, 631 of 731 ADEs identified were detected using automated CDS with the majority of ADEs described as moderate or severe.

While research shows that automated CDS alerts are useful in the clinical setting, alerts for ADE detection can be ineffective at preventing harm because alerts are generated with minimal time for intervention or more often alerts are generated after the patient is already experiencing an ADE. This is apparent in the use of the alerts targeted at antidote administration designed for detection and not prevention since the event is already in the midst of treatment. Table 2[17,37-39] provides examples of alerts designed for event detection. Another type of alert geared to detection are abnormal laboratory value alerts with thresholds that exceed the recommended laboratory limit or higher. Alert thresholds with abnormal values higher than acceptable are often targeted at high specificity and low sensitivity, thus possibly reducing alert fatigue but limiting the value in ADE prevention[40]. Still antidote alerts and alerts set with a high abnormal laboratory value thresholds can be useful in understanding the environment, providing an opportunity to assess for causal factors and preventing future events through systematic changes[37]. It can even be beneficial to identify non-preventable ADEs using CDS systems to mitigate the intensity of the injury[9].

ADE PREVENTION CONSIDERATIONS FOR ALERT DEVELOPMENT

The next step in CDS advancement is predicting impending injury/end-organ damage and identifying events using pre-emptive triggers with ample time to intervene. This is the ideal application of a drug related hazardous condition (DRHC), which is the early identification of a drug-related event before the ADE occurs[3,4]. Ten drugs are responsible for over sixty percent of preventable ADEs, including anticoagulants, opiate agonists, and insulin[41]. This suggests that ADEs are not as random as one thinks and it is practical to use this information to build effective CDS. Also, these preventable events are triggered by the progressive decline in laboratory and physiologic markers allowing time for intervention and prevention of harm.

CDS that generates alerts to prevent ADEs utilizing patient laboratory values and drug information has great potential to improve patient outcomes. For example, Moore *et al*[42] suggests to create an alert to prevent a

Table 2 Examples of alerts designed to detect drug-related events

Ref.	Alert designed for detection
Stockwell *et al*[37]	Abnormal laboratory value exceeding recommended upper limit
	Examples
Harinstein *et al*[38]	ACE inhibitor/ARB and patient's serum potassium is > 6 mmol/L
	INR > 4 and on warfarin
	Blood glucose < 40 mg/dL and on antidiabetic agent
	Platelet count < 50000/mm^3 and on a drug that causes thrombocytopenia
Kane-Gill *et al*[39]	Unexpected discontinuation of drug
Kane-Gill *et al*[17,39]	Antidote evaluations such as flumazenil, naloxone, sodium polystyrene, protamine, dextrose 50%; lepirudin use; argatroban use

ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; INR: International normalized ratio.

severe hypoglycemic state by warning when the occurrence of three consecutive low glucose occurs in the presence of a new anti-diabetic medication. The alert should be generated as the glucose levels deteriorate, even before the patient reaches an unacceptable glucose level and experiences mental status changes. Another example of a prevention alert is a patient that does not have a bowel movement in 24 h following initiation of an opioid. In this scenario, there is no need to wait until the patient becomes impacted if a bowel stimulant is begun. Using CDS to generate alerts for ADE prevention have been tested with success[9,35,42-48]. More examples of preventative alerts are provided in Table 3.

MOVING TOWARDS BETTER ADE PREVENTION

Percent change in laboratory values instead of absolute cut points and trajectory analysis

Movement in the area of ADE prevention requires clinicians to change the mindset of specific cut points in the laboratory values and consider percent change and percent change over time when appropriate. An example of this is identifying drug induced AKI. Previous CDS alerts were built on an absolute serum creatinine value of $\geqslant$ 1.5 mg/dL or an absolute increase in serum creatinine of 0.5 mg/dL[49,50]. This approach does not account for the patient's baseline serum creatinine and is likely to miss important events in patients with low baselines (*e.g.*, young women, vegetarians) or result in false positives in patients with underlying chronic kidney disease. Others have applied knowledge to signal an alert at a 50% increase in serum creatinine from baseline; however, that may miss small changes in serum creatinine and miss opportunities for early intervention[51]. Recent alerts are designed on the Kidney Disease Improving Global Outcomes (KDIGO) criteria or the serum creatinine component of the KDIGO criteria when urine output is unavailable[52,53]. According to the KDIGO guidelines, a patient is classified as AKI stage 1 if there is a 0.3 mg/dL increase in serum creatinine in 48 h or an increase in serum increase of 1.5-1.9 times baseline in 7 d. This abrupt change considers time and baseline values providing a more detailed assessment of kidney function and opportunities for early alert and interventions. If a baseline serum creatinine is unavailable, then there are methods of estimation to consider[54]. Stage 2 and Stage 3 AKI alerts per KDIGO may not provide opportunity for prevention but appropriate management at this point may mitigate severity and prevent permanent injury.

The concept of trajectory analysis applied to alerts would allow for a pre-emptive alert to be generated when there is a percent change in the laboratory value over a specified period. This would predict that the laboratory value would eventually be out of an acceptable range before it actually reaches the unacceptable range. Signals for alerts are set to a triglyceride of > 400 mg/dL (unacceptable range) when receiving propofol. There would be an advantage to scanning for a percent increase over a couple of days instead of waiting for the absolute number to be achieved. Importantly, this could be applied to abnormal international normalized ratio (INR) values for patient receiving warfarin. Waiting until an INR of 4 or 5 occurs before being alerted could waste valuable time in preventing an ADE, instead a 20% rise daily over 3 d could be a preventative trigger. This concept could also be applied to drug concentrations. The key to the successful use a trajectory analysis will be supporting the percent change as clinically meaningful by selecting percent changes relative to the occurrence of an ADE. Table 4 provides an example of using percent change for drug-induced thrombocytopenia instead of applying an absolute cut point[38].

Biomarkers

The use of DRHCs or biochemical, physiologic, or clinical status change caused by medications, portending further injury is sometimes difficult when our biomarkers lag behind the actual injury[3,4]. This is true in the case of AKI. Generating an alert after identifying a spike in serum creatinine may be too late as there is already significant damage and loss of kidney function[55].

Cystatin C, is a better detector of kidney injury when compared with serum creatinine and some research suggests that serum cystatin C can discriminate between patients that develop AKI and patients whose serum creatinine will return to baseline in 48 h[55]. This biomarker shows promise for early detection and earlier intervention. Additionally, a study by Frazee *et al*[56] shows that biomarkers can also improve drug dosing. This study showed that vancomycin dosing in the ICU can be improved 2.5 fold when using cystatin C and serum creatinine to estimate GFR as opposed to just serum creatinine alone[56]. Interestingly, some biomarkers can also identify the type of kidney injury and the location of damage. If these are included in the signals for alert generations, clinicians will be able to

Table 3 Examples of preventative alerts

Ref.	Drug related hazardous condition for alert detection	Adverse drug event prevention	Criteria for prevention alert
Rommers *et al*[43]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Elderly patient who is not taking a PPI and is started on an NSAID
Moore *et al*[42]	Hypoglycemia	Mental status changes	Receiving a new antidiabetic agent and 3 consecutive low glucose results that are steadily declining over a period of time
Moore *et al*[42]	Hypokalemia	Dysrhythmia	Drug started causing hypokalemia + potassium level under 3.8 mEq/L
Moore *et al*[42]	Thrombocytopenia	Bleed	Drug started causing thrombocytopenia and platelets slowly decrease over 50000/mm^3 within 4 d
Moore *et al*[42]	Hyperkalemia	Dysrhythmia	Drug started causing hyperkalemia + potassium level over 5.5 mEq/L and increasing slowly over 72 h
Raschke *et al*[35]	C. difficile	Permanent gastrointestinal disorders (*i.e.*, irritable bowel syndrome, colectomy)	Antidiarrheal and recent aggressive antibiotic therapy OR history of Clostiridum difficile
Rommers *et al*[43] and Silverman *et al*[44]	Before DRHC occurs-eventually digoxin level elevated	Dysrhythmia, confusion	Patient with 3 consecutive increasing serum creatinine levels and also on digoxin therapy (or other renally cleared drugs would apply such as metformin, enoxaparin, vancomycin)
Rommers *et al*[43]	Constipation	Bowel obstruction	Narcotic started recently and patient has a history of constipation or narcotic started recently and patient has not had a bowel movement in over 24 h
Van Doormaal *et al*[45]	Constipation	Bowel obstruction	Opioid prescribed without a co-prescription of a stimulant laxative
Van Doormaal *et al*[45]	KDIGO stage 1 AKI-in the future biomarkers may be the early sign of AKI before SCr rise	KDIGO stage 3 AKI	Sulfonamide urea derivate is prescribed and the patient has a creatinine clearance of less than 10 mL/min
DiPoto *et al*[46]	Before a DRHC occurs-eventually hemoglobin drop	Bleed	Patient has epidural and started on an anticoagulant or antiplatelet
DiPoto *et al*[46]	Sedation	Mental status changes	Fentanyl patch and no documented history of long-acting opioid use
Silverman *et al*[44] and Jha *et al*[47]	ALT rising	Hepatic failure	Hepatotoxic drug and ALT increase by 20%
Silverman *et al*[44] and Jha *et al*[47]	Osmolarity increasing	Mental status changes, risk of death	Lorazepam use and osmolarity increasing

DRHC: Drug related hazardous condition; KDIGO: Kidney Disease Improving Global Outcomes; AKI: Acute kidney injury; ALT: Alanine aminotransferase.

make a quicker treatment decisions.

Another biomarker panel that is currently available in clinical practice is urinary tissue inhibitor of metalloproteinase (TIMP-2) and insulin-like growth factor-binding protein (IGFBP7). This combination of biomarkers available in Nephrocheck™ predict patients at risk for developing AKI within 12 to 24 h following sample collection[57]. This makes TIMP-2/IGFBP7 a valuable marker to consider when designing preventative alerts in the future as we learn about the impact of using these biomarkers on patient care.

Drug induced liver injury also continues to be problematic, and clinicians can benefit from early identification of this injury. Research continues to find biomarkers to indicate drug injury such as microRNAs and serum metabolites presenting as better indicators than ALT[58]. Biomarkers, such as the ones discussed above, can be employed in the future to guide clinicians in making early interventions with CDS alerts.

Drug combinations

The risk of an ADE may change when drugs are combined. Non-critically ill children receiving aminoglycosides or other nephrotoxins for more than 3 d in the hospital are at risk for drug induced AKI[59]. AKI can be prevented by using CDS to alert clinicians when patients receive 3 or more nephrotoxins followed by close monitoring of serum creatinine[59]. This CDS application resulted in improved patient outcomes including a 42% decrease in the observance of AKI intensity[60]. Future studies need to test this CDS in critically ill and non-critically ill adults. Constructing alerts based on thoughtful consideration of high-risk drug combinations has the potential to prevent ADEs.

Drug induced physiologic events

As noted, the majority of CDS for ADE prevention includes abnormal laboratory concentrations as the trigger for an alert. Less frequently, hospitals report surveillance of drug-induced physiologic events[17]. In general, we have created better CDS to identify patients undergoing clinical deterioration or at the first signs of sepsis by incorporating blood pressure, heart rate and respiratory rate into alerts[61,62]. Physiologic parameters such as blood pressure are drug induced and can be the next set of preventative ADE alerts we develop to improve patient care[3].

Predictive analytics and forecasting models

Using a holistic approach to predict the risk of disease

Table 4 Alerts to predict an impeding adverse drug event using percent changed in the laboratory value

Ref.	Drug related hazardous condition for alert detection	Adverse drug event preventing	Criteria for prevention alert
Harinstein *et al*[38]	Platelet drop	Bleed	⩾ 50% decrease in platelets between most recent and second most recent platelet count
Harinstein *et al*[38]	Platelet drop	Bleed	2 consecutive decreases in platelets with ⩾ 25% difference between the third most recent and the most recent platelet count

Table 5 Summary of proposed approaches to developing clinical decision support to prevent adverse drug events

Proposed approach	Description
Trajectory analysis	Identify laboratory values as they are on the incline or decline before they reach a critical value
Biomarkers	Use biomarkers that identify patients at risk for organ damage
Drug combinations	Generate alerts for drug combinations that place the patient at risk for drug-induced injury
Drug induced physiologic events	Add alerts for possible drug induced alterations in physiologic parameters to clinical decision support
Predictive analytics and forecasting models	Develop models that predict possible drug induced injury based on risk factors and use this information for advanced alerts using machine learning for adaptive response

may be the best way to prevent unfavorable health outcomes, such as ADEs. In the case of AKI, many predictive models have been developed, though not necessarily in the critical care setting where there is a need[63,64]. Variables included in predictive models are age, gender, race, co-morbidities and acute conditions. Combining known patient risk factors with laboratory data and biomarkers would make an ideal predictive model and aid in preventative ADE alert development. This model also could employ machine learning techniques and incorporate population/region specific data to better predict patient risk and outcomes to accommodate adaptive changes (Table 5).

CONCLUSION

The concern for harmful outcomes associated ADEs, especially preventable ADEs makes reliable and effective CDS systems a necessary addition for surveillance, especially for critically ill patients. CDS systems can be used to further improve patient outcomes when directed at preventing ADEs and moving beyond detection. CDS designed to generate alerts portending injury allows providers time for intervention. Studies designed to maximize the benefit of preventative alerts and determine the impact on patient outcomes are needed.

REFERENCES

1 **Kane-Gill S**, Weber RJ. Principles and practices of medication safety in the ICU. *Crit Care Clin* 2006; **22**: 273-290, vi [PMID: 16678000 DOI: 10.1016/j.ccc.2006.02.005]
2 **Nebeker JR**, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004; **140**: 795-801 [PMID: 15148066 DOI: 10.7326/0003-4819-140-10-200405180-00017]
3 **Kane-Gill SL**, LeBlanc JM, Dasta JF, Devabhakthuni S. A multicenter study of the point prevalence of drug-induced hypotension in the ICU. *Crit Care Med* 2014; **42**: 2197-2203 [PMID: 25014064 DOI: 10.1097/CCM.0000000000000499]
4 **Kane-Gill SL**, Dasta JF, Schneider PJ, Cook CH. Monitoring abnormal laboratory values as antecedents to drug-induced injury. *J Trauma* 2005; **59**: 1457-1462 [PMID: 16394922 DOI: 10.1097/01.ta.0000196009.42623.50]
5 **Kane-Gill SL**, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. *Crit Care Med* 2010; **38**: S83-S89 [PMID: 20502179 DOI: 10.1097/CCM.0b013e3181dd8364]
6 **Institute for Healthcare Improvement**. IHI Global Trigger Tool for Measuring Adverse Events, 2016. Available from: URL: http://www.ihi.org/resources/pages/tools/ihiglobaltriggertoolformeasuringaes.aspx
7 **Rothschild JM**, Churchill W, Erickson A, Munz K, Schuur JD, Salzberg CA, Lewinski D, Shane R, Aazami R, Patka J, Jaggers R, Steffenhagen A, Rough S, Bates DW. Medication errors recovered by emergency department pharmacists. *Ann Emerg Med* 2010; **55**: 513-521 [PMID: 20005011 DOI: 10.1016/j.annemergmed.2009.10.012]
8 **Cullen DJ**, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit Care Med* 1997; **25**: 1289-1297 [PMID: 9267940 DOI: 10.1097/00003246-199708000-00014]
9 **Agency for Healthcare Research and Quality**. Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs. Rockville, MD: Report No.: AHRQ Publication Number 01-0020. Available from: URL: http://archive.ahrq.gov/research/findings/factsheets/errors-safety/aderia/ade.html
10 **Kane-Gill SL**, Kirisci L, Verrico MM, Rothschild JM. Analysis of risk factors for adverse drug events in critically ill patients*. *Crit Care Med* 2012; **40**: 823-828 [PMID: 22036859 DOI: 10.1097/CCM.0b013e318236f473]
11 **Camiré E**, Moyen E, Stelfox HT. Medication errors in critical care: risk factors, prevention and disclosure. *CMAJ* 2009; **180**: 936-943 [PMID: 19398740 DOI: 10.1503/cmaj.080869]
12 **Kane-Gill SL**, Kowiatek JG, Weber RJ. A comparison of voluntarily reported medication errors in intensive care and general care units. *Qual Saf Health Care* 2010; **19**: 55-59 [PMID: 20172884 DOI: 10.1136/qshc.2008.027961]
13 **Latif A**, Rawat N, Pustavoitau A, Pronovost PJ, Pham JC. National study on the distribution, causes, and consequences of voluntarily reported medication errors between the ICU and non-ICU settings. *Crit Care Med* 2013; **41**: 389-398 [PMID: 23263619 DOI: 10.1097/CCM.0b013e318274156a]
14 **Seynaeve S**, Verbrugghe W, Claes B, Vandenplas D, Reyntiens D, Jorens PG. Adverse drug events in intensive care units: a cross-sectional study of prevalence and risk factors. *Am J Crit Care* 2011; **20**: e131-e140 [PMID: 22045149 DOI: 10.4037/ajcc2011818]
15 **Institute of Medicine**. Preventing Medication Errors. Washington, DC: National Academies Press, 2007. Available from: URL: http://www.nap.edu/read/11623/chapter/1#ix
16 **Stockwell DC**, Kane-Gill SL. Developing a patient safety surveillance system to identify adverse events in the intensive care unit. *Crit Care Med* 2010; **38**: S117-S125 [PMID: 20502165 DOI:

10.1097/CCM.0b013e3181dde2d9]
17 **Kane-Gill SL**, Devlin JW. Adverse drug event reporting in intensive care units: a survey of current practices. *Ann Pharmacother* 2006; **40**: 1267-1273 [PMID: 16849619 DOI: 10.1345/aph.1H088]
18 **Rozich JD**, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care* 2003; **12**: 194-200 [PMID: 12792009 DOI: 10.1136/qhc.12.3.194]
19 **Anthes AM**, Harinstein LM, Smithburger PL, Seybert AL, Kane-Gill SL. Improving adverse drug event detection in critically ill patients through screening intensive care unit transfer summaries. *Pharmacoepidemiol Drug Saf* 2013; **22**: 510-516 [PMID: 23440931 DOI: 10.1002/pds.3422]
20 **Osheroff JA**, Teich JM, Middleton B, Steen EB, Wright A, Detmer DE. A roadmap for national action on clinical decision support. *J Am Med Inform Assoc* 2007; **14**: 141-145 [PMID: 17213487 DOI: 10.1197/jamia.M2334]
21 **Braden BJ**, Corritore C, McNees P. Computerized decision support systems: implications for practice. *Stud Health Technol Inform* 1997; **46**: 300-304 [PMID: 10175414]
22 **Sim I**, Gorman P, Greenes RA, Haynes RB, Kaplan B, Lehmann H, Tang PC. Clinical decision support systems for the practice of evidence-based medicine. *J Am Med Inform Assoc* 2001; **8**: 527-534 [PMID: 11687560 DOI: 10.1136/jamia.2001.0080527]
23 **Hripcsak G**, Clayton PD, Jenders RA, Cimino JJ, Johnson SB. Design of a clinical event monitor. *Comput Biomed Res* 1996; **29**: 194-221 [PMID: 8812070 DOI: 10.1006/cbmr.1996.0016]
24 **Jha AK**, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, Burdick E, Seger DL, Vander Vliet M, Bates DW. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; **5**: 305-314 [PMID: 9609500 DOI: 10.1136/jamia.1998.0050305]
25 **Classen DC**, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA* 1991; **266**: 2847-2851 [PMID: 1942452 DOI: 10.1001/jama.1991.03470200059035]
26 **Levy M**, Azaz-Livshits T, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized surveillance of adverse drug reactions in hospital: implementation. *Eur J Clin Pharmacol* 1999; **54**: 887-892 [PMID: 10027665 DOI: 10.1007/s002280050571]
27 **Murff HJ**, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform* 2003; **36**: 131-143 [PMID: 14552854 DOI: 10.1016/j.jbi.2003.08.003]
28 **Morimoto T**, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care* 2004; **13**: 306-314 [PMID: 15289635 DOI: 10.1136/qhc.13.4.306]
29 **Bates DW**, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *J Am Med Inform Assoc* 2003; **10**: 115-128 [PMID: 12595401 DOI: 10.1197/jamia.M1268]
30 **Handler SM**, Altman RL, Perera S, Hanlon JT, Studenski SA, Bost JE, Saul MI, Fridsma DB. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. *J Am Med Inform Assoc* 2007; **14**: 451-458 [PMID: 17460130 DOI: 10.1197/jamia.M2369]
31 **Tegeder I**, Levy M, Muth-Selbach U, Oelkers R, Neumann F, Dormann H, Azaz-Livshits T, Criegee-Rieck M, Schneider HT, Hahn E, Brune K, Geisslinger G. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. *Br J Clin Pharmacol* 1999; **47**: 557-564 [PMID: 10336581 DOI: 10.1046/j.1365-2125.1999.00926.x]
32 **Health Information Technology**. Meaningful Use Regulations, 2015. Available from: URL: http://www.healthit.gov/policy-researchers-implementers/meaningful-use-regulations
33 **Pedersen CA**, Schneider PJ, Scheckelhoff DJ. ASHP national survey of pharmacy practice in hospital settings: Prescribing and transcribing-2013. *Am J Health Syst Pharm* 2014; **71**: 924-942 [PMID: 24830997 DOI: 10.2146/ajhp140032]
34 **Evans RS**, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother* 1994; **28**: 523-527 [PMID: 8038479]
35 **Raschke RA**, Gollihare B, Wunderlich TA, Guidry JR, Leibowitz AI, Peirce JC, Lemelson L, Heisler MA, Susong C. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. *JAMA* 1998; **280**: 1317-1320 [PMID: 9794309 DOI: 10.1001/jama.280.15.1317]
36 **Tawadrous D**, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX. Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. *Am J Kidney Dis* 2011; **58**: 903-914 [PMID: 21944664 DOI: 10.1053/j.ajkd.2011.07.022]
37 **Stockwell DC**, Kirkendall E, Muething SE, Kloppenborg E, Vinodrao H, Jacobs BR. Automated adverse event detection collaborative: electronic adverse event identification, classification, and corrective actions across academic pediatric institutions. *J Patient Saf* 2013; **9**: 203-210 [PMID: 24257063 DOI: 10.1097/PTS.0000000000000055]
38 **Harinstein LM**, Kane-Gill SL, Smithburger PL, Culley CM, Reddy VK, Seybert AL. Use of an abnormal laboratory value-drug combination alert to detect drug-induced thrombocytopenia in critically Ill patients. *J Crit Care* 2012; **27**: 242-249 [PMID: 22520497 DOI: 10.1016/j.jcrc.2012.02.014]
39 **Kane-Gill SL**, Bellamy CJ, Verrico MM, Handler SM, Weber RJ. Evaluating the positive predictive values of antidote signals to detect potential adverse drug reactions (ADRs) in the medical intensive care unit (ICU). *Pharmacoepidemiol Drug Saf* 2009; **18**: 1185-1191 [PMID: 19728294 DOI: 10.1002/pds.1837]
40 **Kilickaya O**, Schmickl C, Ahmed A, Pulido J, Onigkeit J, Kashani K, Gajic O, Herasevich V, Pickering B. Customized reference ranges for laboratory values decrease false positive alerts in intensive care unit patients. *PLoS One* 2014; **9**: e107930 [PMID: 25233485 DOI: 10.1371/journal.pone.0107930]
41 **Winterstein AG**, Hatton RC, Gonzalez-Rothi R, Johns TE, Segal R. Identifying clinically significant preventable adverse drug events through a hospital's database of adverse drug reaction reports. *Am J Health Syst Pharm* 2002; **59**: 1742-1749 [PMID: 12298112]
42 **Moore C**, Li J, Hung CC, Downs J, Nebeker JR. Predictive value of alert triggers for identification of developing adverse drug events. *J Patient Saf* 2009; **5**: 223-228 [PMID: 22130215 DOI: 10.1097/PTS.0b013e3181bc05e5]
43 **Rommers MK**, Teepe-Twiss IM, Guchelaar HJ. A computerized adverse drug event alerting system using clinical rules: a retrospective and prospective comparison with conventional medication surveillance in the Netherlands. *Drug Saf* 2011; **34**: 233-242 [PMID: 21332247 DOI: 10.2165/11536500-000000000-00000]
44 **Silverman JB**, Stapinski CD, Huber C, Ghandi TK, Churchill WW. Computer-based system for preventing adverse drug events. *Am J Health Syst Pharm* 2004; **61**: 1599-1603 [PMID: 15372836]
45 **van Doormaal JE**, Rommers MK, Kosterink JG, Teepe-Twiss IM, Haaijer-Ruskamp FM, Mol PG. Comparison of methods for identifying patients at risk of medication-related harm. *Qual Saf Health Care* 2010; **19**: e26 [PMID: 20584702 DOI: 10.1136/qshc.2009.033324]
46 **DiPoto JP**, Buckley MS, Kane-Gill SL. Evaluation of an automated surveillance system using trigger alerts to prevent adverse drug events in the intensive care unit and general ward. *Drug Saf* 2015; **38**: 311-317 [PMID: 25711668 DOI: 10.1007/s40264-015-0272-1]
47 **Jha AK**, Laguette J, Seger A, Bates DW. Can surveillance systems identify and avert adverse drug events? A prospective evaluation of a commercial application. *J Am Med Inform Assoc* 2008; **15**: 647-653 [PMID: 18579834 DOI: 10.1197/jamia.M2634]
48 **Peterson JF**, Williams DH, Seger A, Gandhi TK, Bates DW. Drug-lab triggers have the potential to prevent adverse drug events in outpatients. *J Am Med Inform Assoc* 2002; **9**: s39-s40 [DOI: 10.1197/jamia.M1223]
49 **Leung AA**, Schiff G, Keohane C, Amato M, Simon SR, Cadet B, Coffey M, Kaufman N, Zimlichman E, Seger DL, Yoon C, Bates DW. Impact of vendor computerized physician order entry on patients with renal impairment in community hospitals. *J Hosp Med*

2013; **8**: 545-552 [PMID: 24101539 DOI: 10.1002/jhm.2072]
50 **Rind DM**, Safran C, Phillips RS, Wang Q, Calkins DR, Delbanco TL, Bleich HL, Slack WV. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med* 1994; **154**: 1511-1517 [PMID: 8018007 DOI: 10.1001/archinte.1994.00420130107014]
51 **Flynn N**, Dawnay A. A simple electronic alert for acute kidney injury. *Ann Clin Biochem* 2015; **52**: 206-212 [PMID: 24763854 DOI: 10.1177/0004563214534832]
52 **James MT**, Hobson CE, Darmon M, Mohan S, Hudson D, Goldstein SL, Ronco C, Kellum JA, Bagshaw SM. Applications for detection of acute kidney injury using electronic medical records and clinical information systems: workgroup statements from the 15(th) ADQI Consensus Conference. *Can J Kidney Health Dis* 2016; **3**: 9 [PMID: 26925245 DOI: 10.1186/s40697-016-0100-2]
53 **Kellum JA**, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013; **17**: 204 [PMID: 23394211 DOI: 10.1186/cc11454]
54 **Ahmed A**, Vairavan S, Akhoundi A, Wilson G, Chiofolo C, Chbat N, Cartin-Ceba R, Li G, Kashani K. Development and validation of electronic surveillance tool for acute kidney injury: A retrospective analysis. *J Crit Care* 2015; **30**: 988-993 [PMID: 26070247 DOI: 10.1016/j.jcrc.2015.05.007]
55 **Gobe GC**, Coombes JS, Fassett RG, Endre ZH. Biomarkers of drug-induced acute kidney injury in the adult. *Expert Opin Drug Metab Toxicol* 2015; **11**: 1683-1694 [PMID: 26548752 DOI: 10.1517/17425255.2015.1083011]
56 **Frazee EN**, Rule AD, Herrmann SM, Kashani KB, Leung N, Virk A, Voskoboev N, Lieske JC. Serum cystatin C predicts vancomycin trough levels better than serum creatinine in hospitalized patients: a cohort study. *Crit Care* 2014; **18**: R110 [PMID: 24887089 DOI: 10.1186/cc13899]
57 **Gunnerson KJ**, Shaw AD, Chawla LS, Bihorac A, Al-Khafaji A, Kashani K, Lissauer M, Shi J, Walker MG, Kellum JA. TIMP2• IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. *J Trauma Acute Care Surg* 2016; **80**: 243-249 [PMID: 26816218 DOI: 10.1097/TA.0000000000000912]
58 **Weiler S**, Merz M, Kullak-Ublick GA. Drug-induced liver injury: the dawn of biomarkers? *F1000Prime Rep* 2015; **7**: 34 [PMID: 25926985 DOI: 10.12703/P7-34]
59 **Goldstein SL**, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, Kirkendall ES. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. *Kidney Int* 2016; **90**: 212-221 [PMID: 27217196 DOI: 10.1016/j.kint.2016.03.031]
60 **Goldstein SL**, Kirkendall E, Nguyen H, Schaffzin JK, Bucuvalas J, Bracke T, Seid M, Ashby M, Foertmeyer N, Brunner L, Lesko A, Barclay C, Lannon C, Muething S. Electronic health record identification of nephrotoxin exposure and associated acute kidney injury. *Pediatrics* 2013; **132**: e756-e767 [PMID: 23940245 DOI: 10.1542/peds.2013-0794]
61 **Hayden GE**, Tuuri RE, Scott R, Losek JD, Blackshaw AM, Schoenling AJ, Nietert PJ, Hall GA. Triage sepsis alert and sepsis protocol lower times to fluids and antibiotics in the ED. *Am J Emerg Med* 2016; **34**: 1-9 [PMID: 26386734 DOI: 10.1016/j.ajem.2015.08.039]
62 **Sawyer AM**, Deal EN, Labelle AJ, Witt C, Thiel SW, Heard K, Reichley RM, Micek ST, Kollef MH. Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. *Crit Care Med* 2011; **39**: 469-473 [PMID: 21169824 DOI: 10.1097/CCM.0b013e318205df85]
63 **Sutherland SM**, Chawla LS, Kane-Gill SL, Hsu RK, Kramer AA, Goldstein SL, Kellum JA, Ronco C, Bagshaw SM. Utilizing electronic health records to predict acute kidney injury risk and outcomes: workgroup statements from the 15(th) ADQI Consensus Conference. *Can J Kidney Health Dis* 2016; **3**: 11 [PMID: 26925247 DOI: 10.1186/s40697-016-0099-4]
64 **Cheungpasitporn W**, Kashani K. Electronic Data Systems and Acute Kidney Injury. *Contrib Nephrol* 2016; **187**: 73-83 [PMID: 26882100 DOI: 10.1159/000442367]

P- Reviewer: Chan CH, Slomiany BL **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.212

World J Crit Care Med 2016 November 4; 5(4): 212-218
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Case Control Study

Interprofessional, multiple step simulation course improves pediatric resident and nursing staff management of pediatric patients with diabetic ketoacidosis

Linnea M Larson-Williams, Amber Q Youngblood, Dawn Taylor Peterson, J Lynn Zinkan, Marjorie L White, Hussein Abdul-Latif, Leen Matalka, Stephen N Epps, Nancy M Tofil

Linnea M Larson-Williams, Department of Pediatric Endocrinology, Georgia Regents University, Augusta, GA 30912, United States

Amber Q Youngblood, J Lynn Zinkan, Children's of Alabama, Pediatric Simulation Center, Birmingham, AL 35233, United States

Dawn Taylor Peterson, Department of Medical Education, University of Alabama School of Medicine, Birmingham, AL 35233, United States

Marjorie L White, Department of Pediatric Emergency Medicine, Office of Interprofessional Simulation, University of Alabama at Birmingham, Birmingham, AL 35233, United States

Hussein Abdul-Latif, Department of Pediatric Endocrinology, University of Alabama at Birmingham, Birmingham, AL 35233, United States

Leen Matalka, Pediatric Residency, University of Alabama at Birmingham, Birmingham, AL 35233, United States

Stephen N Epps, Department of Pediatrics, Louisiana State University, Baton Rouge, LA 70803, United States

Nancy M Tofil, Department of Pediatric Critical Care, University of Alabama in Birmingham, Birmingham, AL 35233, United States

Author contributions: Larson-Williams LM led all simulation sessions, designed the initial simulation, knowledge tests and assisted in manuscript writing and editing; Youngblood AQ assisted with simulations, manuscript writing and editing; Peterson DT assisted with study design, manuscript editing; White ML assisted with simulation sessions, study design, manuscript editing; Abdul-Latif H assisted with simulation design, knowledge tests and manuscript editing; Matalka L and Epps SN assisted with data review and statistics and manuscript writing; Tofil NM was senior advisor overseeing study design, simulation session, statistical analysis and manuscript writing and editing; all authors contributed to this paper.

Supported by A University of Alabama at Birmingham Department of Pediatrics Founders Fund Grant.

Institutional review board statement: This study was approved by the ethics committee at University of Alabama at Birmingham.

Informed consent statement: All subjects gave informed consent.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Technical appendix, statistical code and dataset available from the corresponding author at ntofil@peds.uab.edu.

Manuscript source: Invited manuscript

Correspondence to: Nancy M Tofil, MD, Department of Pediatric Critical Care, University of Alabama in Birmingham, 1600 5th Ave South CPPI 102, Birmingham, AL 35233, United States. ntofil@peds.uab.edu
Telephone: +1-205-6389387
Fax: +1-205-9756505

Received: May 17, 2016
Peer-review started: May 17, 2016

First decision: July 5, 2016
Revised: July 20, 2016
Accepted: August 6, 2016
Article in press: August 8, 2016
Published online: November 4, 2016

Abstract

AIM

To investigate the use of a multidisciplinary, longitudinal simulation to educate pediatric residents and nurses on management of pediatric diabetic ketoacidosis.

METHODS

A multidisciplinary, multiple step simulation course was developed by faculty and staff using a modified Delphi method from the Pediatric Simulation Center and pediatric endocrinology department. Effectiveness of the simulation for the residents was measured with a pre- and post-test and a reference group not exposed to simulation. A follow up post-test was completed 3-6 mo after the simulation. Nurses completed a survey regarding the education activity.

RESULTS

Pediatric and medicine-pediatric residents (n = 20) and pediatric nurses (n = 25) completed the simulation course. Graduating residents (n = 16) were used as reference group. Pretest results were similar in the control and intervention group (74% ± 10% *vs* 76% ± 15%, P = 0.658). After completing the intervention, participants improved in the immediate post-test in comparison to themselves and the control group (84% ± 12% post study; P < 0.05). The 3-6 mo follow up post-test results demonstrated knowledge decay when compared to their immediate post-test results (78% ± 14%, P = 0.761). Residents and nurses felt the inter-disciplinary and longitudinal nature of the simulation helped with learning.

CONCLUSION

Results suggest a multidisciplinary, longitudinal simulation improves immediate post-intervention knowledge but important knowledge decay occurs, future studies are needed to determine ways to decrease this decay.

Key words: Interdisciplinary; Education; Simulation; Diabetic ketoacidosis; Pediatrics

Core tip: Our paper describes how an interprofessional simulation improved the understanding of the medically complex disorder of pediatric diabetic ketoacidosis (DKA). This was shown in our data collection both by improvements in test scores from pre-simulation to post-simulation, as well as when compared to the control group. Few studies have looked at simulation as an educational tool for DKA. Our simulation course identified gaps in knowledge, communication, and patient care. Therefore, demonstrating that interprofessional simulation is a useful tool to teach a team based approach and focus on communication between nursing staff and physicians when taking care of critically ill children.

Larson-Williams LM, Youngblood AQ, Peterson DT, Zinkan JL, White ML, Abdul-Latif H, Matalka L, Epps SN, Tofil NM. Interprofessional, multiple step simulation course improves pediatric resident and nursing staff management of pediatric patients with diabetic ketoacidosis. *World J Crit Care Med* 2016; 5(4): 212-218 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/212.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.212

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life threatening condition that results from a lack of insulin and one of the more common causes of pediatric intensive care unit (ICU) admissions[1-4]. Without insulin, counter-regulatory hormones increase leading to an accelerated, potentially fatal, catabolic state[5-7]. If treatment including insulin, electrolyte replacement, and fluids are administered appropriately, the catabolic process can be reversed[6-8]. DKA occurs in approximately 29% of patients with new onset type 1 diabetes mellitus and in 10% of patients with new onset type 2 diabetes mellitus[4,6]. Mortality related to DKA is less than 5% with 90% due to cerebral edema[1,3,4,6,7]. Other complications that increase risk for morbidity and mortality include electrolyte abnormalities, acute renal failure and acute pancreatitis[1,5,7]. In order to decrease these, early recognition and appropriate ICU management is required[4,6-9].

Resident education of DKA largely consists of lectures, reading articles, and informal instruction from pediatric faculty and senior residents. Nursing education is less formal, often through self-directed learning, computer-based training and informal bedside teaching. Simulation based learning is an effective tool to supplement traditional teaching methods due to it providing a safe learning environment learners, incorporating aspects of adult learning theory and promoting multidisciplinary learning[10-15].

In an effort to standardize DKA education and focus on interprofessional teaching, we created a multistep, longitudinal simulation course. The scenario begins at diagnosis of DKA, proceeds through a standardized treatment course including management of fluids, insulin, electrolyte replacement, monitoring for complications, and finishes when the patient transitions to subcutaneous insulin. Our primary hypothesis is that pediatric residents exposed to this multidisciplinary, longitudinal simulation improve their DKA knowledge compared to our reference group, graduating senior

residents not exposed to the intervention. Our secondary hypothesis is that by conducting the intervention in an inter-disciplinary fashion, both nurses and physicians will better understand each other's roles in the care of patients with DKA.

MATERIALS AND METHODS

Subjects

Pediatric and combined medicine/pediatric residents participated in the simulation course as part of their scheduled endocrinology rotation and were invited during their elective rotations if they were not already scheduled for endocrinology. Graduating third year pediatric residents and fourth year medicine/pediatric residents prior to initiation of this course were the reference group. Pediatric nurses from the intensive care unit and step down unit participated with the residents. Sessions were conducted approximately once a month from September 2013 through March 2015.

Description of protocol/scenario development

The research was approved by Institutional Review Board at the University of Alabama in Birmingham. A scripted scenario was developed by simulation and endocrinology experts by a modified Delphi process to provide a uniform educational experience for our participants. An accelerated time sequence was used. The scenario was a patient with new onset diabetes in DKA. Once the diagnosis was confirmed, a plan of care was constructed with the nurses to include patient monitoring, administration of medications, correction of electrolyte imbalances, and schedule for lab draws. Participants were required to manage electrolyte abnormalities, administer appropriate fluid management, and monitor glycemic control while on an insulin drip. All participants were confronted with development of cerebral edema during the care of their patient. The simulated patient's response was based on the provider's reactions to changes in labs and clinical course. Actions performed were documented using a structured checklist created by endocrinologists. Once the patient met appropriate criteria, the resident provided instruction to the nurses regarding transition to subcutaneous insulin. Following the case, there was a participant-centered debriefing led by a content expert in pediatric endocrinology and a simulation nurse educator. Key points in the diagnosis and management of DKA were covered.

Outcome measures

The effectiveness of the simulation for the residents was measured based on a pre- and post-test created by endocrinology and educational experts. Participants completed a pre-test prior to the simulation (Table 1). The same post-test was given immediately after completion of the simulation and a second retention post-test was administered three to six months after the course. The reference group completed the same test in their last month of residency. The nursing staff completed a survey following the conclusion of the scenario and debriefing session.

Statistical analysis

Statistical analysis was performed using SPSS software (Chicago, IL). A χ^2 test evaluated for categorical differences between the intervention and reference groups of residents. Paired and unpaired *t* tests compared test scores both within the intervention group and reference group respectively. A *P* value of < 0.05 was considered statistically significant. Feedback comments were evaluated for common themes.

RESULTS

Forty-five subjects participated including twenty residents and twenty-five nurses. Seventeen monthly sessions were conducted. The reference group was 72% (16/22) of senior residents in their last month of training (June 2013). No personal history of diabetes mellitus type 1 was reported. Only one participant cared for a family member with diabetes. Exposure to these patients prior to the simulation was not significantly different amongst the two populations. Table 2 shows the demographics.

There was no statistical difference between the reference group's knowledge assessment test and the intervention group's pre-test, 75% ± 10% *vs* 77% ± 15%, $P = 0.66$. Figure 1 shows the assessment scores of the intervention group at the three time periods tests; pre-test, initial post-test and 4-6 mo follow-up test. There was a significant improvement after the intervention but knowledge decay at the follow-up assessment. In addition, the intervention group had significant improvement in their test scores when compared to the reference group after the intervention (75% ± 10% *vs* 84% ± 12%, $P = 0.02$). While overall score did not improve between the pre-test and the second post-test in the simulation group, specific questions involving fluid management and cerebral edema noted sustained improvement. This improvement is also noted when compared to the reference group.

No insulin or bicarbonate boluses were administered during any of the simulation activities. Only four participants administered more than one fluid bolus. All participants recognized the possibility of cerebral edema and 80% (16/20) of residents communicated this to the parent. Only half completed a neurological exam despite the concern for cerebral edema.

Ninety-two percent (23/25) of nurses were from the step down ICU and 8% (2/25) were from the pediatric ICU. The majority were new critical care nurses with 80% (20/25) having < 5 years of experience. Sixty-four percent of (16/25) cared for < 5 patients per month with DKA. All nursing participants found the experience positive and provided a better understanding of the diagnosis and management of DKA. Ninety-six percent (24/25) of believed the simulation to be more beneficial

Table 1 Demographic and test questions

Demographic information

1 What year in residency are you?
PGY1 PGY2 PGY3 PGY4
2 Circle the residency program you are currently enrolled in.
Pediatrics Med-Peds Emergency medicine
3 Have you done an endocrine rotation during your residency?
Yes No
(1) If yes, what year in your training did you do this rotation?
PGY1 PGY2 PGY3 PGY4
4 Do you personally have type 1 diabetes?
Yes No
(1) If yes, have you ever been treated for DKA?
Yes No
5 Have you ever actively cared for a family member or close friend with diabetes?
Yes No
6 Have you ever cared for a patient with DKA during your training?
Yes No
(1) If yes, what rotations did you take care of these patients? Please list the rotations
(2) Approximately how many patients have you cared with DKA
0-5 patients 5-10 patients 10-20 patients > 20 patients

Test questions ([1]correct answers, some questions have more than one answer)

1 Match the best words that define diabetic ketoacidosis (DKA) with the appropriate lab value

A Dehydration	(1) BS > 200 mg/dL[1]
B Ketosis[1]	(2) Bicarb < 19, Ph < 7.35
C Acidosis[1]	(3) Urine or serum ketones[1]
D Polydipsia	(4) Bicarb < 15, pH < 7.3[1]
E Vomiting	(5) Spec grav > 1.030
F Hyperglycemia[1]	(6) Glycosuria

2 Which of the following signs/symptoms best describes a patient with DKA?
A Vomiting/diarrhea, hypokalemia
B Fever, leukocytosis
C Rapid deep breathing, altered mental status, vomiting, polyuria[1]
D Polyuria, polydipsia, nocturia
3 Which of the following is not a known complication that can occur during management of DKA?
A Cerebral Edema
B Hypokalemia
C Pancreatitis
D Hematuria[1]
E Rhabdomyolysis
F Hypercholermic metabolic acidosis
G Mucormycosis
4 Which of the following explanations best explains the best initia[1] therapy for DKA after initial fluid resuscitation?
A Continuous IVF with 1/2NS or NS to replace fluid losses over 48 h, insulin gtt at 0.1 units/kg per hour[1]
B Continuous IVF with 1/2NS or NS to replace fluid losses over 48 h, insulin gtt at 0.05 units/kg per hour
C Maintenance IVF with 1/2NS or NS, insulin gtt at 0.1 units/kg per hour
D Maintenance IVF with 1/2NS or NS, IV insulin bolus followed by insulin gtt at 0.1 units/kg per hour
E Twice maintenance IVF with 1/2NS or NS, insulin gtt at 0.1 units/kg per hour
F Sodium bicarbonate administration, IV insulin bolus IV followed by insulin gtt at 0.1 units/kg per hour, maintenance fluids with 1/2NS or NS
5 What labs and how often should labs be drawn on a patient in DKA, including D-sticks?
A D-sticks Q1H, serum electrolytes Q4H
B D-sticks Q15 minutes, serum electrolytes Q2H
(1) D-sticks Q1H, serum electrolytes Q2H initially then Q4H once steady improvement is noted[1]
(2) D-sticks Q1H, serum electrolytes Q2H twice, then Q6H once steady improvement is noted
6 When should the patient's neurological status be assessed?
A On admission, every hour during treatment, as needed for acute changes[1]
B Every hour during treatment
C On admission, every hour for the first four hours of treatment and then as needed for acute changes
D On admission and as needed for acute changes
7 When should dextrose be added to your treatment of DKA?
A When blood sugar drops by more than 100 mg/dL in an hour
B When blood sugar is less than or equal to 250 mg/dL
C When blood sugar drops by more than 75 mg/dL in an hour
D When blood sugar is less than or equal to 300 mg/dL
E A and B
F A and D[1]
G C and D
H B and C
8 When should potassium not be added to the IVF?
A When potassium is < 5.5
B When patient has urinated
C When no EKG abnormalities are noted on cardiac monitor
D When patient has evidence of acute renal failure on lab evaluation[1]
9 Identify three signs/symptoms of cerebral edema
A Headache[1]
B Altered mental status[1]
C Hyperactivity
D Hypotension
E Bradycardia[1]
F Tachycardia
10 Over what period of time should you correct a patient in DKA's dehydration?
A Immediately
B Over 12 h
C Over 24 h
D Over 48 h[1]
E Over 72 h
11 When is the patient at the greatest risk for developing cerebral edema?
A On admission/before treatment
B At initiation of treatment
C Several hours into treatment[1]
D At the time of transition
12 Describe the process of how to transition a patient off an insulin drip onto SQ insulin (Do not need to describe calculating doses of insulin. Just the basic process)
A Order food tray, when food arrives, administer long acting insulin and mealtime SQ insulin, allow patient to eat, approximately one hour later discontinue the insulin gtt, and remove dextrose from fluids[1]
B Discontinue insulin gtt, administer long acting insulin when arrives
C Administer long acting SQ insulin, one hour later allow patient to eat and administer mealtime insulin, discontinue insulin gtt, remove dextrose from fluids
D Order food tray, when food arrives, allow patient to eat, administer long acting insulin and mealtime SQ insulin, approximately one hour later discontinue the insulin gtt
13 When should the insulin drip be stopped during the treatment of DKA?
A When the blood sugar drops by > 200 mg/dL
B During transport
C When the bicarb is 19
D When long acting SQ insulin has been given in consultation with endocrine[1]
14 Which of the following therapies is appropriate treatment of DKA?
A Bicarb administration
B Several hour delay or interruption in receiving insulin gtt
C Rapid drop in glucose during treatment
D Multiple fluid boluses at the beginning of treatment unless patient is hemodynamically unstable
E Starting the insulin drip one hour after IV fluid hydration has been initiated[1]

15 On a scale from 1 to 5, how beneficial did you find the simulation exercise?
1 2 3 4 5
Least helpful Most helpful
16 How would you improve this simulation exercise? (add this to the immediate post-test and not the one done at 3-6 mo)

[1]Correct answer.

than previous education on DKA. Residents echoed this positive response with all identifying the simulation as beneficial especially the interdisciplinary nature of the course.

Qualitative analysis found the following overall learning themes: (1) activity "felt like real life" by having the residents and nurses' work together; (2) longitudinal progression of events allowed learners to see a patient in different stages of treatment; (3) debriefing discussions regarding pathophysiology and linking it to treatment was helpful; and (4) early recognition of cerebral edema and management. Suggestions for improvement included: (1) utilize electronic order entry system; (2) provide written handouts; and (3) participate in the simulation earlier in training.

DISCUSSION

A multidisciplinary, longitudinal simulation can improve understanding of a medically complex disorder such as DKA. This is demonstrated by improvements in test scores from pre-simulation to initial post-simulation as well as when compared to the reference group. Certain aspects of DKA management including fluid administration and cerebral edema recognition showed sustained improvement. In an environment where patient exposure is often fragmented due to nursing shift schedules and duty hour restrictions, the longitudinal nature of this course allows participants to see a patient from initial diagnosis until transition to subcutaneous insulin. This aspect along with the multidisciplinary approach makes it unique amongst previously described studies[12-19].

Volkova *et al*[14] designed a multidisciplinary approach for implementation of DKA guidelines. Internal medicine residents were educated *via* computer based testing/supportive reading materials and separate nursing education was conducted through lectures/reading materials. Documentation of compliance to guidelines and knowledge assessments were performed on the residents. Improvement in both areas was noted. Our studied allowed for simultaneous learning analogous to patient care which added benefit in that healthcare professionals learn firsthand the complexities of effective communication when taking care of critically ill patients. Fung *et al*[15] conducted a systemic review regarding the use of interdisciplinary and interprofessional simulation as an education tool for crisis resource management. Specific gains including improvement in team communication and subsequently overall patient care were noted in three of the studies reviewed. Interprofessional simulation also provides a forum for learners to practice leadership roles in emergency situations. Brown *et al*[16] in 2014 demonstrated that a multidisciplinary simulation could be used to improve radiation oncology resident training for medical emergencies.

Few studies have looked specifically at simulation as a DKA educational tool. Schneider Sarver *et al*[17] developed a three part simulation involving management of an adolescent patient with mild, moderate, and severe DKA for nursing students which showed knowledge improvement. Lee Chin *et al*[18] compared high-fidelity simulation *vs* case-based learning modules for DKA and thyroid storm for senior pharmacy students. Both groups demonstrated knowledge improvements but the simulation group had higher post-test scores. Problem-based DKA simulation case series for medical students supplementing their basic science material or computer-based simulations as part of an outpatient endocrine rotation showed knowledge gains compared to traditional learning methods[19,20].

Our simulation course identified knowledge, communication and patient care gaps. For example, only half of residents completed a thorough neurological exam despite clinical evidence concerning for cerebral edema. When asked about this during debriefing, residents identified wanting to "rush" through the exam and not identifying a need to perform a more thorough exam. All nursing participants notified the resident physicians regarding the patient's clinical changes consistent with cerebral edema but only a few clearly communicated their concern was cerebral edema. Another example of communication breakdown was timing of insulin drip initiation in regards to fluid boluses and initiation of intravenous fluids. Sometimes fluid boluses and insulin drips were administered around the same time without clarification asked for by the nursing staff or provided by the prescribers. Per 2014 International Society for Pediatric and Adolescent Diabetes guidelines, delaying insulin drip initiation 1-2 h after beginning fluid resuscitation therapy can help decrease the risk of cerebral edema[4].

Knowledge decay over time has been reported as a concern in medical education literature[21,22]. In adult advanced life support training a recent review demonstrated that knowledge and skill decay can occur as quickly as six weeks after initial training with more significant decay noted at 6-12 mo which can be attenuated if subjects have more clinical topic exposure[21]. Doumouras *et al*[22] specifically discussed the use of simulation and retention of knowledge and skills for crisis resource management training and showed retention of skills, particularly team based skills, was maintained if a repeated intervention was utilized. These findings may help explain the lack of sustained knowledge improvement in our population. The exposure of our cohort to DKA patients between the conclusion of the simulation and the second post-test was not documented. Residents with more exposure to these

Table 2 Demographic Information for Control and Intervention Groups *n* (%)

Category	Control Group (*n* = 16)	Intervention Group (*n* = 20)	*P* value
Residency training year			0.003
PGY 2	0 (0)	8 (40)	
PGY 3/4	16 (100)	12 (60)	
Type of residency			0.192
Pediatric	13 (81)	19 (95)	
Medicine-pediatric	3 (19)	1 (5)	
Treated DKA in residency	16 (100)	20 (100)	0.192
Endocrine rotation only	2 (13)	4 (20)	
ICU rotation only	5 (31)	1 (5)	
Both endocrine and ICU rotation	6 (37)	9 (45)	
Other (ED, night float)	3 (19)	6 (30)	
Estimated number of patients treated with DKA			0.825
1-10	2 (13)	4 (20)	
10-20	8 (50)	9 (45)	
> 20	6 (37)	7 (35)	

PGY: Post graduate year; DKA: Diabetic ketoacidosis; ICU: Intensive care unit; ED: Emergency department.

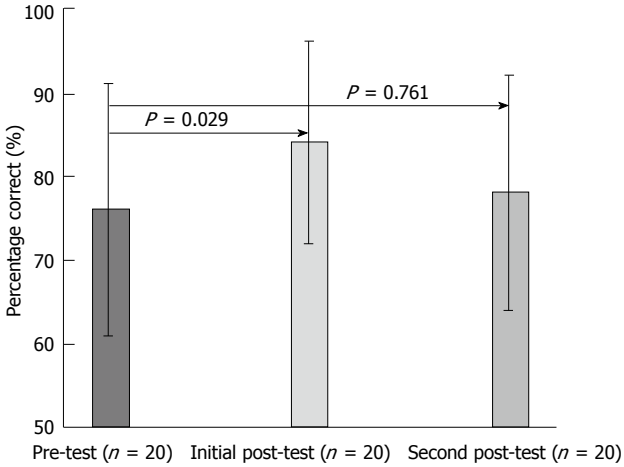


Figure 1 Assessment Scores for Intervention Group with standard deviation and respective *P* values.

patients to reinforce skills learned during the simulation may have performed better on the second post-test. Along those same lines, no structured reinforcement was offered between the conclusion of the simulation and the second post-test and this may have improved retention scores.

While our paper looks at the improvement of pediatric DKA management through simulation, we saw different methods utilized in each scenario. This difference in management of DKA in the pediatric population has been seen in other areas as well. Skitch and Valani[23] looked at the protocols of thirteen pediatric tertiary centers in Canada and reported many differences in the management of DKA. In comparison, a survey in pediatric centers in the Italian Society for Pediatric Diabetology and Endocrinology recognized significant differences in DKA management among their centers as well[24]. Both articles reference the need for evidence-based guidelines to be utilized across the board for best practice[23,24]. Although, DKA is managed through different methods, preventative care for these patients is of utmost importance. Crossen *et al*[25] concluded that signs of impending DKA were seen in children with type I diabetes who had recent emergency department visits and had infrequent subspecialty primary care visits. Chafe *et al*[26] utilized a focus study group of patients and families to identify ways to reduce episodes of DKA in the youth population. This project identified factors that put the youth at increased risks and recognized areas to improve those odds.

Limitations of this study included the relatively small number of participants especially in regards to numbers in the individual groups; reference, intervention and nurses. Recruitment of participants was limited due to the complex scheduling issues that are faced by both nursing staff and resident physicians. Other limitations include the reliance on participants to accept the realism in simulation activities. We chose to use a high-fidelity mannequin for the simulation to help reduce these issues. Each debriefing was designed to cover certain basic topics with all participants however may not have been identical. Finally, we did not assess if this intervention helped in actual care of patients with DKA.

Our study demonstrates that an interprofessional, longitudinal simulation improves short term understanding regarding the management of pediatric DKA. Subjectively, nurses found the interprofessional simulation improved their knowledge as well. It may be a useful tool to teach a team based approach and focus on communication between nursing staff and physicians when taking care of critically ill children. Unfortunately knowledge gains were not sustained at the 3-6 mo follow up sessions. Further studies are needed to investigate the impact of this simulation on patient care, specific changes in healthcare provider practices, and methods to reduce knowledge decay.

COMMENTS

Background

Diabetic ketoacidosis (DKA) is the most common pediatric endocrine emergency and understanding its management is important for the healthcare team. Experience and training in DKA management is variable and often separated by healthcare disciplines. Simulation may be an important tool to help standardize DKA training.

Research frontiers

Inter-disciplinary training with simulation is becoming an important way to train medical providers.

Innovations and breakthroughs

This is the first article to evaluate the role of inter-disciplinary simulation training in the management of pediatric DKA. Important knowledge gains were seen after the intervention but were not sustained on 3 mo follow-up.

Applications

Simulation is important tool in medical education and its role continues to

expand.

Peer-review

Nice research dealing with a public health problem.

REFERENCES

1 **Kitabchi AE**, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM. Hyperglycemic crises in diabetes. *Diabetes Care* 2004; **27** Suppl 1: S94-102 [PMID: 14693938 DOI: 10.2337/diacare.27.2007.S94]

2 **Klein M**, Sathasivam A, Novoa Y, Rapaport R. Recent consensus statements in pediatric endocrinology: a selective review. *Endocrinol Metab Clin North Am* 2009; **38**: 811-825 [PMID: 19944294 DOI: 10.1016/j.ecl.2009.09.003]

3 **Rewers A**. Current controversies in treatment and prevention of diabetic ketoacidosis. *Adv Pediatr* 2010; **57**: 247-267 [PMID: 21056741 DOI: 10.1016/j.yapd.2010.098.001]

4 **Wolfsdorf JI**, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, Lee WW, Mungai LN, Rosenbloom AL, Sperling MA, Hanas R. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Pediatr Diabetes* 2014; **15** Suppl 20: 154-179 [PMID: 25041509 DOI: 10.1111/pedi.12165]

5 **Rosenbloom AL**. The management of diabetic ketoacidosis in children. *Diabetes Ther* 2010; **1**: 103-120 [PMID: 22127748 DOI: 10.1007/S13300-010-0008-2]

6 **Wolfsdorf J**, Craig ME, Daneman D, Dunger D, Edge J, Lee W, Rosenbloom A, Sperling M, Hanas R. Diabetic ketoacidosis in children and adolescents with diabetes. *Pediatr Diabetes* 2009; **10** Suppl 12: 118-133 [PMID: 19754623 DOI: 10.1111/j.1399-5448.2009.00569.x]

7 **Sherry NA**, Levitsky LL. Management of diabetic ketoacidosis in children and adolescents. *Paediatr Drugs* 2008; **10**: 209-215 [PMID: 18590342]

8 **Hsia DS**, Tarai SG, Alimi A, Coss-Bu JA, Haymond MW. Fluid management in pediatric patients with DKA and rates of suspected clinical cerebral edema. *Pediatr Diabetes* 2015; **16**: 338-344 [PMID: 25800410 DOI: 10.1111/pedi.12268]

9 **Watts W**, Edge JA. How can cerebral edema during treatment of diabetic ketoacidosis be avoided? *Pediatr Diabetes* 2014; **15**: 271-276 [PMID: 24866063 DOI: 10.1111/pedi.12155]

10 **Grant DJ**, Marriage SC. Training using medical simulation. *Arch Dis Child* 2012; **97**: 255-259 [PMID: 21920872 DOI: 10.1136/archdischild-2011-300592]

11 **Weinberg ER**, Auerbach MA, Shah NB. The use of simulation for pediatric training and assessment. *Curr Opin Pediatr* 2009; **21**: 282-287 [PMID: 19381090 DOI: 10.1097/MOP.0b013e32832b32dc]

12 **Okuda Y**, Bryson EO, DeMaria S, Jacobson L, Quinones J, Shen B, Levine AI. The utility of simulation in medical education: what is the evidence? *Mt Sinai J Med* 2009; **76**: 330-343 [PMID: 19642147 DOI: 10.1002/msj.20127]

13 **Tofil NM**, Morris JL, Peterson DT, Watts P, Epps C, Harrington KF, Leon K, Pierce C, White ML. Interprofessional simulation training improves knowledge and teamwork in nursing and medical students during internal medicine clerkship. *J Hosp Med* 2014; **9**: 189-192 [PMID: 24420579 DOI: 10.1002/jhm.2126]

14 **Volkova NB**, Fletcher CC, Tevendale RW, Munyaradzi SM, Elliot S, Peterson MW. Impact of a multidisciplinary approach to guideline implementation in diabetic ketoacidosis. *Am J Med Qual* 2008; **23**: 47-55 [PMID: 18187590 DOI: 10.1177/1062860607311015]

15 **Fung L**, Boet S, Bould MD, Qosa H, Perrier L, Tricco A, Tavares W, Reeves S. Impact of crisis resource management simulation-based training for interprofessional and interdisciplinary teams: A systematic review. *J Interprof Care* 2015; **29**: 433-444 [PMID: 25973615 DOI: 10.3109/13561820.2015.1017555]

16 **Brown LC**, Laack TA, Ma DJ, Olivier KR, Laack NN. Multidisciplinary medical simulation: a novel educational approach to preparing radiation oncology residents for oncologic emergent on-call treatments. *Int J Radiat Oncol Biol Phys* 2014; **90**: 705-706 [PMID: 25304952 DOI: 10.1016/j.ijrobp.2014.06.053]

17 **Schneider Sarver PA**, Senczakowicz EA, Slovensky BM. Development of simulation scenarios for an adolescent patient with diabetic ketoacidosis. *J Nurs Educ* 2010; **49**: 578-586 [PMID: 20672775 DOI: 10.3928/01484834-20100630-07]

18 **Lee Chin K**, Ling Yap Y, Leng Lee W, Chang Soh Y. Comparing effectiveness of high-fidelity human patient simulation vs case-based learning in pharmacy education. *Am J Pharm Educ* 2014; **78**: 153 [PMID: 25386018 DOI: 10.5688/ajpe788153]

19 **Nandate K**, Abola R, Murray WB, Whitfield C, Lang C, Sinz E. Simulation of diabetic ketoacidosis for cellular and molecular basics of medical practice. *Simul Healthc* 2009; **4**: 232-236 [PMID: 19915443 DOI: 10.1097/SIH.0b013e31819e139d]

20 **Wong RW**, Lochnan HA. A web-based simulation of a longitudinal clinic used in a 4-week ambulatory rotation: a cohort study. *BMC Med Educ* 2009; **9**: 8 [PMID: 19187554 DOI: 10.1186/1472-6920-9-8]

21 **Yang CW**, Yen ZS, McGowan JE, Chen HC, Chiang WC, Mancini ME, Soar J, Lai MS, Ma MH. A systematic review of retention of adult advanced life support knowledge and skills in healthcare providers. *Resuscitation* 2012; **83**: 1055-1060 [PMID: 22391016 DOI: 10.1016/j.resuscitation.2012.02.027]

22 **Doumouras AG**, Keshet I, Nathens AB, Ahmed N, Hicks CM. A crisis of faith? A review of simulation in teaching team-based, crisis management skills to surgical trainees. *J Surg Educ* 2012; **69**: 274-281 [PMID: 22483124 DOI: 10.1016/j.jsurg.2011.11.004]

23 **Skitch SA**, Valani R. Treatment of Pediatric Diabetic Ketoacidosis in Canada: A Review of Treatment Protocols from Canadian Pediatric Emergency Departments. *CJEM* 2015; **17**: 656-661 [PMID: 26461431 DOI: 10.1017/cem.2016.56]

24 **Zucchini S**, Scaramuzza AE, Bonfanti R, Buono P, Cardella F, Cauvin V, Cherubini V, Chiari G, d'Annunzio G, Frongia AP, Iafusco D, Maltoni G, Patera IP, Toni S, Tumini S, Rabbone I. A Multicenter Retrospective Survey regarding Diabetic Ketoacidosis Management in Italian Children with Type 1 Diabetes. *J Diabetes Res* 2016; **2016**: 5719470 [PMID: 26649321 DOI: 10.1155/2016/5719470]

25 **Crossen SS**, Wilson DM, Saynina O, Sanders LM. Outpatient Care Preceding Hospitalization for Diabetic Ketoacidosis. *Pediatrics* 2016; **137**: pii: e20153497 [PMID: 27207491]

26 **Chafe R**, Albrechtsons D, Hagerty D, Newhook LA. Reducing episodes of diabetic ketoacidosis within a youth population: a focus group study with patients and families. *BMC Res Notes* 2015; **8**: 395 [PMID: 26323283 DOI: 10.1186/s13104-015-1358-7]

P- Reviewer: Sergi CM, Tarantino G, Wang R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.219

World J Crit Care Med 2016 November 4; 5(4): 219-227
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Determination of functional prognosis in hospitalized patients following an intensive care admission

Natália A Ferreira, Agnaldo José Lopes, Arthur S Ferreira, George Ntoumenopoulos, Jerffesson Dias, Fernando S Guimaraes

Natália A Ferreira, Agnaldo José Lopes, Arthur S Ferreira, Fernando S Guimaraes, Rehabilitation Sciences Post-Graduation Program, Augusto Motta University Centre, Rio de Janeiro 21041-020, Brazil

Natália A Ferreira, Jerffesson Dias, Physical Therapy Department, Barra D'Or Hospital, Rio de Janeiro 22775-002, Brazil

Agnaldo José Lopes, Post-Graduation Program in Medical Sciences, State University of Rio de Janeiro, Rio de Janeiro 20550-900, Brazil

George Ntoumenopoulos, George Ntoumenopoulos, Graduate School of Health Sciences, University of Technology Sydney, Sydney NSW 2007, Australia

Fernando S Guimaraes, Physical Therapy Department, Federal University of Rio de Janeiro, Rio de Janeiro 21941-913, Brazil

Author contributions: Ferreira NA, Lopes AJ and Guimaraes FS designed the research and wrote the paper; Ferreira AS and Dias J performed the research and contributed for the project; Ferreira NA analyzed the data and reviewed the final version of the paper; Ntoumenopoulos G wrote and reviewed the final version of the paper.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Augusto Motta University Centre.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data obtained from the hospital database.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Fernando S Guimaraes, PT, PhD, Associate Professor, Rehabilitation Sciences Post-Graduation Program, Augusto Motta University Centre, Praça das Nações, 34, Bonsucesso, Rio de Janeiro 21041-010, Brazil. fguimaraes_pg@yahoo.com.br
Telephone: +55-21-991243760
Fax: +55-21-24385178

Received: March 7, 2016
Peer-review started: March 9, 2016
First decision: May 19, 2016
Revised: July 1, 2016
Accepted: August 17, 2016
Article in press: August 18, 2016
Published online: November 4, 2016

Abstract

AIM

To investigate the factors associated with the functional progress of hospitalized patients following an intensive care admission.

METHODS

Retrospective study including data from a cohort of 198 hospitalized patients following an intensive care admission and not requiring mechanical ventilation in a single tertiary referral hospital. A generalized linear model was used to identify the main effects of clinical and demographic variables on the outcomes of functionality (KATZ Index of Independence in Activities of Daily Living) and muscle strength (MRC Scale). The covariates identified as independent predictors were

analysed using the receiver operating characteristic curves. The analysis differentiated the periods in the intensive care unit (ICU), in the Ward (WARD) and the total time of hospital stay (TOT).

RESULTS

Considering the functional outcome (ΔKATZ), the variables that significantly contributed to the model (P < 0.05) were the KATZ and MRC on admission, age, sepsis (no), and total length of stay (TLS). Regarding the muscle strength outcome model (ΔMRC), the predictors were MRC on admission, Simplified Acute Physiology Score III, previous stroke, TLS, and sex (female). The variable age (AUC = 0.664) discriminated the $\Delta KATZ_{ICU}$. The variables age (AUC = 0.712), KATZ in ICU (AUC = 0.590) and on ward admission (AUC = 0.746), and MRC on ward admission (AUC = 0.721) were discriminative for $\Delta KATZ_{WARD}$. For $\Delta KATZ_{TOT}$ the variables KATZ on ICU admission (AUC = 0.621) and TLS (AUC = 0.617) were discriminative. For ΔMRC_{ICU} the variables SAPSIII (AUC = 0.661) and MRC on ICU admission (AUC = 0.653) were discriminative. MRC on ICU (AUC = 0.681) and ward admission (AUC = 0.553) were discriminative for ΔMRC_{WARD}. TLS (AUC = 0.649) and MRC on ward admission (AUC = 0.696) discriminative for the ΔMRC_{TOT}.

CONCLUSION

Specific functional, clinical and demographical variables at ICU admission are associated with the functional prognosis during the hospitalization period.

Key words: Muscle strength; Intensive care units; Activities of daily living; Rehabilitation; Early mobilization; Post-intensive care unit syndrome

Core tip: In spite of the advances in critical care, functional deficits are commonly observed during and after the hospitalization period. This retrospective study aimed to investigate the factors associated with the functional progress in a cohort of patients that underwent a mobilization protocol, from the intensive care unit (ICU) to the hospital discharge. As functional ability, muscle strength, low illness severity score at ICU and ward admission, absence of sepsis and stroke, longer total length of stay, male gender and younger age were predictors of favourable patients' functional progress, these variables should be taken in consideration when planning rehabilitative strategies for hospitalized patients following an intensive care admission.

Ferreira NA, Lopes AJ, Ferreira AS, Ntoumenopoulos G, Dias J, Guimaraes FS. Determination of functional prognosis in hospitalized patients following an intensive care admission. *World J Crit Care Med* 2016; 5(4): 219-227 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/219.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.219

INTRODUCTION

The advances in critical care have led to increased survival, however, physical and psychological deficits are commonly observed during and after the hospitalization period[1]. Intensive care unit acquired weakness (ICU-AW) is currently recognized as an important complication of critical illness. It is defined as symmetrical weakness in upper and lower limbs and is diagnosed with a medical research council (MRC) score sum less than 48[2]. Prolonged bed rest, systemic inflammation, hyperglycaemia, sedation, sepsis, malnutrition, patient immobilization, use of corticosteroids and neuromuscular blockers, among others, are considered risk factors for ICU-AW and, consequently, poorer functional outcome[3,4].

According to the World Health Organization International Classification of Functioning, Disability and Health[5,6], the key measures of physical function can be categorized as: (1) mobility: Including balance, lying, sitting, standing, shifting the body's centre of gravity; (2) muscle function: Strength; (3) walking and moving: Including walking independently, walking with assistance, walking short and long distances; (4) self-care: Activities of daily living (ADL) such as washing, dressing, toileting, grooming and eating; and (5) self-reported quality of life (QOL). Although 26 different functional instruments have been described for use in critically ill patients, proper assessment tools addressing impairment, activity limitations and participation restrictions need to be developed to be utilized across different time points of recovery[7]. The KATZ Index of Independence in Activities of Daily Living (KATZ ADL)[8] was first developed to assess the functional status in non-hospitalized older adults, and has been applied across a wide range of patient populations[9] and is one of the few functional scales that have been used both in critical care[10-12] and in the ward settings[11,13-15]. Similarly, the MRC, which was initially developed to assess the volitional muscle strength in outpatients[16], has been broadly used in critical care patients with a very good interrater reliability[17], however there are limitations to the use of volitional measures of muscle function in critically ill patients[18].

The literature however is still scarce concerning the factors that may determine the patients' functional recovery during the in-hospital period following a stay in intensive care. The ability to predict patient functional progress may contribute to the individualization of rehabilitative interventions. Additionally, the functional assessment throughout different time points of the in-hospital period, from the ICU admission/discharge to hospital discharge, using measures of muscle function and self-care may improve the understanding of the relationship between these two functional domains.

Thus, the primary objective of this study was to identify the factors that determine the functional progress of a cohort of patients that required an

intensive care admission without the need for mechanical ventilation and underwent a mobilization protocol, from the ICU admission to hospital discharge. Secondarily, we aimed at evaluate the association between the KATZ ADL index and the MRC scale during the same hospitalization period.

MATERIALS AND METHODS

Design

Retrospective study including data from a cohort of 198 hospitalized patients in a single tertiary referral hospital. The medical records from patients admitted to the ICU at the Barra D'Or Hospital between September 2013 and December 2014 were screened according to the eligibility criteria.

The generalized linear model was used to identify the main effects of clinical and demographic variables on the outcomes of functionality and muscle strength during the hospitalization period. The study was approved by the Institutional Research Board and Ethics Committee.

Participants

Data was obtained from non-mechanically ventilated patients presenting with at least one of the following criteria: KATZ score $\geqslant$ 3, MRC $\leqslant$ 48, diagnosis of pulmonary or cardiovascular disease, and cooperative (Richmond Agitation-Sedation Scale between 0 and 2) who stayed at least 48 h at the ICU and underwent the mobilization protocol. Records of patients who died during the period of the study, with neuromuscular disease, returned to the ICU after discharge or with incomplete data were not included.

Mobilization protocol and functional assessment

Eligibility criteria and procedures for the mobilization protocol followed the framework proposed by Hanekom *et al*[19] (2011). According to their clinical and functional condition, the patients progressed from passive and active mobilization and from being recumbent to ambulation as able. For patients unable to mobilize out of bed, lower limb strengthening exercises were included. Neuromuscular electrical stimulation and in-bed cycling exercises were not used. The interventions were undertaken daily on a twice a day basis.

The peripheral muscle strength was assessed by the MRC scale[16,17] which uses a 6-point scale from 0 (no contraction) to 5 (full contraction through range against resistance) of 12 muscle groups: Bilateral shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and foot dorsiflexion. The representative score for each patient is the sum of the points given for each muscle group (maximum = 60).

The overall functional performance was assessed using the KATZ ADL index, which was culturally adapted for the Brazilian population[20]. This index assesses the subjects' ability to perform the following activities of daily living independently: Bathing, dressing, toileting, transferring, continence, and feeding. The scoring system gives a numerical score from "0" (independent in the six functions) to "6" (dependent in the six functions).

The mobilization protocol, muscle strength and functional performance were performed by the physical therapy team, who were periodically trained to ensure a these procedures were applied in a standardised way. The patients underwent the mobilization protocol from the ICU admission until the hospital discharge. Functional and muscle strength assessments were undertaken on three key periods: ICU admission, ICU discharge and hospital discharge.

Statistical analysis

Differences (delta, Δ) between the output and input values of hospital sectors were established as categorical outcomes ($\Delta SCORE_{period} = OUT_{score,period} - IN_{score,period}$). Such differences were calculated for periods of stay only in the ICU (ICU), only in the ward (WARD) and for the total hospital stay (TOT). Thus, considering that in the KATZ scoring system higher values are representative of poor functionality, the following categorization was set as $\Delta KATZ_{period} = 1$ if the sector's output score is lower than the input or $\Delta KATZ_{period} = 0$ if the sector's output score is higher or equal than the input. Conversely, considering that the MRC score is directly proportional to the functionality, the categorization was set as $\Delta MRC_{period} = 1$ if the sector's output score is greater than the input, $\Delta MRC_{period} = 0$ if the output score is equal or lower than the input.

Descriptive statistics included mean ± SD, median (minimum; maximum) or proportions for subjects aged < 65 years, $\geqslant$ 65 years, and the whole sample. Data between age groups were compared using independent-sample *t* tests for continuous variables, χ^2 test for categorical variables, and Fisher's exact test for dichotomous variables. Plots represent mean values alongside the 95%CI. Binary logistic, generalized linear model was used to identify the main effects of the factors (gender, "male" = 1; sepsis, "yes" = 1; COPD, "yes" = 1; dementia, "yes" = 1, previous stroke, "yes" = 1; and cause of ICU admission) and covariates (age; SAPSⅢ; length of stay; KATZ at admission; MRC at admission) on the outcomes of functionality and muscle strength ($\Delta KATZ_{period}$ and ΔMRC_{period}, respectively). The covariates identified as independent predictors were analysed using the receiver operating characteristic (ROC) curves. The value of state variable was coded "0" or "1", aiming to mirror the curve above the reference diagonal to facilitate the data interpretation. Cut-off points were determined by the minimal distance calculated as

$$d = \sqrt{(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2}$$ [21].

The association between MRC and KATZ scores was assessed through the Spearman's correlation coefficient, and all the results were considered significant when $P < 0.05$. All statistical analyses were performed with SPSS software (IBM Inc., United States).

Table 1 Subjects characteristics (n = 198)

Variables	Levels	Age < 65 yr	Age ≥ 65 yr	*P* value	All sample	
		Mean ± SD	Mean ± SD		Mean ± SD	Median (Min; max)
		n = 39	n = 159		n = 198	
Age, yr		50.5 ± 12.2	82.7 ± 8.6	NT	76.4 ± 15.9	80 (24; 101)
KATZ at ICU admission, score		3.9 ± 1.4	4.3 ± 1.4	0.207	4.2 ± 1.4	4 (0; 6)
MRC at ICU admission, score		46.6 ± 15.1	39.1 ± 14.9	0.007	40.6 ± 15.2	44 (0; 60)
KATZ at ward admission, score		2.7 ± 2.1	4.2 ± 1.6	< 0.001	3.9 ± 1.8	4 (0; 6)
MRC at ward admission, score		48.1 ± 15.0	40.0 ± 15.1	0.004	41.6 ± 15.3	45.5 (0; 60)
KATZ at hospital discharge, score		2.5 ± 2.2	4.0 ± 1.8	< 0.001	3.7 ± 2	4 (0; 6)
MRC at hospital discharge, score		50.6 ± 15.4	41.9 ± 14.0	0.002	43.6 ± 14.7	48 (0; 60)
Hospital length of stay, d		9.9 ± 7.0	12.1 ± 9.8	0.117	12 ± 9	9 (2; 52)
SAPS3, %		43.8 ± 8.8	53.7 ± 8.6	< 0.001	51.7 ± 9.5	51 (27; 89)
Gender, *n* (%)	Female	17 (14)	104 (86)	0.017	121 (61)	-
	Male	22 (29)	55 (71)	-	77 (39)	-
Sepsis, *n* (%)	No	19 (20)	74 (80)	0.859	93 (47)	-
	Yes	20 (19)	85 (81)	-	105 (53)	-
COPD, *n* (%)	No	37 (21)	142 (79)	0.377	179 (90)	-
	Yes	2 (11)	17 (89)	-	19 (10)	-
Dementia, *n* (%)	No	39 (27)	108 (73)	< 0.001	147 (74)	-
	Yes	0 (0)	51 (100)	-	51 (26)	-
Previous stroke, *n* (%)	No	38 (22)	134 (78)	0.032	172 (87)	-
	Yes	1 (4)	25 (96)	-	26 (13)	-
Cause of ICU admission, *n* (%)	Cardiovascular	4 (33)	8 (67)	0.646	12 (6)	-
	Gastrointestinal	3 (16)	16 (84)	-	19 (10)	-
	Neoplastic	0 (0)	1 (100)	-	1 (1)	-
	Neurologic	4 (25)	12 (75)	-	16 (8)	-
	Renal	8 (23)	27 (77)	-	35 (18)	-
	Pulmonary	16 (21)	62 (79)	-	78 (39)	-
	Others	4 (11)	33 (89)	-	37 (19)	-

KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council; SAPS3: Simplified acute physiology score; COPD: Chronic obstructive pulmonary disease; NT: Not tested.

RESULTS

A total of 198 subjects (121 females, 61%) aged 24 to 101 years (76.4 ± 15.9 years) were considered eligible for the study. From these, 78 were hospitalized for lung disease, 105 for sepsis, 19 had COPD, 51 had dementia and 26 had a prior stroke. The average length of hospital stay was 12 ± 9 d, and the average SAPSIII score was 51.7 ± 9.5 (Table 1). In the analysis of deltas for KATZ, 24.7% of the patients improved and 63.1% remained stable in $\Delta KATZ_{ICU}$, 23.7% improved and 66.7% remained stable in $\Delta KATZ_{WARD}$, and 36.4% improved and 51.5% remained stable in $\Delta KATZ_{TOT}$. For MRC, 28.8% improved and 57.1% remained stable in ΔMRC_{ICU}, 35.4% improved and 52.5% remained stable in ΔMRC_{WARD} and 47.0% showed improvement, and 35.4% remained stable in ΔMRC_{TOT}. The proportion of elderly patients (≥ 65 years) in the group was 80.3%. One hundred and thirty-four (67.7%) patients had a MRC < 48 at ICU discharge (consistent with the definition of ICU-AW), with only minimal improvement at hospital discharge with 122 (61.6%) with the MRC < 48. The functional and muscle strength progress through the different time points of the study are shown in Figure 1.

Considering the functional outcome during the ICU stay ($\Delta KATZ_{ICU}$), the variables that significantly contributed to the model were age (Wald χ^2 = 10.060, P = 0.002), KATZ at ICU admission (Wald χ^2 = 7.385, P = 0.007), MRC at ICU admission (Wald χ^2 = 4.837, P = 0.028) and previous stroke (Wald χ^2 = 4.671, P < 0.031). For the ward period ($\Delta KATZ_{WARD}$) the significant predictors were age (Wald χ^2 = 6.520, P = 0.011), KATZ at ward admission (Wald χ^2 = 12.782, P < 0.001), MRC at ward admission (Wald χ^2 = 4.418, P = 0.036), and sepsis (Wald χ^2 = 4.528, P = 0.033). Similarly, age (Wald χ^2 = 8.077, P = 0.004), total length of stay (Wald χ^2 = 6.629, P = 0.010) and KATZ at ward admission (Wald χ^2 = 10.099, P = 0.001) contributed for the functional outcome model considering the total length of stay ($\Delta KATZ_{TOT}$) (Table 2).

Regarding the muscle strength outcome during the ICU stay (ΔMRC_{ICU}), the SAPSIII (Wald χ^2 = 5.789, P = 0.016), MRC at ICU admission (Wald χ^2 = 9.645, P = 0.002) and previous stroke (Wald χ^2 = 8.815, P = 0.003) were significant predictors. For the ward period (ΔMRC_{WARD}) the predictors were the MRC at ICU admission (Wald χ^2 = 20.013, P < 0.001) and MRC at ward admission (Wald χ^2 = 12.085, P = 0.001). At hospital discharge (ΔMRC_{TOT}), the total length of stay (Wald χ^2 = 4.799, P = 0.028), MRC at ward admission (Wald χ^2 = 4.406, P = 0.036) and sex (Wald χ^2 = 3.864, P = 0.049) contributed for the model (Table 2).

Among the significant predictors in the generalized linear model analysed using the ROC curve, age (AUC = 0.664, cut-off = 78.5 years) was the only variable that discriminated the $\Delta KATZ_{ICU}$. For the ΔMRC_{ICU} the variables SAPSIII (AUC = 0.661, cut-off = 50.0%)

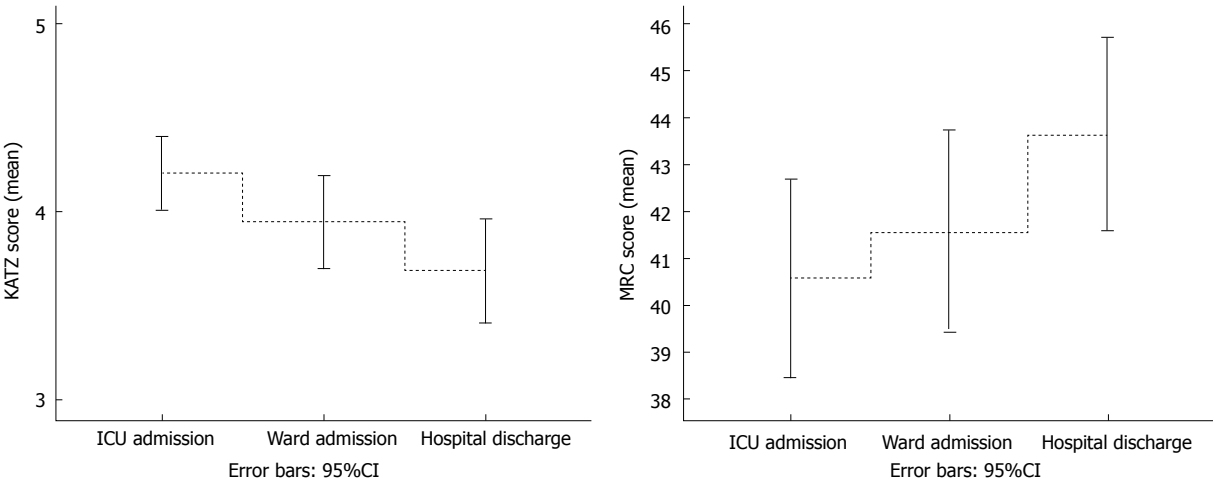


Figure 1 Functional progress through the different time points of the study. KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council Scale. Dashed lines represent step changes in mean values of scores between sequential time points of the study. ICU: Intensive care unit.

and MRC at ICU admission (AUC = 0.653, cut-off = 37 points) were discriminative. For $\Delta KATZ_{WARD}$, the variables of age (AUC = 0.712, cut-off = 81.5 years), KATZ at ICU admission (AUC = 0.590, cut-off = 4.5 points), KATZ at ward admission (AUC = 0.746, cut-off = 2.5 points), and MRC at ward admission (AUC = 0.721, cut-off = 47 points) were discriminative. The variables that significantly discriminated the ΔMRC_{WARD} were MRC at ICU admission (AUC = 0.681, cut-off = 44.5 points) and MRC at ward admission (AUC = 0.553, cut-off = 43.3 points). Finally, total length of stay (AUC = 0.617, cut-off = 11.5 d) and KATZ at ICU admission (AUC = 0.621, cut-off = 3.5 points) were the only variables that discriminated the $\Delta KATZ_{TOT}$. Whereas total length of stay (AUC = 0.649, cut-off = 10.5 d) and MRC at ward admission (AUC = 0.696, cut-off = 37 points) were the variables that significantly discriminated the ΔMRC_{TOT} (Figure 2 and Table 3).

There were weak significant associations between ΔMRC_{ICU} and $\Delta KATZ_{ICU}$ ($\rho = 0.264$; $P < 0.001$), ΔMRC_{ICU} and $\Delta KATZ_{WARD}$ ($\rho = 0.151$; $P = 0.034$) and ΔMRC_{TOT} and $\Delta KATZ_{TOT}$ ($\rho = 0.183$; $P = 0.010$).

DISCUSSION

Overall muscle strength and functional progress during hospitalization

The results of this study showed that, in spite of being cooperative and undergoing a mobilization protocol, only a small percentage of the patients in ICU improved their muscle strength (28.8%) and functional status (24.7%) in this setting. The same was observed in the ward period, with improvements in 35.4% of patients for muscle strength and 23.7% of patients for KATZ ADL index. This cohort of patients had low functional and muscle strength scores at hospital discharge, *i.e.,* KATZ = 3.7 and MRC = 43.6. Advanced age was identified as one of the determining factors of unfavourable functional progress in our study, and with the high prevalence of aged patients in our sample (80.3%, *i.e.,* 167 patients older than 65 years of age) this must have contributed to the poor functional progress during hospitalization and at hospital discharge. As shown in Table 1, elderly patients had more severe clinical condition at admission, as well as lower MRC scores and higher prevalence of previous stroke. Besides aging, these factors may have also contributed to the poorer functional scores observed on the ward and at hospital discharge in comparison with the younger subgroup.

Nevertheless, when considering the sample as a whole, there was a clear trend in improving MRC and KATZ scores throughout the hospitalization period (Figure 1). These results are in accordance with the study of van der Schaaf *et al*[22] (2009) who followed a sample of 255 participants during the ICU stay. In this study, even with a younger sample (mean age = 58.8 years), they found that 69% of the subjects had persistent limitations for the activities daily living even one year after the hospital discharge. In our study length of stay was a significant predictor of improvement in muscle strength and functional status when considering the total time of hospitalization. This suggests that the in-hospital functional and muscle strength recovery may be time-dependent. Hence[12] the extent of improvements in functional outcomes during hospitalization should be incorporated in hospital discharge planning. However, the evidence is still inconclusive regarding the benefits of exercise-based interventions on functional exercise capacity and health-related quality of life for survivors of critical illness[23]. Further research into the rehabilitation during hospitalization and post hospital discharge are required[24].

Predictors of muscle strength and functional improvement

A total of 134 (67.7%) and 122 (61.6%) of the patients presented with ICU-AW at ICU and hospital discharge, respectively. The high incidence of ICU-AW in this cohort of patients may be due to the high prevalence of sepsis

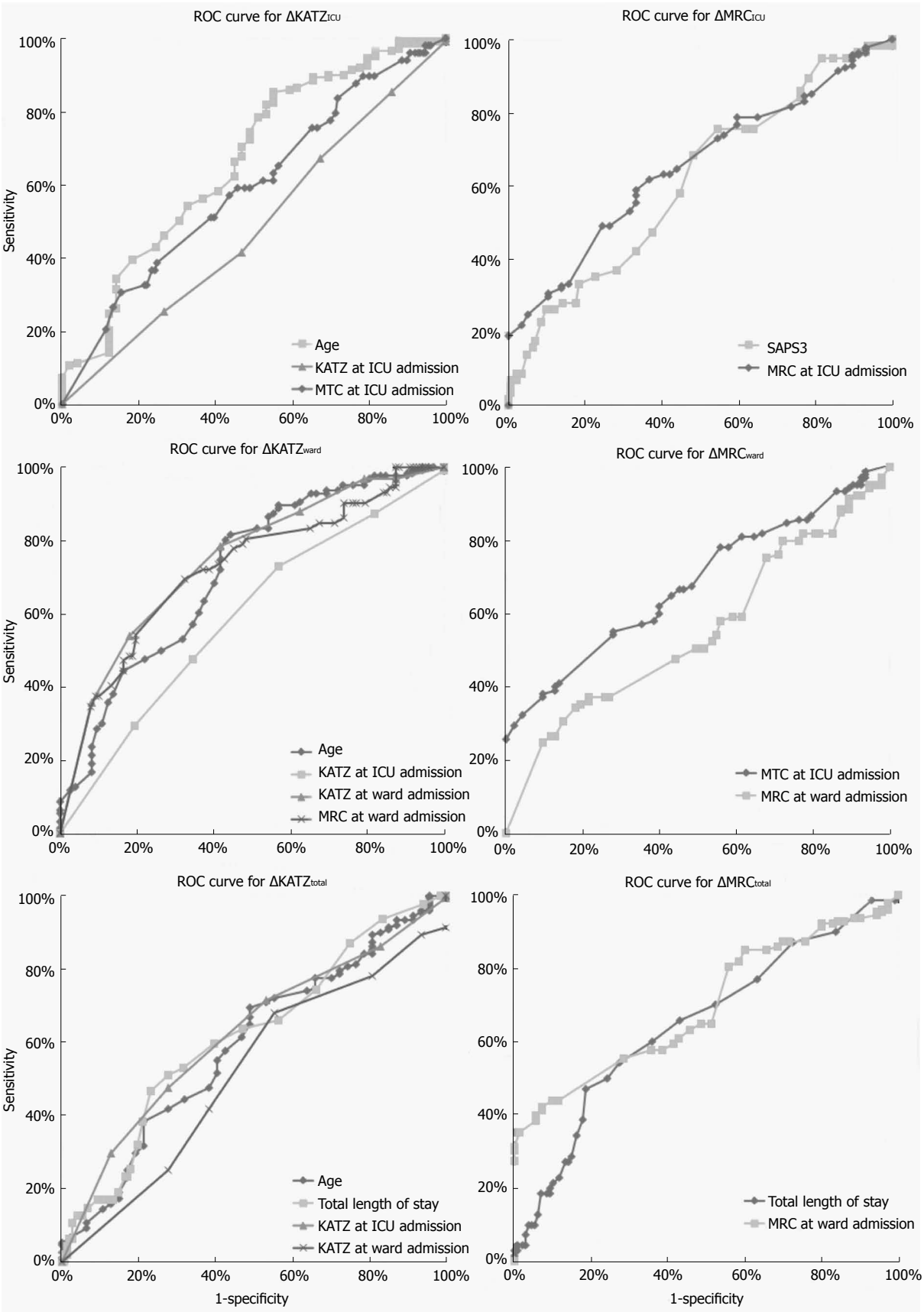


Figure 2 Receiver operator characteristics curves of improvement in KATZ ADL index (left panels) and MRC scores (right panels) during ICU stay (top panels), ward stay (center panels) and at hospital discharge (bottom panels). ΔKATZICU improvement of at least 1 point in the KATZ Index Score during the ICU stay; ΔMRCICU: Improvement of at least 1 point in the MRC Score during the ICU stay; ICU: Intensive care unit; KATZ ADL: KATZ Index of Independence in Activities of Daily Living; MRC: Medical research council.

Table 2 Generalized linear model results for functional outcomes (n = 198)

Functional outcome		ΔKATZ					ΔMRC				
		Test for model effects		Parameter estimates			Test for model effects		Parameter estimates		
Comparison	Variable	Wald χ^2	*P* (Sig.)	B	Lower 95%CI	Upper 95%CI	Wald χ^2	*P* (Sig.)	B	Lower 95%CI	Upper 95%CI
ICU	Age, yr	10.006	0.002	0.043	0.016	0.069	1.430	0.232	0.016	-0.010	0.042
	SAPS3, %	1.312	0.252	-0.023	-0.063	0.017	5.789	0.016	-0.053	-0.097	-0.010
	Length of stay in ICU, d	1.295	0.255	-0.040	-0.110	0.029	3.145	0.076	-0.068	-0.144	0.007
	KATZ at ICU admission, score	7.385	0.007	-0.562	-0.967	-0.157	0.399	0.528	0.119	-0.251	0.489
	MRC at ICU admission, score	4.837	0.028	-0.045	-0.084	-0.005	9.645	0.002	0.057	0.021	0.093
	Sex (male = 1)	0.069	0.792	-0.108	-0.913	0.697	0.733	0.392	0.341	-0.440	1.123
	Sepsis (no)	0.105	0.745	-0.133	-0.934	0.669	0.088	0.766	-0.122	-0.924	0.680
	COPD (no)	0.184	0.668	-0.302	-1.683	1.078	0.479	0.489	-0.488	-1.870	0.894
	Dementia (no)	0.238	0.626	-0.261	-1.312	0.789	1.478	0.224	-0.622	-1.626	0.381
	Previous stroke (no)	4.671	0.031	-1.782	-3.398	-0.166	8.815	0.003	-2.667	-4.428	-0.906
	Cause of ICU admission	3.785	0.706	NS	NS	NS	7.956	0.241	NS	NS	NS
Ward	Age, yr	6.520	0.011	0.040	0.009	0.071	1.235	0.267	0.016	-0.012	0.043
	SAPS3, %	0.137	0.711	0.008	-0.034	0.050	0.029	0.865	-0.004	-0.046	0.039
	Length of stay in ward, d	2.726	0.099	-0.047	-0.102	0.009	1.014	0.314	-0.028	-0.083	0.027
	KATZ at ICU admission, score	9.241	0.002	-0.858	-1.411	-0.305	1.185	0.276	0.228	-0.183	0.639
	MRC at ICU admission, score	1.339	0.247	0.034	-0.024	0.092	20.013	< 0.001	0.223	0.125	0.320
	KATZ at ward admission, score	12.782	< 0.001	0.867	0.392	1.342	0.503	0.478	0.123	-0.217	0.464
	MRC at ward admission, score	4.418	0.036	-0.064	-0.123	-0.004	12.085	0.001	-0.170	-0.265	-0.074
	Sex (male = 1)	0.548	0.459	0.306	-0.504	1.115	0.971	0.324	-0.361	-1.079	0.357
	Sepsis (no)	4.528	0.033	0.940	0.074	1.805	0.740	0.390	0.332	-0.424	1.087
	COPD (no)	0.035	0.852	-0.122	-1.404	1.160	1.978	0.160	0.881	-0.347	2.108
	Dementia (no)	0.138	0.710	-0.206	-1.290	0.879	0.063	0.803	0.120	-0.822	1.063
	Previous stroke (no)	0.362	0.548	-0.377	-1.606	0.852	0.067	0.796	-0.144	-1.231	0.943
	Cause of ICU admission	6.186	0.403	NS	NS	NS	4.222	0.647	NS	NS	NS
Total	Age, yr	8.077	0.004	1.465	-3.56	6.490	0.243	0.622	0.007	-0.019	0.033
	SAPS3, %	0.816	0.366	0.044	0.014	0.075	0.832	0.362	0.019	-0.021	0.059
	Total length of stay, d	6.629	0.010	-0.021	-0.066	0.024	4.799	0.028	-0.039	-0.075	-0.004
	KATZ at ICU admission, score	10.269	0.001	-0.056	-0.098	-0.013	0.024	0.876	-0.031	-0.424	0.362
	MRC at ICU admission, score	0.257	0.612	0.826	0.321	1.331	1.077	0.299	-0.024	-0.069	0.021
	KATZ at ward admission, score	10.099	0.001	0.014	-0.040	0.069	0.006	0.937	-0.014	-0.364	0.336
	MRC at ward admission, score	2.743	0.098	-0.752	-1.215	-0.288	4.406	0.036	0.049	0.003	0.095
	Sex (male = 1)	0.157	0.692	-0.047	-0.102	0.009	3.864	0.049	-0.751	-1.499	-0.002
	Sepsis (no)	1.589	0.208	0.169	-0.668	1.007	0.439	0.508	0.247	-0.484	0.978
	COPD (no)	0.002	0.968	0.594	-0.330	1.517	1.076	0.300	0.570	-0.507	1.648
	Dementia (no)	0.028	0.866	-0.026	-1.318	1.265	0.629	0.428	-0.363	-1.261	0.534
	Previous stroke (no)	0.046	0.831	-0.097	-1.226	1.032	3.273	0.070	0.911	-0.076	1.899
	Cause of ICU admission	12.048	0.061	NS	NS	NS	2.985	0.811	NS	NS	NS

KATZ: KATZ Index of Independence in Activities of Daily Living; SAPS3: Simplified acute physiology score; MRC: Medical Research Council; COPD: Chronic obstructive pulmonary disease; NS: No significant; A: Significant differences for categories cardiovascular and respiratory; B: Significant differences for categories gastrointestinal and respiratory.

Table 3 Receiver-operating characteristic curve analysis for significant factors for predicting functional outcomes

Functional outcomes		ΔKATZ					ΔMRC				
		AUC	Cut-off	Sensitivity	Specificity	*P* (Sig.)	AUC	Cut-off	Sensitivity	Specificity	*P* (Sig.)
ICU	Age, yr	0.664	78.5	41%	42%	0.001	[1]	[1]	[1]	[1]	[1]
	SAPS3, %	[1]	[1]	[1]	[1]	[1]	0.661	50.5	68%	52%	0.014
	KATZ at ICU admission, score	0.515	4.5	47%	58%	0.753	[1]	[1]	[1]	[1]	[1]
	MRC at ICU admission, score	0.592	45.5	57%	56%	0.053	0.653	37	44%	35%	0.001
Ward	Age, yr	0.712	81.5	32%	47%	< 0.001	[1]	[1]	[1]	[1]	[1]
	KATZ at ICU admission, score	0.590	4.5	35%	52%	0.035	[1]	[1]	[1]	[1]	[1]
	MRC at ICU admission, score	[1]	[1]	[1]	[1]	[1]	0.681	44.5	39%	42%	< 0.001
	KATZ at ward admission, score	0.746	2.5	63%	12%	< 0.001	[1]	[1]	[1]	[1]	1
	MRC at ward admission, score	0.721	47	69%	67%	< 0.001	0.553	43.3	54%	48%	0.200
Total	Age, yr	0.592	81.5	38%	52%	0.058	[1]	[1]	[1]	[1]	[1]
	Total length of stay, d	0.617	11.5	51%	72%	0.016	0.649	10.5	54%	73%	0.001
	KATZ at ICU admission, score	0.621	3.5	53%	28%	0.012	[1]	[1]	[1]	[1]	[1]
	KATZ at ward admission, score	0.515	4.5	38%	58%	0.750	[1]	[1]	[1]	[1]	[1]
	MRC at ward admission, score	[1]	[1]	[1]	[1]	[1]	0.696	37	51%	35%	< 0.001

[1]Variables with no significant effect on the generalized linear model were not analyzed using ROC curves. KATZ: KATZ Index of Independence in Activities of Daily Living; MRC: Medical Research Council; SAPS3: Simplified acute physiology score; AUC: Area under the curve.

(53%) and increased age in our sample[25,26].

Nonetheless, higher MRC scores at ICU admission were predictive for the improvement in muscle strength and functionality during the ICU stay. These results reinforce the concept that more attention by physical therapists should be given to patients with reduced muscle strength at ICU admission. In this way, the early application of rehabilitation may benefit selected patients. Specifically the application of electrical muscle stimulation[27] or in-bed cycling[28] in the patient group who are un-cooperative or with very poor muscle strength may be beneficial but requires more prospective evaluation.

Interestingly, the KATZ indexes at ICU admission were predictive only for the functional improvement. As a minimum degree of muscle strength is needed for performing the self-care activities, it is likely that individuals with higher KATZ scores had strength about 4-5 in the muscles assessed by the MRC scale. Thus, due to the ceiling effect, further improvements in muscle strength were not detected in patients with higher KATZ scores.

Surprisingly, dementia, considered an exclusion criterion in some mobilization trials 1[11] was not a predictor of no-improvement in muscle strength. Conversely, previous stroke, which results in variable degrees of neuromuscular disability, was predictive of non-improvements in KATZ and MRC scores during the ICU stay.

Functional assessment

The functional progression of hospitalized patients is dependent on many factors. For example, nutritional status, use of certain drugs (corticosteroids, neuromuscular blockers, *etc.*), hyperglycaemia, and multiple organ failure[3,29,30], among others might have influenced the results of this research. Although it can be considered a limitation, we used a representative sample of critically ill patients, and our outcomes provided functional, demographic and clinical parameters to be used as general predictors of muscle strength and functional progress during the hospitalization period. We believe that the findings of this study add new relevant information for the early rehabilitation and mobilization protocols, as well as to serve as a starting point for further research on the individual factors to be considered for these types of intervention.

The functional assessment instrument used in this study was not originally developed for use in the intensive care unit. Similarly, other functional instruments designed for outpatients, such as the Barthel Index and the functional independence measure (FIM) have been used in intensive care[6]. As many ICU patients may present with a very low functional capacity, it is likely that these general functional instruments have some limitation concerning their clinimetric properties. For example in ICU there may be potential for a floor or ceiling effect; limited ability to detect meaningful change (responsiveness) and/or minimal clinically important difference[7]. To date there are no instruments designed to follow the functional progress of patients' from ICU admission to hospital discharge and beyond. Therefore, such general scales seem to be useful for the long term prospective functional monitoring, for both clinical and research purposes.

As intubated and mechanically ventilated patients were not included in this study, it was not possible to analyse the influence of this factor on muscle strength and functional progress during hospitalization. Although muscle weakness is associated with prolonged weaning from mechanical ventilation, there is large variability in the reported prevalence of ICU-AW among mechanically ventilated patients[31]. Therefore, future studies should address if mechanical ventilation is an independent predictor of peripheral muscle strength and functional progress in critically ill patients. Another limitation of the study is that data from deceased patients were not included and analysed. As we used secondary records and patients with incomplete data were excluded, this information was not available in our database. Our study did not focus on mortality outcomes and it hence it would not have been possible to analyze functional progress of these subjects throughout all time points.

In conclusion, better functional patient condition and low severity of illness score at ICU admission, absence of sepsis and stroke, longer total length of stay and age lower than 78.5 years are predictors of favourable patient functional progress during hospitalization following an intensive care admission.

COMMENTS

Background

The advances in critical care have led to increased patient survival, however, severe deficits in physical and psychological status are commonly observed during and after the hospitalization period. The possibility of predicting the patients' functional progress may assist to contribute to individualized rehabilitative interventions in this cohort of patients'. The authors investigated the determining factors of functional progress in a cohort of patients that required intensive care unit (ICU) admission without mechanical ventilation that underwent a mobilization protocol, from the ICU to hospital discharge.

Research frontiers

It un-clear which factors influence the patients' functional recovery during the in-hospital period after a stay in ICU. This study identifies the clinical and functional characteristics that influence the functional progress of hospitalized patients.

Innovations and breakthroughs

These results demonstrated a high prevalence of Intensive Care Unit Acquired Weakness and functional impairments at hospital discharge, similar to previous research. The authors have defined key clinical and functional parameters that predict the functional progress of hospitalized patients who underwent a standardized mobilization protocol through the ICU and the ward setting.

Applications

The rehabilitation of hospitalized patients who require an ICU admission without mechanical ventilation should take into account the predictors of poor functional outcomes identified in this study.

Peer-review

This is a well-written manuscript about functional rehabilitation and muscle strength following an ICU admission.

REFERENCES

1 **Bemis-Dougherty AR**, Smith JM. What follows survival of critical illness? Physical therapists' management of patients with post-intensive care syndrome. *Phys Ther* 2013; **93**: 179-185 [PMID: 22836007 DOI: 10.2522/ptj.20110429]

2 **Hough CL**, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Crit Care* 2011; **15**: R43 [PMID: 21276225 DOI: 10.1186/cc10005]

3 **Koukourikos K**, Tsaloglidou A, Kourkouta L. Muscle atrophy in intensive care unit patients. *Acta Inform Med* 2014; **22**: 406-410 [PMID: 25684851 DOI: 10.5455/aim.2014.22.406-410]

4 **Ntoumenopoulos G**. Rehabilitation during mechanical ventilation: Review of the recent literature. *Intensive Crit Care Nurs* 2015; **31**: 125-132 [PMID: 26026495 DOI: 10.1016/j.iccn.2015.02.001]

5 **World Health Organization**. International Classification of Functioning, Disability and Health (ICF). [accessed 2015 Jul 25]. Available from: URL: http://www.who.int/classifications/icf/en/

6 **Tipping CJ**, Young PJ, Romero L, Saxena MK, Dulhunty J, Hodgson CL. A systematic review of measurements of physical function in critically ill adults. *Crit Care Resusc* 2012; **14**: 302-311 [PMID: 23230880]

7 **Parry SM**, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU - what should we be using? - an observational study. *Crit Care* 2015; **19**: 127 [PMID: 25888469 DOI: 10.1186/s13054-015-0829-5]

8 **KATZ S**, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; **10**: 20-30 [PMID: 5420677 DOI: 10.1093/geront/10.1_Part_1.20]

9 **White DK**, Wilson JC, Keysor JJ. Measures of adult general functional status: SF-36 Physical Functioning Subscale (PF-10), Health Assessment Questionnaire (HAQ), Modified Health Assessment Questionnaire (MHAQ), KATZ Index of Independence in activities of daily living, Functional Independence Measure (FIM), and Osteoarthritis-Function-Computer Adaptive Test (OA-Function-CAT). *Arthritis Care Res* (Hoboken) 2011; **63** Suppl 11: S297-S307 [PMID: 22588752 DOI: 10.1002/acr.20638]

10 **Brorsson B**, Asberg KH. KATZ index of independence in ADL. Reliability and validity in short-term care. *Scand J Rehabil Med* 1984; **16**: 125-132 [PMID: 64948336]

11 **Schweickert WD**, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; **373**: 1874-1882 [PMID: 19446324 DOI: 10.1016/S0140-6736(09)60658-9]

12 **Winkelman C**, Johnson KD, Hejal R, Gordon NH, Rowbottom J, Daly J, Peereboom K, Levine AD. Examining the positive effects of exercise in intubated adults in ICU: a prospective repeated measures clinical study. *Intensive Crit Care Nurs* 2012; **28**: 307-318 [PMID: 22458998 DOI: 10.1016/j.iccn.2012.02.007]

13 **Wallace M**, Shelkey M. Monitoring functional status in hospitalized older adults. *Am J Nurs* 2008; **108**: 64-71; quiz 71-72 [PMID: 18367933 DOI: 10.1097/01.NAJ.0000314811.46029.3d]

14 **Zaharias E**, Cataldo J, Mackin L, Howie-Esquivel J. Simple measures of function and symptoms in hospitalized heart failure patients predict short-term cardiac event-free survival. *Nurs Res Pract* 2014; **2014**: 815984 [PMID: 24672717 DOI: 10.1155/2014/815984]

15 **Etxeberria-Lekuona D**, Casas Fernández de Tejerina JM, Méndez López I, Oteiza Olaso J, Arteaga Mazuelas M, Jarne Betran V. Multiple hospitalizations at the Department of Internal Medicine of a tertiary hospital. *Rev Clin Esp* 2015; **215**: 9-17 [PMID: 25278435 DOI: 10.1016/j.rce.2014.08.007]

16 **Kleyweg RP**, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991; **14**: 1103-1109 [PMID: 1745285 DOI: 10.1002/mus.880141111]

17 **Vanpee G**, Hermans G, Segers J, Gosselink R. Assessment of limb muscle strength in critically ill patients: a systematic review. *Crit Care Med* 2014; **42**: 701-711 [PMID: 24201180 DOI: 10.1097/CCM.0000000000000030]

18 **Connolly BA**, Jones GD, Curtis AA, Murphy PB, Douiri A, Hopkinson NS, Polkey MI, Moxham J, Hart N. Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Crit Care* 2013; **17**: R229 [PMID: 24112540 DOI: 10.1186/cc13052]

19 **Hanekom S**, Gosselink R, Dean E, van Aswegen H, Roos R, Ambrosino N, Louw Q. The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: synthesis of evidence and expert opinion and its translation into practice. *Clin Rehabil* 2011; **25**: 771-787 [PMID: 21504951 DOI: 10.1177/0269215510397677]

20 **Lino VT**, Pereira SR, Camacho LA, Ribeiro Filho ST, Buksman S. Cross-cultural adaptation of the Independence in Activities of Daily Living Index (KATZ Index). *Cad Saude Publica* 2008; **24**: 103-112 [PMID: 18209838 DOI: 10.1590/S0102-311X2008000100010]

21 **Yarnold PR**. UniODA vs. ROC Analysis: Computing the "Optimal" Cut-Point. *Opitmal Data Analysis* 2014; **3**: 117-120. Available from: URL: http://optimalprediction.com/files/pdf/V3A29.pdf

22 **van der Schaaf M**, Beelen A, Dongelmans DA, Vroom MB, Nollet F. Functional status after intensive care: a challenge for rehabilitation professionals to improve outcome. *J Rehabil Med* 2009; **41**: 360-366 [PMID: 19363570 DOI: 10.2340/16501977-0333]

23 **Connolly B**, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, Hart N, Walsh TS, Blackwood B. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. *Cochrane Database Syst Rev* 2015; **(6)**: CD008632 [PMID: 26098746 DOI: 10.1002/14651858.CD008632.pub2]

24 **Denehy L**, Elliott D. Strategies for post ICU rehabilitation. *Curr Opin Crit Care* 2012; **18**: 503-508 [PMID: 22914429 DOI: 10.1097/MCC.0b013e328357f064]

25 **Lipshutz AK**, Gropper MA. Acquired neuromuscular weakness and early mobilization in the intensive care unit. *Anesthesiology* 2013; **118**: 202-215 [PMID: 22929731 DOI: 10.1097/ALN.0b013e31826be693]

26 **Batt J**, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med* 2013; **187**: 238-246 [PMID: 23204256 DOI: 10.1164/rccm.201205-0954SO]

27 RETRACTED ARTICLE: Neuromuscular electrical stimulation in critically ill patients in the intensive care unit: a systematic review. *Einstein* (Sao Paulo) 2014; **12**: 361-365 [PMID: 25865154 DOI: 10.1590/S1679-45082014RW2955]

28 **Parry SM**, Berney S, Warrillow S, El-Ansary D, Bryant AL, Hart N, Puthucheary Z, Koopman R, Denehy L. Functional electrical stimulation with cycling in the critically ill: a pilot case-matched control study. *J Crit Care* 2014; **29**: 695.e1-695.e7 [PMID: 24768534 DOI: 10.1016/j.jcrc.2014.03.017]

29 **de Jonghe B**, Lacherade JC, Sharshar T, Outin H. Intensive care unit-acquired weakness: risk factors and prevention. *Crit Care Med* 2009; **37**: S309-S315 [PMID: 20046115 DOI: 10.1097/CCM.0b013e3181b6e64c]

30 **Puthucheary ZA**, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, Hopkinson NS, Phadke R, Dew T, Sidhu PS, Velloso C, Seymour J, Agley CC, Selby A, Limb M, Edwards LM, Smith K, Rowlerson A, Rennie MJ, Moxham J, Harridge SD, Hart N, Montgomery HE. Acute skeletal muscle wasting in critical illness. *JAMA* 2013; **310**: 1591-1600 [PMID: 24108501]

31 **Hashem MD**, Nelliot A, Needham DM. Early Mobilization and Rehabilitation in the ICU: Moving Back to the Future. *Respir Care* 2016; **61**: 971-979 [PMID: 27094396]

P- Reviewer: Farand P, Hokama A, Juneja D **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.228

World J Crit Care Med 2016 November 4; 5(4): 228-234
ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Prospective Study

Early debridement and delayed primary vascularized cover in forearm electrical burns: A prospective study

Aniruddh Mene, Gautam Biswas, Atul Parashar, Anish Bhattacharya

Aniruddh Mene, Gautam Biswas, Atul Parashar, Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Anish Bhattacharya, Department of Nuclear Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Author contributions: Mene A contributed to the collection of data, organization of manuscript; Biswas G contributed to the conception and design of study, data analysis; Parashar A contributed to the conception and design of study, data analysis, manuscript preparation and review; Bhattacharya A contributed to data analysis and manuscript review.

Institutional review board statement: The format of study was reviewed and approved by the Ethics Committee/Institutional Review Board duly constituted for clinical study at Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh, India.

Informed consent statement: All study participants, or their legal guardian were explained in their own language about the inclusion in the study. Informed written consent was duly taken prior to enrollment in the study.

Conflict-of-interest statement: None of the authors have any conflicts of interests to report.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Dr. Atul Parashar, Associate Professor, Department of Plastic Surgery, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. atulparashar@hotmail.com
Telephone: +91-172-2756792

Received: April 20, 2016
Peer-review started: April 22, 2016
First decision: June 6, 2016
Revised: July 19, 2016
Accepted: August 6, 2016
Article in press: August 8, 2016
Published online: November 4, 2016

Abstract

AIM

To look into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue in electrical burns.

METHODS

A total of 16 consecutive patients sustaining full thickness forearm burns over a period of one year were included in the study group. Debridement was undertaken within 48 h in 13 patients. Three patients were taken for debridement after 48 h. Debridement was repeated within 2-4 d after daily wound assessment and need for further debridement.

RESULTS

On an average two debridements (range 1-4) was required in our patients for the wound to be ready for definitive cover. Interval between each debridement ranged from 2-18 d. Fourteen patients were provided vascularized cover after final debridement (6 free flaps, 8 pedicled flaps). Functional assessment of gross hand function done at 6 wk, 2 mo, 3 mo and 6 mo follow-up.

CONCLUSION

High-tension electrical burns lead to significant morbi-

dity. These injuries are best managed by early decompression followed by multiple serial debridements. The ideal timing of free flap coverage needs further investigation.

Key words: Early debridement; Vascularized cover; Electrical burns; Forearm

Core tip: High-voltage electrical injuries lead to be a significant morbidity associated with severe socioeconomic implications. There is conflicting evidence in the literature regarding progressive tissue necrosis in this devastating injury. We looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which can potentially prevent further progression of this pathology. We found that the phenomenon of ongoing necrosis was not halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Electrical injuries were progressive in nature and required multiple radical debridement until the wound is ready for definitive cover.

Mene A, Biswas G, Parashar A, Bhattacharya A. Early debridement and delayed primary vascularized cover in forearm electrical burns: A prospective study. *World J Crit Care Med* 2016; 5(4): 228-234 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/228.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.228

INTRODUCTION

Contact electrical injuries are a cause of significant damage to tissues, which often result in amputations to the extremities. Unlike the damage caused by thermal burns, high-voltage electrical burns tend to cause a severe and complex injury pattern. There can also be associated neurologic, cardiac, renal, gastrointestinal, ophthalmologic, and psychiatric disturbances[1]. Thus, electrical burns are associated with a significant morbidity, including high amputation rate which in turn is a cause of higher socioeconomic implications[2]. In a study by Noble *et al*[1], 45% of patients with electrical burns needed to change their profession and 32% were not able to return to work. Majority of the high voltage electrical injuries occur at the workplace in the adult age group. In children, injury is usually accidental occurring while playing near high voltage power supply lines[3].

The vascular endothelium provides a high resistant to the flow of electrical current; therefore, the damage was more significant along inner vascular wall. Initially, large blood vessels may appear patent, but if the endothelium was damaged mural thrombi would form, resulting in thrombosis and distal limb ischemia[4]. Thus, considering the conflicting evidence in the literature regarding progressive tissue necrosis, and high amputation rates of this devastating injury, we looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which was hypothesized to prevent further progression of this pathology.

MATERIALS AND METHODS

This was a prospective study which was conducted over a period of 12 mo in the Department of Plastic Surgery at a tertiary level teaching hospital, to include all patients of electrical forearm burns. Those patients with associated life threatening injuries, or obviously charred limb at the time of presentation were excluded. Over a period of 1 year, 81 patients presented with history of sustaining electrical burns. Among these forty-two patients (51.85%) sustained injury to forearm, with or without involvement of other parts of body. However in 18 patients (42.8%) the limb was charred following contact and were excluded. Three (6.9%) patients with severe head injury and 5 (11.9%) patients with spinal cord injury resulting in paraplegia were excluded from the study. Thus, out of total 81 patients, 16 patients fulfilled the inclusion criteria and were included in the study. Patients presenting within 48-96 h were assessed for depth of tissue involved, both clinically and with PET findings. Those presenting later than 96 h were assessed for tissue involvement during debridement.

All patients sustaining these injuries were males and the mean age was 26 years. All injuries were due to high voltage electric contact over hand and forearm. Those presenting within 48 h (n = 6) were infused with Lactated Ringer's infusion with monitoring of urine output, ECG monitoring, and circulatory assessment at 1 hourly intervals as per standard burn resuscitation protocols. Baseline investigations were done on admission and were monitored daily for 7 d. Assessment of urine for myoglobin and renal parameters were done on admission and repeated everyday if deranged. ECG was performed at admission to rule out cardiac irregularities and to assess for hyperkalemia. Those with deranged renal function (n = 2, 12.5%) were assessed and managed in collaboration with nephrologist.

The area of burn was examined and dimensions measured from bony landmarks. The graphical tracing of the injured area was used to measure the length and breadth of the wound while depth of involvement was assessed mainly by identifying structures involved during debridement. Distal limb viability was assessed by examining presence or absence of distal pulsations, capillary refill time and pulse oximetry readings compared with opposite healthy limb if uninjured. In the presence of compromise in the circulation, subjective neurosensory disturbance, pain with passive stretch of intrinsic musculature, decrease in oximetry readings to affected digits or extremity, liberal fasciotomy

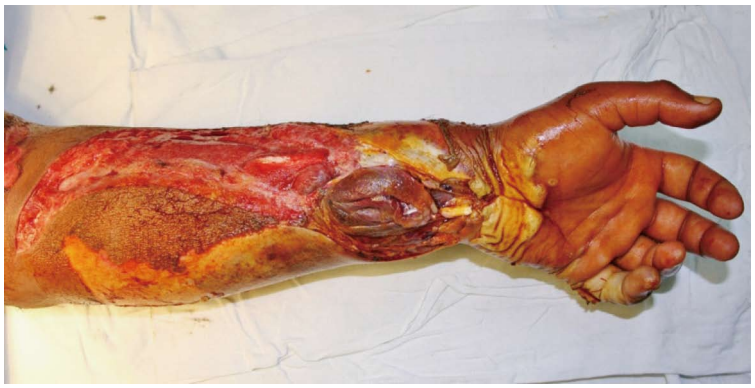


Figure 1 Electrical burns involving volar forearm.

was done with standard defined incisions to release the compartment pressure. Circulatory status was examined and noted at 4 hourly intervals for 24 h and 8 hourly thereafter for 4 d.

Of 16 patients in the study group only 4 patients presented within 96 h and were assessed with PET FDG scan for the depth of tissue involvement. The scan was performed using a Discovery STE-16 PET-CT scanner (GE Healthcare, Milwaukee, United States) after intravenous injection of 370-444 MBq (10-12 mCi) of F-18 FDG. Debridement was undertaken within 48 h in 13 patients. The presence of obvious necrosis was indication for necrectomy. Three patients were taken for debridement after 48 h. One out of 3 had only fasciotomy wound with viable muscles clinically. On primary wound assessment in 2 patients, muscles were not obviously necrotic and were reassessed before debridement. Procedure was conducted under regional or general anesthesia, using tourniquet in all cases. Extent of involvement of muscles, tendons, nerves and vessels were noted. Bleeding, colour and contractility of muscles, along with status of tendons nerves and vessels were noted after tourniquet release.

Debridement was repeated within 2-4 d after daily wound assessment and need for further debridement. On an average two debridements (range 1-4) was required in our patients for the wound to be ready for definitive cover. Interval between each debridements ranged from 2-18 d.

Flap cover was planned depending upon status of the wound. Distant pedicled flaps and free flaps were used to resurface these defects. Locoregional flaps were not available for use due to the nature of the injuries. A total of 8 distant pedicled and 6 free flaps were undertaken. The functional and aesthetic outcome was assessed at 6 wk, 2 mo, 3 mo and 6 mo follow-up. Clinical assessment was done for median, ulnar, and radial nerves, and touch sensations at respective nerve territory were noted. ROM both active and passive of all joints of hand was documented. Patients were provided with activities of daily living (ADL) charts at 3 mo follow-up and asked to score depending on the scale of easy to difficulty in performing outlined tasks. These were scored as 1-no difficulty in performing the activity, 2-mild difficulty, 3-moderate difficulty, 4-severe difficulty, 5-cannot do at all. These activities were reassessed at 6 mo follow-up and any improvement or change of score was noted.

The statistical methods used in this study were approved in ethics committee/institute review board which has biostatistician as a co-opted member.

RESULTS

A total of 16 patients satisfied the inclusion criteria and constituted the study group. Patient's age ranged from 10-45 years, average age being 26 years. All of these 16 patients were males. Incidence of electrical injuries during work was 81.25%. Ten patients were farmers working at the field near transformers, three were electricians injured while repairing high voltage lines. The three pediatric age group patients had contact with high-tension cables running nearby, while playing or flying kite.

All patients were right handed and all injuries were due to high voltage. The dominant hand was affected in 12 of the 16 patients. Bilateral limbs were involved in seven patients Seven (7/16 - 44%) patients required fasciotomy. Fasciotomy was done under local anesthesia in emergency room with standard defined incisions to release the compartment pressure. Of 16 patients, derangement of renal function was observed in two patients (12.5%). One patient required multiple sittings of haemodialysis and other patient was managed conservatively with forced diuresis and urine alkalinization. On assessment of wound prior to debridement the average surface area involved was found to be 40.37 cm^2 (range 5-82.5 cm^2). The volar forearm was involved in 14 patients; while 2 patients had involvement of hand, and thumb (Figure 1). The hand as a whole was viable in all patients, except two patients who had non-viable little finger which required debridement. Patients had involvement of either median, ulnar nerve. Radial nerve was not involved as injury was predominantly on volar aspect of forearm. Three patients showed involvement of combined median and ulnar nerve. Involvement of only median nerve was seen in two patients, while only ulnar nerve was involved in six patients.

PET scan was done in four patients for assessment

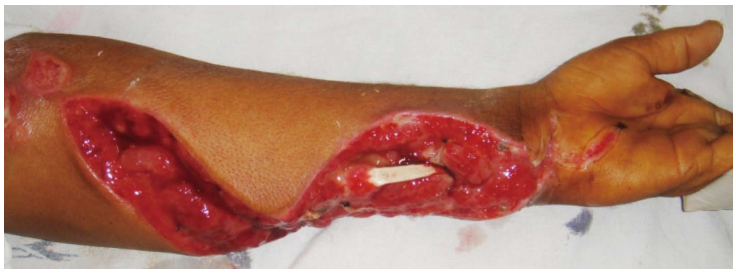


Figure 2 Forearm electrical burns after multiple debridements.

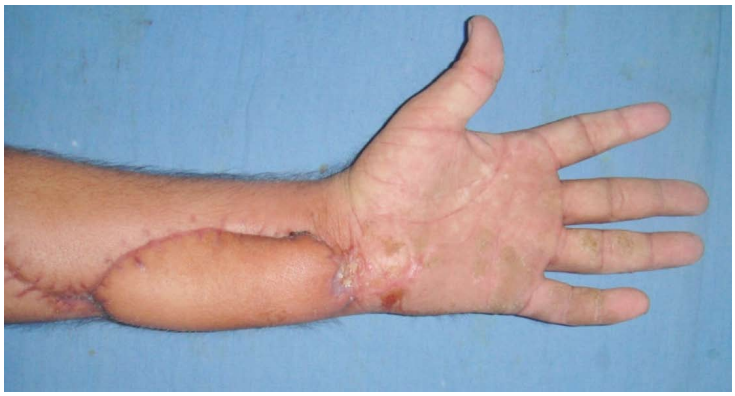


Figure 3 Final outcome after flap cover.

of involvement of deeper tissues focusing on accuracy and predictability of PET in assessing this. FDG uptake was adequately seen in upper third proximal muscle bellies of volar forearm. Pronater quadratus was involved in three cases, *i.e.*, showed no glucose uptake. Flexor digitorum profundus was involved in all four patients. Flexor digitorum superficialis was injured in three-patients. The debridement findings in these patients correlated well with PET findings.

Debridement was undertaken under regional or general anesthesia, tourniquet was used in all cases. Debridement was considered to be complete when clinically there was no evidence of obvious necrotic tissues or slough in the wound (Figure 2). Patients underwent regular dressings and removal of obvious necrotic tissues during dressings. Debridement was repeated under anesthesia and tourniquet control in 10 patients and in six patients single debridement was done. Seven patients with bilateral limb involvement required more than one debridement, range 2-4 (mean 3 debridements). Three patients with unilateral limb involvement required more than one debridement (mean 2). The mean surface area of the wound after final debridement was measured 47 cm^2 (range 5-96 cm^2) from initial measurement of 40.37 cm^2 showing 15.9% increase. Fourteen patients were provided vascularized cover after final debridement (6 free flaps, 8 pedicled flaps) (Figure 3); two patients had viable muscles exposed post fasciotomy, which were covered with skin graft.

Free flaps were selected on the basis of size and shape of wound, tissue requirement, availability of the recipient vessels and general condition of patient. Distant pedicled flap was selected in cases with recipient vessels involvement, associated proximal injury leading to impaired venous return of distal part, and associated co morbidities. Of the 6 free flaps, anterolateral thigh flap (n-2), latissimus dorsi flap (n-1), thoracodorsal artery perforator flap (n-2), and lateral arm flap (n-1) were done. In four patients, ulnar artery was used as a recipient vessel, while in two patients radial artery was used as a recipient vessel. Three out of six free flaps necrosed. All patients in whom flaps failed had undergone single debridement before flap transfer. The status of wound prior to flap transfer in these three patients showed apparently healthy looking and viable muscles. The vessels including radial and ulnar artery were patent proximally. All three flaps were transferred between 2-8 d post injury. Earliest free flap was done 2 d after debridement in which flap necrosed. Three flaps, which survived, were transferred after two weeks of injury. In case of distant pedicled flaps, 2 groin flaps, 1 bipedicled abdominal flap, 5 thoraco-umbilical flaps were used.

Functional assessment of gross hand function done at 6 wk, 2 mo, 3 mo and 6 mo follow-up. Patients were provided with ADL charts and asked to score depending on the scale of easy to difficulty in performing outlined tasks. The ADL score in all 16 patients were between 3-5. There was no progression and/or improvements in scores at three and six months follow-up.

DISCUSSION

The aims of treatment in electrical burns are to achieve good final function with good cosmetic appearance along with early return to a normal productive life. The aim of present study was to assess whether the extent of forearm injury and tissue damage was progressive and to determine whether early debridement and

vascularized cover prevented progressive tissue necrosis and halted further progression.

Electrical injury usually affects young age group individuals; the incidence is high amongst males as compared to females because of work related nature of injury. The age group involved in various studies ranged from 10-50 years[5-7]. In our study, we observed 81.25% of the injuries to occur during work. Majority of our patients were farmers injured while working in the fields near transformers. We also observed a clear relationship between hand dominance and limb involved as 75% of our patients had dominant limb affected by injury supporting the observation that most of injuries occurred at workplace.

There is a significant variation in the rate of escharotomy/fasciotomy in electrical burns, which ranges from 9.2% to 54%[1,4,5]. Although, some studies advocate an immediate decompression[8], this concept has been questioned by others[9]. Mann *et al*[9] advocated selective decompression only in the presence of signs of compartment syndrome. They have based their algorithm on a continuous clinical evaluation and they opine that selective, non-immediate decompression may preserve tissue thus contributing to lower amputation rates. They did fasciotomy in 22% of their patients within 24 h. We opted for decompressive fasciotomy within 48 h of injury in 56% of patients.

d'Amato *et al*[3] and Ferreiro *et al*[5] in their individual studies supported the fact of early and radical debridement of all the necrotic tissues in electrical burns. d'Amato *et al*[3] also suggested the value of extended fasciotomy to access the viability of muscles. They said debride when necessary, and relieve the pathologic elevation of compartment pressures in an attempt to prevent ongoing neuromuscular damage. These observations support the need of early exploration with wide exposure of deep muscle compartments to assess the extent of injury in high-voltage burns. In present study, we did fasciotomy in nine patients with signs of increased compartment pressure and found that neuromuscular damage could be prevented with extended fasciotomies.

Scheker *et al*[8] were also of opinion that a wound should be radically debrided and cover should be provided immediately, they have proven this method of treatment to be superior to conservative debridement and delayed vascularized cover. They concluded that immediate reconstruction of severe upper extremity injuries is associated with increased function, lesser complications and a shorter hospital stay. According to authors, immediate reconstruction also permits earlier mobilization thereby preventing the tendon adhesions. We opted for radical debridement in our patients; however, the ongoing progression of tissue necrosis prevented us from immediate reconstruction.

García-Sánchez *et al*[2] observed myoglobinuria in 70% of their patients, while Mann *et al*[9] had reported 53.2% patients had myoglobinuria. In neither of these studies, authors observed their patients requiring haemodialysis for renal failure. Ferreiro *et al*[5] required hemodialysis in 3% of their patients. We observed two patients with myoglobinuria, one of which required haemodialysis. Both patients showed improvement in their renal functions after debridement. Thus, we observed that low urine output, and persistent acidosis is indication for exploration and debridement rather than conservative management of myoglobinuria.

Ferreiro *et al*[5] reported that the most frequently affected nerves were the ulnar and the median nerves. In their series, the incidence of peripheral neurological injury was 30%. The permanent peripheral neurological injury was located at the point of entry of the current in 88% of the cases and there was no recovery of sensations or movement during a period of six months after the trauma. Mazzetto-Betti *et al*[7] had ulnar clawing in 22% and median claw in 5% of cases. Analyzing hand sensation in their study, the radial nerve was the least affected among the patients. Sensation improvement was worst for the median nerve. In present study, we observed 38% patients with injury to ulnar nerve, while median nerve was affected in 12.5% of patients. Combined median and ulnar nerve was seen in 19% patients while none of our patients had involvement of radial nerve because of predominant involvement of volar forearm in our patients.

Burn wound depth is a significant determinant of patient treatment and morbidity. Devgan *et al*[10] reviewed modalities for the assessment of burn wound depth and concluded that Indo cyanine green video angiography or Laser Doppler Imaging is appropriate to best assess the depth of acute burn wounds. Nettelblad *et al*[11] used MRI as diagnostic modality in two patients with electrical burns. They suggested that the alteration of tissue signal exhibited by necrosed muscle is not specific to the injury mechanism. Smith *et al*[12] investigated the use of 18FDG PET scanning for assessment of skeletal muscle viability. They concluded that FDG-PET scanning could determine skeletal muscle viability in patients with peripheral vascular disease and in patients following free-flap transfer. In our study, we used FDG PET for assessment of muscle viability in four patients who presented within 96 h of injury. The numbers were less because of varied timing of presentation of patients. The findings at debridement correlated well with PET findings and the investigation aided the surgeon during debridement. The tool can be used in conjunction with clinical evaluation for deep muscle necrosis in electrical burns but further studies are needed in this context to reach any definitive conclusion.

The distant microvascular tissue transfer primarily aims at improving limb salvage rates in electrical burns. The transfer of well vascularized distant tissue in an ischemic bed can potentially lead to preservation of tissues. However, the best timing for free microvascular tissue transfer in electrical burn injuries remains debatable. Sauerbier *et al*[13] reported a higher free flap failure rate of 24% in electrical burns during primary

reconstruction (within 5-21 d after trauma). In their later publication, they described a "vulnerable phase" of 3 wk after trauma in which vascular instability may compromise free flap success[14]. In contrast to this finding, Koul *et al*[15] found no variation in flap survival when performing microvascular tissue transfer in this vulnerable phase. Similar findings were reported earlier by Ninkovic *et al*[16]. Our own results favor the hypothesis of a vulnerable phase. In our series, flap failure due to microvascular thrombosis was seen exclusively in flaps transferred during the first 2 weeks. In our study, we found that the injury was progressive in nature and eventually required multiple radical debridements until the wound was ready for definitive cover. The phenomenon of ongoing necrosis was not found to be halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Shen *et al*[17] also observed the phenomenon of distal flap necrosis and wound bed necrosis in early coverage of forearm electrical burns. Dega *et al*[18] were also able to achieve stable wound bed in patients of electrical burns after 12 d.

In present study, we observed average 61 d of hospital stay, which was directly related to number of procedures patient required for definitive wound cover. Handschin *et al*[19] reported average 44 d of hospital stay and Noble *et al*[1] in their study reported hospital stay 24.5 ± 21 d in electrical injuries.

The return to work data in the existing literature is rare and is difficult to interpret. A retrospective review by Mazzetto-Betti *et al*[7] reports that 72% patients retired or changed their job. Kidd *et al*[6] however reported that average time to return to work was 101 d post injury. Six patients in our study, returned to work after average 98 d post injury. Amongst these, three were students, two were farmers, and they adapted to use their contra-lateral uninjured limb. One patient was electrician who changed his job and presently doing farming with uninjured limb. None of our patients with bilateral involvement returned to work.

Following analysis of 16 patients of forearm electrical burns, it was concluded from the study that: (1) most common victims of electrical injury were young adult males. It affected the dominant limb more commonly and injury predominantly occurred at the workplace; (2) fasciotomy performed within 48 h of injury with slightest evidence of compartment syndrome was found to be limb saving; (3) there was a direct correlation between the point of entry of the current and the resulting neurological injury; (4) the clinical and PET assessment of deeper soft tissue involvement showed that injury affected periosseus tissues more than superficial muscles and skin; (5) electrical injuries were progressive in nature and required multiple radical debridement until the wound is ready for definitive cover; (6) the phenomenon of ongoing necrosis was not halted in our study and all our early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma; and (7) distant pedicled flaps offered a viable and safe option for early coverage of hand and forearm defect in the presence of recipient vessel injury. To conclude, high-tension electrical burns represent a severe injury with significant morbidity and the time tested concepts of early fasciotomy followed by repeated debridements remain the procedure of choice. The ideal timing of free flap coverage for these wounds needs further investigation.

COMMENTS

Background

High-voltage electrical burns are found to be associated with a significant morbidity leading to severe socioeconomic implications. Considering the conflicting evidence in the literature regarding progressive tissue necrosis in this devastating injury, the authors looked into the management options of early debridement of the wound, followed by vascularized cover to bring in fresh blood supply to remaining tissue, which can potentially prevent further progression of this pathology.

Research frontiers

The timing of flap coverage in electrical burns is debatable because of presence of progressive tissue necrosis following electrical insult. Flaps done at first debridement can fail because of progression of tissue necrosis.

Innovations and breakthroughs

The authors found that the phenomenon of ongoing necrosis was not halted and all their early flaps failed to ingress the blood flow to the so-called ischemic zone post trauma. Serial debridements were required to achieve viable tissue bed. In addition distant pedicled flaps also allowed for safe and early coverage of hand and forearm defect and this method of reconstruction represented alternative to free tissue transfer in the presence of recipient vessel injury.

Applications

The study results suggest that electrical burns do lead to progressive tissue necrosis and any flap coverage should be contemplated after this process has stabilized.

Terminology

Progressive tissue necrosis is seen in electrical burns because of progressive microvascular thrombosis. This requires multiple stages of debridements.

Peer-review

The study on electrical burns is relatively well-presented. It is an interesting article in this field.

REFERENCES

1 **Noble J**, Gomez M, Fish JS. Quality of life and return to work following electrical burns. *Burns* 2006; **32**: 159-164 [PMID: 16448771]

2 **García-Sánchez V**, Gomez Morell P. Electric burns: high- and low-tension injuries. *Burns* 1999; **25**: 357-360 [PMID: 10431986 DOI: 10.1016/S0305-4179(98)00189-2]

3 **d'Amato TA**, Kaplan IB, Britt LD. High-voltage electrical injury: a role for mandatory exploration of deep muscle compartments. *J Natl Med Assoc* 1994; **86**: 535-537 [PMID: 8064905]

4 **Herrera FA**, Hassanein AH, Potenza B, Dobke M, Angle N. Bilateral upper extremity vascular injury as a result of a high-voltage electrical burn. *Ann Vasc Surg* 2010; **24**: 825.e1-825.e5 [PMID: 20472384 DOI: 10.1016/j.avsg.2010.02.027]

5 **Ferreiro I**, Meléndez J, Regalado J, Béjar FJ, Gabilondo FJ. Factors influencing the sequelae of high tension electrical injuries. *Burns* 1998; **24**: 649-653 [PMID: 9882065 DOI: 10.1016/S0305-4179(98)00082-5]

6 **Kidd M**, Hultman CS, Van Aalst J, Calvert C, Peck MD, Cairns BA. The contemporary management of electrical injuries: resuscitation, reconstruction, rehabilitation. *Ann Plast Surg* 2007; **58**: 273-278 [PMID: 17471131 DOI: 10.1097/01.sap.0000250837.18740.d9]

7 **Mazzetto-Betti KC**, Amâncio AC, Farina JA, Barros ME, Fonseca MC. High-voltage electrical burn injuries: functional upper extremity assessment. *Burns* 2009; **35**: 707-713 [PMID: 19203837 DOI: 10.1016/j.burns.2008.10.002]

8 **Scheker LR**, Ahmed O. Radical debridement, free flap coverage, and immediate reconstruction of the upper extremity. *Hand Clin* 2007; **23**: 23-36 [PMID: 17478250 DOI: 10.1016/j.hcl.2006.12.003]

9 **Mann R**, Gibran N, Engrav L, Heimbach D. Is immediate decompression of high voltage electrical injuries to the upper extremity always necessary? *J Trauma* 1996; **40**: 584-587; discussion 584-589 [PMID: 8614037 DOI: 10.1097/00005373-199604000-00011]

10 **Devgan L**, Bhat S, Aylward S, Spence RJ. Modalities for the assessment of burn wound depth. *J Burns Wounds* 2006; **5**: e2 [PMID: 16921415]

11 **Nettelblad H**, Thuomas KA, Sjöberg F. Magnetic resonance imaging: a new diagnostic aid in the care of high-voltage electrical burns. *Burns* 1996; **22**: 117-119 [PMID: 8634117 DOI: 10.1016/0305-4179(95)00104-2]

12 **Smith GT**, Wilson TS, Hunter K, Besozzi MC, Hubner KF, Reath DB, Goldman MH, Buonocore E. Assessment of skeletal muscle viability by PET. *J Nucl Med* 1995; **36**: 1408-1414 [PMID: 7629586]

13 **Sauerbier M**, Ofer N, Germann G, Baumeister S. Microvascular reconstruction in burn and electrical burn injuries of the severely traumatized upper extremity. *Plast Reconstr Surg* 2007; **119**: 605-615 [PMID: 17230097 DOI: 10.1097/01.prs.0000246512.47204.da]

14 **Ofer N**, Baumeister S, Megerle K, Germann G, Sauerbier M. Current concepts of microvascular reconstruction for limb salvage in electrical burn injuries. *J Plast Reconstr Aesthet Surg* 2007; **60**: 724-730 [PMID: 17482533 DOI: 10.1016/j.bjps.2006.12.010]

15 **Koul AR**, Patil RK, Philip VK. Early use of microvascular free tissue transfer in the management of electrical injuries. *Burns* 2008; **34**: 681-687 [PMID: 18241999 DOI: 10.1016/j.burns.2007.08.025]

16 **Ninkovic M**, Deetjen H, Ohler K, Anderl H. Emergency free tissue transfer for severe upper extremity injuries. *J Hand Surg Br* 1995; **20**: 53-58 [PMID: 7759937 DOI: 10.1016/S0266-7681(05)80017-8]

17 **Shen YM**, Hu XH, Mi HR, Yu DN, Qin FJ, Chen H, Wang H, Zhang GA. Early treatment of high-voltage electric burn wound in the limbs. *Zhonghua Shaoshang Zazhi* 2011; **27**: 173-177 [PMID: 21781461]

18 **Dega S**, Gnaneswar SG, Rao PR, Ramani P, Krishna DM. Electrical burn injuries. Some unusual clinical situations and management. *Burns* 2007; **33**: 653-665 [PMID: 17161540 DOI: 10.1016/j.burns.2006.09.008]

19 **Handschin AE**, Vetter S, Jung FJ, Guggenheim M, Künzi W, Giovanoli P. A case-matched controlled study on high-voltage electrical injuries vs thermal burns. *J Burn Care Res* 2009; **30**: 400-407 [PMID: 19349896 DOI: 10.1097/BCR.0b013e3181a289a6]

P- Reviewer: Inchauspe AA, Losanoff JE, Mocellin S
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Wu HL

World Journal of Critical Care Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5492/wjccm.v5.i4.235

World J Crit Care Med 2016 November 4; 5(4): 235-250
ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Plasma-Lyte 148: A clinical review

Laurence Weinberg, Neil Collins, Kiara Van Mourik, Chong Tan, Rinaldo Bellomo

Laurence Weinberg, Department of Surgery, Perioperative Pain Medicine Unit, University of Melbourne, Victoria 3084, Australia

Laurence Weinberg, Kiara Van Mourik, Chong Tan, Department of Anesthesia, Austin Hospital, Heidelberg, Melbourne, Victoria 3084, Australia

Neil Collins, Department of Anesthesia, Joondalup Health Campus, Joondalup, Perth 6027, Australia

Rinaldo Bellomo, Department of Intensive Care, Austin Hospital, Heidelberg, Melbourne, Victoria 3084, Australia

Author contributions: Weinberg L, Collins N and Van Mourik K performed the literature review and wrote the paper; Tan C and Bellomo R assisted in the writing of the manuscript.

Conflict-of-interest statement: Weinberg L is a recipient of research grants from Baxter Healthcare and is the Principle Investigator for the SPLIT-Major Surgery study. Bellomo R is a recipient of research grants from Baxter Healthcare and is a Principle Investigator for the SPLIT major surgery study. Baxter Healthcare is not involved in the design, collection of data, analyses, or interpretation of data from any Baxter sponsored fluid intervention study at the Austin Hospital. This review has been initiated and written independently of Baxter Healthcare or any other commercial institution.

Data sharing statement: No additional data available.

Manuscript source: Invited manuscript

Correspondence to: Laurence Weinberg, Associate Professor, Department of Anesthesia, Austin Hospital, Studley Rd, Heidelberg, Melbourne, Victoria 3084, Australia. laurence.weinberg@austin.org.au

Telephone: +61-3-94965000
Fax: +61-3-94596421

Received: March 27, 2016
Peer-review started: March 30, 2016
First decision: May 13, 2016
Revised: September 20, 2016
Accepted: October 5, 2016
Article in press: October 9, 2016
Published online: November 4, 2016

Abstract

AIM

To outline the physiochemical properties and specific clinical uses of Plasma-Lyte 148 as choice of solution for fluid intervention in critical illness, surgery and perioperative medicine.

METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources including studies that compared Plasma-Lyte 148 to other crystalloid solutions. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". All relevant articles were accessed in full. We summarized the data and reported the data in tables and text.

RESULTS

We retrieved 104 articles relevant to the choice of Plasma-Lyte 148 for fluid intervention in critical illness, surgery and perioperative medicine. We analyzed the data and reported the results in tables and text.

CONCLUSION

Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition

that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to saline in improving physicochemical outcomes. Further large randomized controlled trials assessing the comparative effectiveness of Plasma-Lyte 148 and other crystalloid solutions in measuring clinically important outcomes such as morbidity and mortality are needed.

Key words: Surgery; Anesthesia; Fluid therapy; Crystalloids; Saline; Plasma-Lyte; Hartmann's; Ringers; Acetate; Gluconate; Lactate

Core tip: Plasma-Lyte 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. It is physiologically different to the commonly available crystalloids solutions such as Hartmann's solution and sodium chloride (0.9%). Before using any crystalloid solution as fluid therapy, clinicians should have a fundamental understanding of each fluids specific physiological properties.

Weinberg L, Collins N, Van Mourik K, Tan C, Bellomo R. Plasma-Lyte 148: A clinical review. *World J Crit Care Med* 2016; 5(4): 235-250 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i4/235.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i4.235

INTRODUCTION

The use of intravenous (*IV*) fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection that is generally decided by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. Compared to colloids, crystalloids are often the preferred solution for replacement or maintenance fluid therapy as they are relatively cheap, commonly available, easily transportable and storable with a good shelf life, and have no allergy risk. In addition, crystalloids are easy to manufacture, require no special compatibility testing, are widely available and accessible even in developing countries, and can be freely given to patients with religious objections to blood or blood related products. Currently, sodium chloride 0.9%, commonly referred to as normal saline 0.9% (NS), Ringer's Lactate and Hartmann's solution are commonly available crystalloid solutions worldwide. However, their electrolyte composition is significantly different from that of plasma[1]. In contrast, Plasma-Lyte 148 (PL 148) has physiochemical properties similar to plasma, however PL 148 has yet to be the subject of a detailed clinical review. Therefore, we present a comprehensive review of PL 148, comparing its physiochemical properties to other commonly available crystalloids solutions and evaluating its utility as a buffered fluid solution. We also discuss the role of PL 148 solution in critical care medicine and anesthesia.

MATERIALS AND METHODS

We performed an electronic literature search from Medline and PubMed (*via* Ovid), anesthesia and pharmacology textbooks, and online sources. The following keywords were used: "surgery", "anaesthesia", "anesthesia", "anesthesiology", "anaesthesiology", "fluids", "fluid therapy", "crystalloid", "saline", "Plasma-Lyte", "plasmalyte", "hartmann's", "ringers" "acetate", "gluconate", "malate", "lactate". Only studies that compared PL 148 to other crystalloid solutions were included. Articles in the English language with human and animal studies were considered. Date restrictions were not applied. The last electronic literature update was in December 2015. In total, after appropriate screening against the inclusion criteria, we retrieved 557 references or full-text journal articles for analysis and critical review. Three authors conducted the search and data extraction. Two authors analyzed the results. Including online journal articles and textbooks, 104 articles were included this review.

RESULTS

Description of product

PL 148, also known as Plasma-Lyte A, is a sterile isotonic non-pyrogenic IV crystalloid solution used in clinical medicine to provide water, electrolytes and calories to patients. PL 148 is a trade mark of Baxter International Inc. First patented in 1982, it is available in 1000 mL and 500 mL Viaflex containers and has been commercially available for peri-operative fluid intervention for over 25 years in the United States, Australasia and the United Kingdom. The electrolyte composition of PL 148 more closely reflects the constituents of human plasma compared with both Hartmann's Solution and NS, and is hence considered a more "physiological" solution. It is commonly used as both a resuscitation and maintenance fluid in the critical care setting and for perioperative fluid intervention in elective and emergency surgery.

Each 1000 mL of PL 148 contains 5.26 g sodium chloride, 370 mg potassium chloride, 300 mg magnesium chloride, 3.68 g and 5.02 g of sodium acetate and sodium gluconate respectively; this equates to 140 mmol/L sodium, 5 mmol/L potassium, 1.5 mmol/L magnesium, 98 mmol/L chloride, and 27 mmol/L and 23 mmol/L of acetate and gluconate, respectively. The physiochemical properties of PL 148 compared to plasma and other commonly available crystalloid solutions are summarized

Table 1 Characteristics of common crystalloid solutions compared to human plasma

	Sodium (mmol/L)	Potassium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Acetate (mmol/L)	Gluconate (mmol/L)	Lactate (mmol/L)	Malate (mmol/L)	eSID (mEq/L)	Theoretical osmolarity (mOsmol/kg)	Actual or measured [1]osmolality (mOsmol/kg)	pH
Plasma	136-145	3.5-5.0	0.8-1.0	2.2-2.6	98-106	Nil	Nil	Nil	Nil	42	291	287	7.35-7.45
Sodium chloride (0.9%)	154	Nil	Nil	Nil	154	Nil	Nil	Nil	Nil	0	308	286	4.5-7
Compound sodium Lactate (lactate buffered)	129	5	Nil	2	109	Nil	Nil	29	Nil	29	28	278	5-7
Ringer's lactate (lactate buffered)	130	4	Nil	3	109	Nil	Nil	28	Nil	27	278	256	5-7
Ionosteril® (acetate buffered solution)	137	4	1.25	1.65	110	36.8	Nil	Nil	Nil	36.8	291	20	6.9-7.9
Sterofundin ISO® (acetate and malate buffered)	145	4	1	2.5	127	24	Nil	Nil	5	25.5	309	Not stated	5.1-5.9
Plasma-Lyte 148® (acetate and gluconate buffered)	140	5	1.5	Nil	98-106	27	23	Nil	Nil	50	295	271[2]	7.4[3]

[1]Freezing point depression; [2]Australian and New Zealand formulation; however approximate osmolality may vary depending on country of manufacture; [3]Australian and New Zealand formulation; however pH ranges from 6.5 to 8.0 depending on country of manufacture. Plasma-Lyte 148 manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ringer's Lactate manufactured by Baxter Healthcare, Deerfield, IL, United States; Hartmann's solution manufactured by Baxter Healthcare, Toongabie, NSW, Australia; Ionosteril manufactured by Fresenius Medical Care, Schweinfurt, Germany; Sterofundin ISO manufactured by B. Braun Melsungen AG, Melsungen, Germany.

in Table 1. Unlike Hartmann's solution, which contains calcium, PL 148 is calcium free and therefore compatible with blood and blood components. PL 148 contains no antimicrobial agents. The caloric content is approximately 66 kilojoules/L or 16 kcal/L. The numeric "148" is a derivative of the sum of each of PL 148's cationic concentrations, *i.e.*, 140 mEq (sodium) plus 5 mEq (potassium) plus 3 mEq (magnesium), which equates to a sum total of "148 mEq". The formulation "PL 148 (approximate pH 7.4)" is available in Australia and New Zealand. The formulation is approved by the Australian Therapeutics Goods Administration and registered in both Australia (AUST 231424 and 48512) and Medsafe (New Zealand). The pH of PL 148 is adjusted with sodium hydroxide and reported as approximately 7.4, however depending on country of manufacture, the pH ranges from 6.5 to 8.0. PL 148 is supplied in VIAFLEX™ plastic bag containers produced from a uniquely formulated polyvinyl chloride. VIAFLEX is a trademark of Baxter International Inc. Safety of the polyvinyl chloride has been confirmed in animal and tissue culture toxicology studies.

DISCUSSION

Contraindications and precautions

There are no published cases in the medical literature of PL 148 hypersensitivity reactions, however anaphylactic and hypersensitivity infusion reactions have been reported[2]. As the PL 148 bag is an adaptable or flexible plastic container, it should not be connected in series with other fluid containers due to the risks of air embolism. Pressure infuser bags to increase flow rates should be used very cautiously with any of the PL 148 containers, as any residual air in the container that has not been evacuated prior to administration, can result air embolism. Similarly, the use of open vented IV administration sets can also result in air embolism, and these should not be used with the PL 148 flexible container.

Compatibility with other IV medications

The physical compatibility of PL 148 with medications commonly used in the operating theatre and critical care settings has been investigated[3]. PL 148 was

tested with 87 drugs for physical compatibility immediately on mixing, 1 h and 4 h after mixing. Y-site compatibility was determined by visual examination performed with laboratory light. Turbidity was measured with high-intensity light using a portable turbidimeter. On mixing, visual appearance changes occurred with amiodarone, cyclosporine, propofol and mycophenolate. An increase in turbidity was observed with pantoprazole and phenytoin, amiodarone, cyclosporine, propofol and mycophenolate.

Drug interactions

Similar to all crystalloid solutions, PL 148 should be used cautiously in patients on corticosteroids due to additive risks of sodium and fluid retention. More specific to PL 148, due to its alkalinizing effects, the renal elimination of acidic drugs such as aspirin and barbiturates, or drugs such as lithium, may increase[2]. The renal elimination of alkaline drugs such as quinidine, or dextroamphetamine (dexamphetamine) and sympathomimetics (*e.g.*, ephedrine) may be decreased. At present there is insufficient evidence for any dose adjustment with any of the stated interacting drugs.

Drug and laboratory test interactions

As gluconate plays a role in the galactomannan antigenicity of PL 148, patients receiving PL 148 may test positive for the galactomannan antigen. Previous studies have reported that patients and healthy volunteers receiving PL 148 have demonstrated a false-positive circulating galactomannan test lasting for up to 24 h[4-7]. Galactomannan antigen is a biomarker for pulmonary aspergillosis in immunocompromised patients. Positive test results in patients receiving PL 148 should therefore be interpreted cautiously and the galactomannan antigen should be confirmed by other diagnostic methods[4]. More recently however, Spriet *et al*[8] tested 33 distinct batches of PL 148 and reported that with contemporary sophisticated manufacturing processes, PL 148 does not result in false-positive galactomannan test results.

Carcinogenesis, pregnancy and geriatric patients

There are no studies of PL 148 that have evaluated its carcinogenic and mutagenic potential. It is unknown if PL 148 has any effects on fertility. In the United States, PL 148 is classed as "Category C" in pregnancy. No "category" is stated in the Australian Product Information for PL 148. Drugs in "Category C" may cause harmful, but reversible effects to the fetus or neonate, however do not result in deformity or malformation. The Australian categorization system of medicines for use in pregnancy differs from the Food and Drug Administration categorization in the United States and does not follow a hierarchical structure. To date, there are no animal reproduction studies of PL 148 and it is not known if PL 148 causes foetal adverse effects when administered during pregnancy, or whether PL 148 affects reproduction capacity. There is no evidence to suggest that PL 148 is excreted in breast milk. There is insufficient information to determine if elderly patients respond differently from younger subjects. In general, dose selection of PL 148 in the elderly should take into consideration cardiac, renal, and hepatic function, together with pre-existing comorbidities and pharmacological therapy.

Physiological properties of PL 148

PL148 is marketed as a "physiological" and "balanced" fluid, because its composition closely reflects that of plasma. Its physiochemical properties are however different from the commonly used crystalloids: NS and Hartmann's solution. Outlined below are the key differences between PL 148 and these commonly available crystalloid solutions.

Osmolality: Normal plasma osmolality is 280-296 mOsmol/kg. PL 148 is an isotonic solution with an approximate osmolality of 271 mOsmol/kg (current formulation in Australia and New Zealand), as determined by an osmometer using the technique of freezing-point depression. In other countries, the stated osmolality is approximately 291 mOsmol/kg. Osmolarity is the measure of the solute concentration, or the number of osmoles of solute particles per unit volume of solution. The osmotic pressure of a solution determines how a solvent will diffuse across a semipermeable membrane (osmosis) that separates two solutions of different osmotic concentrations. The osmotic activity of IV fluids is best described by the calculated *in vivo* osmolality (mOsmol/kg) of that solution[9]. Tonicity on the other hand, is a measure of the effective osmotic pressure gradient of two different solutions that are separated by a semipermeable membrane. Therefore, tonicity can be described as the "relative concentration" of solutions, which in turn, determine the direction and degree of diffusion of that solution. The terminology is distinctive; osmolarity is the total concentration of diffusible and non-diffusible solutes, whereas tonicity takes into account the total concentration of only non-diffusible solutes.

PL 148 is considered a "balanced" fluid and isotonic with plasma, because it has a calculated *in vivo* osmolality within the normal physiological range of 270 to 290 mOsmol/kg[10]. Interestingly, NS is considered "hypertonic" with an *in-vitro* osmolality of 308 mOsmol/kg (154 mOsmol/kg Na^+, 154 mOsmol/kg Cl^-). However, as its electrolyte components are only partly active (osmotic coefficient of 0.926[9]), NS is "isotonic" (calculated *in-vivo* osmolality of 287 mOsmol/kg[11]). In contrast to both PL 148 and NS, Hartmann's solution is relatively "hypotonic" with an *in-vivo* osmolality of 254 mOsmol/kg. Fluids that are hypotonic relative to plasma, can result in retention of free water and consequent hyponatremia, effects frequently compounded by the release of anti-diuretic hormone, which is stimulated with critical illness,

anesthesia, and surgical stress[12]. Hypotonic fluids should be used extremely cautiously, if at all, in patients with fluid overload states, hyponatremia, critical illness, or in the setting of raised intracranial pressure. Failure to excrete this water load can cause postoperative fluid balances excess, weight gain, and resulting tissue edema and cellular dysfunction[13].

Chloride concentration: Normal plasma concentration of chloride ranges between 98 and 106 mmol/L. PL 148 contains a physiological amount of chloride (98 mmol/L), whilst Hartmann's solution is slightly hyperchloremic relative to plasma (109 mmol/L). In contrast, NS contains supra-physiological concentrations of chloride (154 mmol/L), with accumulating data and expert opinion supporting the view that large volumes of NS cause a normal anion gap hyperchloremic metabolic acidosis[14]. Even the infusion of IV NS over a few hours has been shown to cause a metabolic acidosis *via* this mechanism[15-19]. Whilst the development of acidosis may result in impaired cardiac contractility, arrhythmias, pulmonary hypertension, renal and splanchnic vasoconstriction and impaired coagulation[10], the physiological benefits of an acidemia include improved oxygen delivery *via* the Bohr effects and acidemic protection against hypoxic stress[10,20-22].

Hyperchloremia has recently been linked to adverse clinical outcomes in several animal and human studies. McCluskey *et al*[23] reviewed the datasets of 22851 surgical patients undergoing non-cardiac surgery with normal chloride concentration and kidney function. Postoperative hyperchloremia (defined as plasma chloride > 110 mmol/L) occurred in 22% of patients. Hyperchloremia was associated with adverse renal outcomes and 30-d mortality. Similarly, the adoption of a chloride-restriction protocol in a university hospital critical care unit was also associated with a decrease in AKI and renal replacement therapy[24]. Finally, in a trial examining outcomes in patients receiving major abdominal surgery who were administered PL 148 or NS for routine perioperative fluid intervention, there was an increased risk of major adverse events, particularly infection and acute kidney injury, among patients who received NS[25]. It was unclear if the higher incidence of AKI was due to hyperchloremia or other confounding factors. The suggested mechanisms of hyperchloremic induced kidney injury include inability of the proximal tubules to reabsorb chloride, increasing transport of chloride to the distal tubule, thereby decreasing glomerular filtration[26-28], hyperchloremic induced thromboxane[29], and inflammatory mediator and cytokine release[30].

In an animal model evaluating the effects of fluid resuscitation with NS *vs* PL 148 on acute kidney injury in sepsis, NS resuscitation resulted in significant hyperchloremia and acidemia[30]. Acute kidney injury severity was increased with NS compared with PL 148 resuscitation, and 24-h survival favored PL 148 resuscitation. In an animal model of hemorrhagic shock, resuscitation with PL 148 resulted in a more effective restoration of blood pressure, and improved biochemical profiles when compared to NS[31]. This study also showed that resuscitation with PL 148 improved renal oxygen consumption. Chowdhury *et al*[32] performed a clinical trial examining kidney blood flow and cortical perfusion in healthy participants who were given 2000 mL of NS or PL 148. Participants receiving NS had reduced renal blood flow and cortical perfusion. Furthermore, in another volunteer study participants received a fast infusion of 2000 mL of NS and renal excretion took more than 2 d[33]. This was further supported by a study by Stenvinkel *et al*[34] where healthy volunteers who received 2000 mL of NS over 2 h were noted to have a decrease in their eGFR by 10%. Recently, in a blinded, cluster randomised, double-crossover trial the renal effects of PL 148 and NS were investigated in patients admitted to four ICUs. In this trial, 1152 patients received PL 148 and 1110 patients received NS[35]. No substantial difference in AKI between the groups was reported. Adequately powered clinical trials are eagerly awaited to evaluate the efficacy of PL 148 and NS in high-risk patients that report clinically important outcomes such as major morbidity and mortality. Current research programs are underway with details on the trial designs already published[36]. There is still ongoing debate as to whether NS should be replaced with balanced crystalloids for both fluid maintenance and resuscitation to minimise acute kidney injury[37,38].

Other electrolytes: Similar to Hartmann's solution, PL 148 has a potassium content of 5 mmol/L; PL 148 should be used cautiously in patients receiving ACE inhibitors or angiotensin II receptor antagonists, calcineurin inhibitors, *e.g.*, tacrolimus, and the immunosuppressant cyclosporine, due to increase the risk of hyperkalemia. Similarly, PL 148 should be used cautiously in patients with hyperkalemia or who are predisposed to severe hyperkalemia, *e.g.*, rhabdomyolysis, severe burns, renal failure, and adrenocortical insufficiency. Unlike Hartmann's solution or Ringer's lactate, PL 148 contains 1.5 mmol/L magnesium and should be used cautiously in patients with hypermagnesemia or who are at risk of hypermagnesemia. Further, in patients receiving PL 148, magnesium levels should be checked before additional magnesium is administered. However, PL 148 is not indicated for the treatment of hypomagnesemia. Hartmann's solution contains calcium and should be used cautiously with blood or blood derivatives, due to the potential risks of precipitation and clot formation[39]. In contrast, PL 148 is calcium free and completely compatible with blood or blood components. The mixing of fluids containing calcium and magnesium with drug salts of phosphates, carbonates, tartrates or sulfates should also be avoided due to risks of forming insoluble calcium or magnesium salts. Mixing calcium-containing solutions, *e.g.*, Hartmann's with ceftriaxone can cause the formation of insoluble ceftriaxone calcium salts[40].

Strong ion difference: An important physicochemical

property of PL 148 compared to other crystalloid solutions is its ability to increase pH in patients with a pre-existing metabolic acidosis. Experimental evidence has shown that the optimal effective *in-vivo* strong ion difference (SID) for an IV fluid not to influence blood pH should be approximately 24 mEq/L[41,42]. Saline 0.9%, with its equal concentrations of sodium and chloride, has a SID of zero. It follows that infusion of NS will significantly reduce the SID of plasma, thus causing a metabolic acidosis. Hartmann's solution is considered to be a "balanced" solution compared to NS, with an effective *in-vivo* SID of 29 mEq/L. PL 148 has a SID of 50, which is the reason it is considered an "alkalinizing" solution. As PL 148 is an alkalinizing solution, its administration may increase plasma pH, which can decrease ionized calcium concentrations. Whilst PL 148 may correct an underlying metabolic acidosis, it should be administered cautiously, if at all, to patients with alkalosis.

Inorganic and metabolic anions in Plasma-Lyte 148

Acetate: Normal physiological levels of acetate are 0.06-0.2 mmol/L in plasma. The acetate concentration in PL 148 is 27 mmol/L. Acetate is no longer used as a hemodialysis buffer in modern dialysis treatments. Although initial studies showed that acetate based solutions were almost as effective as bicarbonate in maintaining acid base homeostasis in patients with cholera[43,44], more recently the use of acetate as a hemodialysis solution has been limited by its association with cardiovascular instability in patients receiving large volume renal replacement therapy[45,46]. Adverse effects of acetate are frequently observed with both high doses and high rates of acetate infusions, particularly in the setting of hemodialysis. Small quantities of acetate in dialysate solutions have been reported to cause supra-physiological acetate plasma concentrations (50 to 100 μmol/L)[47-49]. In addition, use of acetate solutions as a cardiopulmonary prime has also been reported to cause similar plasma concentrations in patients undergoing cardiac surgery[50], although it is unknown if such concentrations are associated with detrimental or adverse clinical outcomes.

Kirkendol *et al*[51] first reported that sodium acetate produced a dose-related decrease in cardiac contractility and blood pressure in a dog model. These initial reports conflicted with further laboratory research as the same investigators showed that a slow infusion of acetate failed to cause adverse hemodynamic effects[52]. Hypoxia and hypotension are reported adverse effects in patients with chronic kidney disease dialyzed with solutions containing acetate[45,53,54]. In a crossover study involving twelve patients undergoing hemo-diafiltration randomized to either acetate or bicarbonate (acetate free) dialysate, Selby *et al*[55] demonstrated that exposure to acetate free dialysate was associated with less deterioration in systemic hemodynamics, and less suppression of myocardial contractility. Similarly, Jacob *et al*[56] examined the effect of acetate on myocardial energy metabolism and reported that acetate levels of 5 mmol/L impacted negatively on fatty acid metabolism in cardiac tissue and impaired cardiac contractility. Whilst the authors cautioned that their observations might be applicable to other parenterally administered acetate solutions, there have been no human studies to support these findings[56]. In contrast, Nitenberg *et al*[57] evaluated the effect of acetate on cardiac function before and after a sodium acetate infusion during dialysis. Cardiac function improved with plasma acetate concentrations of 3.13 mmol/L. PL 148 was shown to have adverse effects in a model of animal model of hypovolemic shock. In a study comparing four resuscitation crystalloids, animals who received PL 148 had worse survival rates and higher plasma lactate concentrations compared with NS and lactated solutions[58]. Ringer's lactate was considered the most favourable crystalloid due to its lower chloride concentration when compared to NS, and absence of acetate and magnesium when compared to PL 148.

The use of PL 148 with acetate as its organic anion may confer several advantages over the lactate-containing crystalloids. One clinical advantage is that unlike lactate metabolism, acetate metabolism is not entirely dependent on hepatic function. Acetate metabolism is preserved in severe shock, in contrast to lactate metabolism, which can be significantly impaired[59]. Lactate may be an important prognostic indicator after liver resection[60], shock states and critical illness[61,62], with strong associations shown with hyperlactatemia and risk of complications and death. Acetate is metabolised more rapidly than lactate, generating bicarbonate within 15 min after its adminstration[63,64]. Acetate is also more alkalinizing than lactate, which may confer benefit in treating patients who are acidemic who require fluid intervention or resuscitation. Ekblad *et al*[65] showed that a continuous infusion of sodium acetate (3 mmol/kg per 24 h) corrected metabolic acidosis in premature infants. More recently, in a larger clinical trial of 78 critically ill trauma patients resuscitation with sodium acetate as an alternative to NS or Hartmann's solution in patients receiving acetate had stable hemodynamic profiles without evidence of hemodynamic instability at any point[66]. In the patients who received acetate, there was a rapid correction of both metabolic acidosis and hyperchloremia. Other reported advantages of acetate are that its metabolism does not depend on age[67], acetate protects against malnutrition without disturbing glucose homeostasis[68], and unlike lactated solutions, acetate does not affect glucose or insulin concentration[68,69]. The conversion of exogenously administered lactate to glucose *via* gluconeogenesis has been reported to cause significant hyperglycemia[70]. In diabetic patients, intraoperative glucose levels have been shown to double following administration of exogenous lactate solutions[71].

Gluconate: PL 148 contains 23 mmol/L of gluconate.

However, there is limited information about the physiological impact or clinical consequences of gluconate. Approximately 80% of gluconate is eliminated *via* renal mechanisms. Compared with HCO_3, lactate or acetate, gluconate exerts little, if any alkalinizing effect[51,72]; therefore its clinical effects *in vivo* as a metabolically degradable anion appear to be very limited. Gluconate may protect against post ischemic cardiac dysfunction and oxidative injury[73], however there is lack of data on acetate and gluconate levels after PL 148 administration in most surgical settings. In a phase II clinical trial of PL 148 *vs* a bicarbonate-based cardiopulmonary bypass prime solution, there was a significant increase in unmeasured anions levels after PL 148 administration, which was still present, albeit in smaller concentrations prior to cessation of CPB[74]. Liskaser *et al*[19] reported similar findings. The unmeasured anions were attributed to acetate and gluconate. Davies *et al*[50] observed that when PL 148 was administered as a cardiopulmonary bypass pump-prime fluid, there were supra-physiologic plasma levels of acetate and gluconate when compared to a bicarbonate pump prime solution. There were no significant differences in systemic inflammation (as measured by Interleukin-6 levels), and the authors advocated larger scale studies to more precisely assess this phenomenon. The implications of supra-physiological gluconate and acetate levels remain undetermined.

Specific indications for PL 148 for perioperative fluid intervention

General surgical setting: There is a paucity of large-scale prospective trials comparing PL 148 to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, NS) solutions. A summary of the clinical trials pertinent to PL 148 are summarized in Table 2. Whilst an accumulating body of retrospective studies suggest that chloride rich solutions such as NS may directly contribute to iatrogenic hyperchloremic metabolic acidosis and adverse renal outcomes[23,25,75], results from larger prospective studies are still eagerly awaited before conclusive evidence is available to influence practice regarding the use of balanced solutions over NS[36]. Based on the current literature, balanced solutions appear to be more physiological than NS, however at present there is insufficient evidence from clinical trials to unequivocally prove that balanced or buffered crystalloid solutions are associated with improved patient outcomes. Further, at present, there is also insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid. Understanding the physicochemical properties of PL 148 is paramount, as this will allow clinicians to individualise its use taking into consideration patients' comorbidity, pathology, existing fluid deficit, and concurrent biochemical derangements.

Diabetic ketoacidosis: PL 148 may have a beneficial role in patients who present in diabetic ketoacidosis[76,77]. In a randomized controlled clinical trial, diabetic patients admitted to the emergency department with ketoacidosis were resuscitated with either PL 148 or NS. Use of PL 148 prevented the development of a hyperchloremic metabolic acidosis[76]. This study did not comment on glycemic control or overall outcomes of the patients. In a similar study by Chua *et al*[77], the outcomes of patients with diabetic ketoacidosis admitted to three major critical care centres across Australia who received PL 148 or NS were evaluated. Use of PL 148 was associated with a more rapid improvement in metabolic acidosis than those who received NS. Patients receiving PL 148 had less hyperchloremia, improved mean arterial pressure, and higher cumulative urine output. Despite a more rapid improvement in metabolic acidosis, no difference was found in overall glycemic control or length of stay in ICU based on the choice of fluid administered.

Brittle diabetic patients: Unlike lactate metabolism, the metabolism of acetate does adversely affect insulin or glucose homeostasis[68,69]. PL 148 may therefore confer clinically advantages in brittle diabetic patients. In contrast, when lactate was supplied exogenously in solutions, gluconeogenesis was the principal metabolic pathway for lactate metabolism[78,79]. Plasma lactate levels as low as three mmol/L significantly increased the rate of gluconeogenesis from exogenously supplied lactate[80]. Although healthy volunteers showed no increase in glucose concentrations following lactate infusion[78,80,81], patients undergoing major surgery receiving lactated solutions can have significant intra-operative increases in blood glucose levels[70]. In diabetic patients, intraoperative glycemic control may also be significantly impaired following the administration of lactate containing solutions[71].

Liver resection and liver transplantation: The use of lactate free solutions in patients undergoing major liver surgery may be beneficial for several reasons. First, the metabolism of acetate into bicarbonate is not entirely dependent on liver metabolism, in contrast to lactate metabolism, which is more reliant on adequate liver metabolism[59]. Lactated solutions may therefore be inadequately metabolized during the anhepatic phase of liver transplantation, during major liver resection surgery or in patients with acute or chronic liver insufficiency undergoing major surgery. Plasma lactate levels are also an important prognostic marker after liver resection[60], shock states and critical illness[61,62,82]. Two recent studies evaluating fluid intervention in patients undergoing major liver resection supported the notion that lactate in Hartmann's solution can independently increase lactatemia[83,84]. A randomised controlled trial involving 104 donors undergoing right hepatectomy compared acid base status, lactate concentrations and liver function test of patients who received PL 148, or Hartmann's solution[83]. PL 148 resulted in lower lactate and bilirubin levels, lower prothrombin times, and higher albumin levels compared to patients receiving Hart-

Table 2 Summary of the Plasma-Lyte 148 clinical trials

Ref.	Title	Objectives	Patient numbers	Findings
Liskaser *et al*[19]	Role of pump prime in the etiology and pathogenesis of CPB-associated acidosis	RCT that compared the development of metabolic acidosis in patients on CPB who had either Hemaccel- Ringer's Solution, or PL 148 as the pump prime fluid	n = 22	All patients developed a metabolic acidosis when the pump prime fluid was delivered Participants who received Hemaccel-ringer's solution developed a hyperchloremic metabolic acidosis, however participants who received PL 148 developed acidosis as a result of an increase in unmeasured ions, likely acetate and gluconate The acidosis was reversed more quickly with PL 148 compared to NS
Yunos *et al*[24]	The biochemical effects of restricting chloride-rich fluids in intensive care	This study evaluated the acid base effects of administration of chloride-restricted fluids to critically ill patients, compared with unrestricted fluid management	n = 1644	Restriction of chloride rich fluids was associated with a reduction in metabolic acidosis (P < 0.001), standard base excess (P < 0.001) and severe acidemia (P < 0.001) The intervention was associated with a greater incidence of severe metabolic alkalosis (P < 0.001)
Shaw *et al*[25]	Major complications, mortality, and resource utilization after open abdominal surgery: NS compared to PL	This observational study compared the post-operative complications, in-hospital mortality and resource utilization after abdominal surgery between patients who received either NS or PL 148 fluid therapy on the day of surgery	n = 31920	Patients who received PL 148 had lower rates of in-hospital mortality (P < 0.001) and major complications (including renal failure requiring dialysis (P < 0.001), post-operative infection (P < 0.006), blood transfusions (P < 0.001), electrolyte disturbance (P < 0.046) and acidosis investigation (P < 0.001) and intervention (P = 0.02)
Aksu *et al*[31]	Balanced *vs* unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation	Animal study in which rats were induced into hemorrhagic shock, and were then resuscitated with either no fluid, PL 148 or NS	n = 6	Both PL 148 and NS restored blood pressure during resuscitation NS was associated with hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.05) PL 148 restored acid base balance more effectively than NS PL 148 was associated with improvement in renal oxygen consumption occurred compared to NS (P < 0.05) Systemic inflammation and oxidative stress were similar with NS or PL 148
Chowdhury*et al*[32]	A randomized, controlled, double blind crossover study on the effects of 2L infusions of NS and PL on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers	The authors used MRI to compare the renal blood flow of healthy male volunteers following a 2L infusion of either PL 148 or NS	n = 12	NS was associated with hyperchloremia (P < 0.0001) and metabolic acidosis (P < 0.025) NS was associated with a decrease in a reduction in mean renal artery flow velocity (P = 0.045) and renal cortical tissue perfusion (P = 0.008), findings not observed after PL 148
Young *et al*[35]	Effect of a buffered crystalloid solution *vs* saline on acute kidney injury among patients in the Intensive Care Unit: The SPLIT randomized clinical trial	A double blind, cluster randomized, double-crossover trial conducted in 4 intensive care units. The primary aim was to determine the effects of PL compared with NS on renal complications	n = 2278	No differences in the incidence of acute kidney injury (P = 0.77) No differences in mortality (P = 0.40)
Omron *et al*[42]	A physicochemical model of crystalloid infusion on acid-base status	In this study, authors used a simulated human model in a standard physiological state to compare the effect of 5 different fluids with varying SID values on the acid-base status of the human model when infused up to 10 L	n = 1	Solutions with a SID greater than 24.5 mEq/L resulted in a progressive metabolic alkalosis Solutions with a SID less than 24.5 mEq/L resulted in a progressive metabolic alkalosis PL 148 (SID of 50 mEqu/L) caused a progressive metabolic alkalosis when administered in high volumes

Davies *et al*[50]	Plasma acetate, gluconate and interleukin-6 profiles during and after CPB: A comparison of PL 148 with a bicarbonate-balanced solution	In this study, acetate levels were compared in elective cardiac surgical patients who received either PL 148 or a bicarbonate- balanced crystalloid as the priming fluid for their cardiopulmonary bypass	n = 30	PL 148 was associated with supraphysiological plasma concentrations of acetate (P < 0.0005) and gluconate (P < 0.0005) after institution of CPB Gluconate levels remained persistently elevated at the end of CPB Plasma concentrations of acetate did not completely return to normal levels until 4 h post separation from CPB There were no significant differences in concentrations of IL-6 between the two priming fluids
Traverso *et al*[58]	Fluid resuscitation after an otherwise fatal hemorrhage: I. Crystalloid solutions	An animal model in of hemorrhagic shock comparing four crystalloid solutions (NS, Ringer's lactate, Plasmalyte-A, and Plasmalyte-R) to prevent death after a fatal hemorrhage	n = 116	Ringers lactate provided the best survival when compared to saline and PL After analyses of arterial blood gas values, biochemistry variables, and hemodynamic metrics such as heart rate and aortic pressure, Ringers lactate was considered the most superior crystalloid solution (P value: not stated)
Morgan *et al*[74]	Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with PL. A randomised single-blinded study	In this RCT, the authors compared the acid- base effects of a bicarbonate-balanced trial crystalloid with those of PL when administered as a 2-L prime in patients undergoing elective cardiac surgery	n = 20	PL 148 was associated with a metabolic acidosis (P = 0.0001) and an increased strong ion gap secondary to a surge of unmeasured anions (likely acetate and gluconate)
Yunos *et al*[75]	Association between a chloride-liberal *vs* chloride-restrictive IV fluid administration strategy and kidney injury in critically ill adults	This study assessed the rates of kidney injury in patients admitted to ICU who received only chloride- restricted fluids such as PL 148 or Hartmann's solution compared to those that also received fluids that were high in chloride concentration, including NS	n = 1533	The incidence of acute kidney injury decreased significantly in patients who received a chloride-restrictive fluid plan compared to those who received fluids high in chloride concentration (P < 0.001) No differences in hospital mortality, hospital or ICU length of stay were observed
Mahler *et al*[76]	Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis	In this prospective single centre study, patients admitted to the emergency department in diabetic ketoacidosis were resuscitated over at least 4 h with either NS or PL 148, and their serum chloride and bicarbonate levels were monitored and compared	n = 45	Resuscitation with NS was associated with higher serum chloride concentrations (P < 0.001) and lower bicarbonate concentrations (P = 0.020) Resuscitation with PL 148 prevented hyperchloremic metabolic acidosis
Chua *et al*[77]	PL 148 *vs* NS for fluid resuscitation in diabetic ketoacidosis	In this retrospective study, the authors compared the plasma biochemistry, hemodynamic and glycemic control in patients admitted to the ICU for management of ketoacidosis who were resuscitated primarily with PL 148 or NS over the first 12 h	n = 23	PL 148 was associated with less hyperchloremia and a more rapid improvement in metabolic acidosis than those who received NS (P < 0.05) PL 148 improved hemodynamic measures including an improved mean arterial pressure at 2-4 h, and higher cumulative urine output at 4-6 h compared the NS group (P < 0.05) No differences were observed in glycemic control or length of stay in ICU based
Shin *et al*[83]	Lactate and liver function tests after living donor right hepatectomy; a comparison of solutions with and without lactate	A randomised controlled compared the acid- base status, lactate levels and liver function tests in patients undergoing hepatectomy for liver transplant who received PL 148 or Hartmann's solution	n = 104	Immediately post hepatectomy, donors who received PL 148 had significantly lower lactate levels (P = 0.005), lower bilirubin concentrations (P < 0.001), shorter prothrombin time (P = 0.009), and higher albumin levels compared to the Hartmann's group There were no significant differences between the groups in albumin, bilirubin, or prothrombin times on post-operative day 5 There were no significant differences in complications or duration of hospital stay

Weinberg *et al*[84]	The effects of PL 148 *vs* Hartmann's solution during major liver resection: a multicentre, double blind, randomized controlled trial	Multicentre RCT investigating the biochemical effects of Hartmann's solution or PL 148 in patients undergoing major liver resection. Primary outcome: Base Excess immediately after surgery. Secondary outcomes: changes in blood biochemistry and hematology	n = 60	Base excess similar in both groups at completion of surgery (P = 0.17) Postoperatively patients receiving Hartmann's solution were more hyperchloremic (P = 0.01) and hyperlactatemic (P = 0.02) Patients receiving PL 148 had higher plasma magnesium levels (P < 0.001) and lower ionized calcium levels (P < 0.001) No significant differences in pH, bicarbonate, albumin and phosphate levels PT and aPTT were significantly lower in the PL 148 group (P < 0.001, P = 0.007)
MacFarlane *et al*[85]	A comparison of PL 148 and NS for intra-operative fluid replacement	RCT that compared the pre-op and post-operative acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery	n = 30	Intra-operatively, NS was associated with increased plasma concentrations of chloride (P < 0.01), decreased levels of bicarbonate (P < 0.01), and an increased base deficit (P < 0.01), compared to PL 148 Less blood loss and higher postoperative hemoglobin in the PL 148 group) (P = 0.03) Total complications were more frequent in the Hartmann's group (P = 0.007) Hyperchloremic metabolic acidosis occurred in patients receiving NS but not in those receiving PL 148
Hadimioglu *et al*[87]	The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation	A blinded RCT investigating the effects of NS, lactated Ringer's, or PL 148 on changes in acid-base balance, potassium and lactate levels during kidney transplantation. Urine volume, serum creatinine, and creatinine clearance were recorded on postoperative days 1, 2, 3 and 7	n = 60	Patients receiving NS had lower pH levels, and higher chloride levels (P value not stated) Lactate levels increased significantly in patients who received Ringer's lactate (P value not stated) No significant changes in acid-base measures or lactate levels occurred in patients who received PL 148 Potassium levels were not significantly changed in any group The best metabolic profile was maintained in patients who receive PL 148
Kim *et al*[88]	Comparison of the effects of NS versus PL on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods	RCT compared the effects of NS and PL 148 on acid-base balance and electrolytes during living donor kidney transplantation using the Stewart and base excess methods	n = 60	Significantly lower values of pH, base excess, and effective strong ion differences during the post-reperfusion period in the NS group (P < 0.05) Hyperchloremic metabolic acidosis present in the NS group (P < 0.05) No differences between the groups in early postoperative graft function (P = 0.3)
Potura *et al*[89]	An acetate-buffered balanced crystalloid *vs* NS in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial	RCT that evaluated the impact of NS *vs* a chloride-reduced, acetate-buffered crystalloid on the incidence of hyperkalemia during cadaveric renal transplantation. The incidence of metabolic acidosis and kidney function were secondary aims	n = 150	The incidence of hyperkalemia differed by less than 17% between groups (P = 0.56) Use of balanced crystalloid resulted in less hyperchloremia (P < 0.001) and metabolic acidosis (P < 0.001) Significantly more patients in the NS group required administration of catecholamines for circulatory support (P = 0.03)
Smith *et al*[99]	Cost-minimization analysis of two fluid products for resuscitation of critically injured trauma patients	A retrospective cost-minimization analysis evaluating fluid and drug acquisition costs, materials and nurse labor costs, and costs associated with electrolyte replacement in patients who received PL 148 or NS	n = 46	Substitution of PL 148 for NS for fluid resuscitation during the first 24 hours after trauma was associated with decreased magnesium replacement requirements (P < 0.001) and a net cost benefit to the institution

Smith *et al*[100]	Does saline resuscitation affect mechanisms of coagulopathy in critically ill trauma patients? An exploratory analysis	An exploratory analysis of a subset of subjects enrolled in a randomized trial comparing the effect of resuscitation with PL 148 and NS on acidosis and electrolyte abnormalities	n = 18	Patients receiving NS were more acidemic at 6 h (mean pH saline 7.31 *vs* PL 148; base excess NS -5.3 mmol/L *vs* 0.6 mmol) (P value: not stated) Kinetics time was shorter (P = 0.06) and alpha angle was significantly greater (P = 0.008) in the PL 148 group NS did not alter endogenous thrombin potential: (P > 0.1) for all variables
Song *et al*[101]	The effect of 0.9% saline *vs* PL 148 on coagulation in patients undergoing lumbar spinal surgery; a randomized controlled trial	This study compared the effect of PL 148 to NS on coagulation assessed by rotation thrombo-elastometry (ROTEM) and acid-base balance in the aforementioned patients	n = 50	Patients receiving NS developed a transient hyperchloremic acidosis (P < 0.05) Coagulation assessed by ROTEM analysis and the amount of blood loss was similar between the groups: (P > 0.1 for all variables)
Young *et al*[102]	Saline *vs* PL in initial resuscitation of trauma patients: a randomized trial	RCT that evaluated the acid-base status of patients who were resuscitated with either PL or NS for the first 24-h post major trauma	n = 46	Significantly greater improvement in base excess (estimated difference 4.1 mmol/L) and less hyperchloremia (estimated difference 7 mmol/L) in patients who were resuscitated with PL compared to those resuscitated with NS (P value: not stated)
Story *et al*[103]	Cognitive changes after saline or PL 148 infusion in healthy volunteers: a multiple blinded, randomized, crossover trial	Randomized, crossover, blinded study of healthy adult volunteers. On separate days, participants received 30 mL/kg over 1 h of either NS or PL. Primary endpoint: reaction time index after infusion - a validated metric of cognitive function	n = 25	NS was also associated with greater metabolic acidosis (P < 0.001) NS was also associated with higher serum chloride levels (P < 0.001) No difference in measures of cognition after infusions of PL 148 or NS (P = 0.39)
Noritomi *et al*[104]	Impact of PL 148 pH 7.4 on acid-base status and hemodynamics in a model of controlled hemorrhagic shock	After controlled hemorrhagic shock was induced, animals were resuscitated with NS, Ringer's lactate solution or PL 148	n = 18	Resuscitation with all three fluids restored cardiac output, and urinary output Resuscitation with PL 148 and Hartmann's Solution both resulted in a reduction in chloride concentration, and increased base excess Resuscitation with NS was associated with an increased chloride concentration (P = 0.018), reduction of base excess (P = 0.042) and a metabolic acidosis (P = 0.045)

PL 148: Plasma-Lyte 148; NS: Normal saline 0.9%; RCT: Randomized clinical trial; CPB: Cardiopulmonary bypass; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; SID: Strong ion difference; ICU: Intensive care unit; IL: Interleukin.

mann's solution. In this single centre study no significant differences in complications or duration of hospital stay between groups were reported. Recently, however, in a multicentre trial evaluating patients undergoing major liver resection[84], patients who received PL 148 had improved biochemical and hematological profiles (acid base homeostasis, electrolyte balance and coagulation status) as well as fewer complications and reduced length of stay. Finally a smaller study by McFarlane *et al*[85] compared the pre-op and post-op acid base status of patients who received either NS or PL 148 whilst undergoing major hepatobiliary or pancreatic surgery. Consistent with the other studies above, patients who received NS intra-operatively were more hyperchloremic and acidemic compared to those who received PL 148. The most favourable crystalloid solution for patients undergoing major liver surgery is still unknown[86].

Renal transplantation: Traditionally, NS is advocated peri-operatively for renal transplant recipients due to concerns about hyperkalemia from balanced solutions, which contain potassium. Although NS is widely advocated in this setting, recent evidence suggests balanced crystalloids such as PL 148 or Hartmann's may be more appropriate. Hadimioglu *et al*[87] performed a randomised clinical trial comparing PL 148, Hartmann's solution, and NS as intraoperative fluid replacement in 90 patients undergoing renal transplant. Those receiving NS had higher chloride, lower pH and lower base excess than the other two groups. Those patients receiving Hartmann's had elevated lactate levels. Potassium levels, urine output, serum urea and creatinine and creatinine clearance were similar between the groups. The authors concluded that all three fluids appear safe in short-duration uncomplicated renal transplant surgery, but the metabolic profile was best maintained with PL 148. Four other randomised controlled trials reported acid-base metrics as primary outcomes[88-91]. All were

underpowered to adequately report endpoints such as hyperkalemia, requirements for dialysis, delayed and long-term graft function, and survival. Two of these studies used an acetate based crystalloid solution for fluid intervention[89,91]. Kim *et al*[88] studied the effects of NS and PL 148 on acid-base homeostasis in patients undergoing living donor kidney transplantation. There was significant hyperchloremic metabolic acidosis in the NS group, but no difference in early postoperative graft function. More recently, Potura *et al*[89] evaluated the effects of NS *vs* a chloride-reduced, acetate-buffered solution (similar in composition to PL 148) on the incidence of hyperkalemia in 150 patients undergoing cadaveric renal transplantation. The incidence of hyperkalemia was not statistically different between the groups. However, use of the buffered solution resulted in less hyperchloremia and metabolic acidosis, and a lower requirement for vasoactive medications.

Raised intracranial pressure and hypo-osmolar states: Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Larger volumes of Ringers lactate are well known to reduce plasma osmolality[92] and result in transient increases in intracranial pressure[93]. The magnitude of the increase in intracranial pressure can be predicted from the reduction of plasma osmolality[9]. In animal models, for every mOsmol/kg reduction in plasma osmolality, there is a mean increase in intracranial pressure of 1.5 mmHg[92,94-98]. Iso-osmolar solutions such as PL 148 or NS may not impact on plasma osmolality to the same extent as hypo-osmolar solutions and may be advantageous in this setting. PL 148 may be advantageous compared to Hartmann's solution in the setting of fluid overload states and iso-osmolar hyponatremia, such as that which occurs in transurethral resection of the prostate syndrome. Given NS's greater tonicity compared to PL 148, NS may be the preferred crystalloid in this setting.

Costs of Plasma-Lyte 148

Currently the net acquisition cost of PL 148 varies significantly between different countries and even between different states within the same country. In Australia, list prices and actual hospital acquisition price differ in accordance with state, individual hospital, local tenders and preferred supplier agreements. In New Zealand, there is different pricing again due to the Pharmaceutical Management Agency, which actively manages government spending on medicines in order to maximize value for medicines, achieving the best health outcomes for the amount of public money spent. In Australia and New Zealand net acquisition costs of 1000 mL PL 148 varies between $2.00 and $5.00; in other countries such as China and South Korea prices appear to be similar. In contrast, net acquisition costs for a 1000 mL bag of Hartmann's solution or NS is Australia is currently less than $2.00. Recently, a retrospective cost-minimization analysis evaluated drug acquisition and expenses related with electrolyte replacement in critically injured trauma patients treated with NS or PL 148[99]. The use of PL 148 was associated with a higher fluid acquisition costs and a decreased need for magnesium supplementation[100]. Considering consumable supplies and nursing labor costs, there was a $12.35 daily cost-differential in patients who received PL 148. Substitution of PL 148 for NS was correlated with reduced magnesium supplementation therapy and overall net cost-benefits for the hospital.

In conclusion, administration of IV fluids is fundamental to the optimal management of patients in anesthesia and critical care medicine. The selection of the appropriate fluid for administration is often based on clinician preference, and to date there is a lack of large-scale prospective research comparing the safety, efficacy and indications of the different types of crystalloid solutions. Whilst NS is the most common IV fluid crystalloid worldwide, large-scale observational studies and small-randomized trials suggest a strong association between its use and adverse biochemical and clinical outcomes. Emerging data supports the use of buffered crystalloid solutions in preference to NS in improving physicochemical outcomes; however currently there is insufficient evidence to recommend this change in practice. Further large randomized controlled trials assessing the comparative effectiveness of PL 148 and NS in higher risk patients by measuring clinically important outcomes such as mortality are currently underway[36].

Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should therefore always be individualized: Qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

COMMENTS

Background

The use of intravenous fluids for maintenance therapy and resuscitation in anesthesia and critical care medicine is universal. There is marked variation in perioperative fluid selection, frequently determined by institution and clinician preference. Such practice variation is related to the paucity of prospective evidence evaluating the comparative safety and efficacy of available crystalloid solutions for both fluid resuscitation and maintenance therapy in the perioperative setting. The authors present a comprehensive review of Plasma-Lyte 148 (PL 148), comparing its physiochemical properties to other commonly available crystalloids solutions.

Research frontiers

PL 148 is an isotonic, buffered intravenous crystalloid solution with a physiochemical composition that closely reflects human plasma. Emerging data supports the use of buffered crystalloid solutions in preference to sodium

chloride (0.9%) in improving physicochemical and clinical outcomes.

Innovations and breakthroughs

There is a paucity of large-scale prospective trials comparing Plasma-Lyte 148 (PL 148) to other fluid buffered (*e.g.*, Hartmann's solution) and non-buffered (*e.g.*, sodium chloride, 0.9%) solutions. Based on the current literature, balanced or buffered solutions appear to be more physiological than sodium chloride (0.9%), however at present there is insufficient evidence from prospective clinical trials to unequivocally prove that such solutions are associated with improved patient outcomes. Further, at present, there is insufficient evidence to advocate for the routine use of PL 148 over other commercially available buffered or non-buffered crystalloid.

Applications

Unlike lactate, acetate metabolism is not entirely dependent on preserved liver function for its metabolism, and the metabolism of acetate does adversely affect insulin or glucose homeostasis. Therefore, PL 148 may more beneficial than a lactate buffered solution in critically ill patients with liver hypoperfusion, liver insufficiency, or for patients undergoing complex liver surgery. PL 148 may also be a favourable solution in brittle diabetic patients. PL 148 is a more alkalinising solution than sodium chloride and Hartmann's solution, and may have a role in correcting severe metabolic academic states where fluid intervention is indicated. Administration of hypo-osmolar solutions such as Hartmann's solution may worsen cerebral oedema and increase intracranial pressure in neurosurgical patients with critical brain injury or existing raised intracranial pressure. Similar to sodium chloride (0.9%), Plasma-Lyte is isotonic, and may be a suitable solution for fluid therapy in this setting. Use of PL 148 should be based on a detailed knowledge of its physicochemical properties, and the pathophysiological condition of the patient. The ideal approach for perioperative fluid therapy should be individualized: qualitatively: Fluid with suitable physicochemical composition individualized to patients' physiological state and specific type of surgery, and quantitatively: The right amount of fluid at the right time and at the right rate.

Terminology

A crystalloid solution is any solution containing electrolytes and non electrolytes. A balanced or buffered crystalloid solution is a crystalloid solution with a physiochemical composition that closely reflects human plasma.

Peer-review

The authors reviewed clinical studies of PL 148. The manuscript is valuable and well written.

REFERENCES

1 **Burdett E**, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K. Perioperative buffered versus non-buffered fluid administration for surgery in adults. *Cochrane Database Syst Rev* 2012; **12**: CD004089 [PMID: 23235602 DOI: 10.1002/14651858.CD004089.pub2]

2 Product information. Plasma-Lyte 148 Replacement IV Infusion. [accessed 2015 Jan 17]. Available from: URL: http://www.baxterhealthcare.com.au/downloads/healthcare_professionals/cmi_pi/plasmalyte148_pi.pdf

3 Y-Site Compatibility of Intravenous Drugs with Plasmalyte 148. Baxter Healthcare, 2015

4 **Petraitiene R**, Petraitis V, Witt JR, Durkin MM, Bacher JD, Wheat LJ, Walsh TJ. Galactomannan antigenemia after infusion of gluconate-containing Plasma-Lyte. *J Clin Microbiol* 2011; **49**: 4330-4332 [PMID: 21976760 DOI: 10.1128/JCM.05031-11]

5 **Hage CA**, Reynolds JM, Durkin M, Wheat LJ, Knox KS. Plasmalyte as a cause of false-positive results for Aspergillus galactomannan in bronchoalveolar lavage fluid. *J Clin Microbiol* 2007; **45**: 676-677 [PMID: 17166959 DOI: 10.1128/JCM.01940-06]

6 **Surmont I**, Stockman W. Gluconate-containing intravenous solutions: another cause of false-positive galactomannan assay reactivity. *J Clin Microbiol* 2007; **45**: 1373 [PMID: 17287325 DOI: 10.1128/JCM.02373-06]

7 **Racil Z**, Kocmanova I, Lengerova M, Winterova J, Mayer J. Intravenous PLASMA-LYTE as a major cause of false-positive results of platelia Aspergillus test for galactomannan detection in serum. *J Clin Microbiol* 2007; **45**: 3141-3142 [PMID: 17670932 DOI: 10.1128/JCM.00974-07]

8 **Spriet I**, Lagrou K, Maertens J, Willems L, Wilmer A, Wauters J. Plasmalyte: No Longer a Culprit in Causing False-Positive Galactomannan Test Results. *J Clin Microbiol* 2016; **54**: 795-797 [PMID: 26719444 DOI: 10.1128/JCM.02813-15]

9 **Zander R**. Fluid management. 2th ed. [accessed 2015 Feb 15]. Available from: URL: http://www.bbraun.com/documents/Knowledge/Fluid_Management_0110.pdf

10 **Morgan TJ**. The ideal crystalloid - what is 'balanced'? *Curr Opin Crit Care* 2013; **19**: 299-307 [PMID: 23743589 DOI: 10.1097/MCC.0b013e3283632d46]

11 **Guidet B**, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, James M. A balanced view of balanced solutions. *Crit Care* 2010; **14**: 325 [PMID: 21067552 DOI: 10.1186/cc9230]

12 **McLoughlin PD**, Bell DA. Hartmann's solution--osmolality and lactate. *Anaesth Intensive Care* 2010; **38**: 1135-1136 [PMID: 21229667]

13 **Cotton BA**, Guy JS, Morris JA, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. *Shock* 2006; **26**: 115-121 [PMID: 16878017 DOI: 10.1016/j.clnu.2008.01.008]

14 **Awad S**, Allison SP, Lobo DN. The history of 0.9% saline. *Clin Nutr* 2008; **27**: 179-188 [PMID: 18313809]

15 **Scheingraber S**, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999; **90**: 1265-1270 [PMID: 10319771 DOI: 10.1097/00000542-199905000-00007]

16 **Waters JH**, Miller LR, Clack S, Kim JV. Cause of metabolic acidosis in prolonged surgery. *Crit Care Med* 1999; **27**: 2142-2146 [PMID: 10548196 DOI: 10.1097/00003246-199910000-00011]

17 **Prough DS**, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. *Anesthesiology* 1999; **90**: 1247-1249 [PMID: 10319767 DOI: 10.1097/00000542-199905000-00003]

18 **Hayhoe M**, Bellomo R, Liu G, McNicol L, Buxton B. The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. *Intensive Care Med* 1999; **25**: 680-685 [PMID: 10470571 DOI: 10.1007/s001340050930]

19 **Liskaser FJ**, Bellomo R, Hayhoe M, Story D, Poustie S, Smith B, Letis A, Bennett M. Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. *Anesthesiology* 2000; **93**: 1170-1173 [PMID: 11046201 DOI: 10.1097/00000542-200011000-00006]

20 **Handy JM**, Soni N. Physiological effects of hyperchloraemia and acidosis. *Br J Anaesth* 2008; **101**: 141-150 [PMID: 18534973 DOI: 10.1093/bja/aen148]

21 **Bonventre JV**, Cheung JY. Effects of metabolic acidosis on viability of cells exposed to anoxia. *Am J Physiol* 1985; **249**: C149-C159 [PMID: 4014448]

22 **Heijnen BH**, Elkhaloufi Y, Straatsburg IH, Van Gulik TM. Influence of acidosis and hypoxia on liver ischemia and reperfusion injury in an in vivo rat model. *J Appl Physiol* (1985) 2002; **93**: 319-323 [PMID: 12070220 DOI: 10.1152/japplphysiol.01112.2001]

23 **McCluskey SA**, Karkouti K, Wijeysundera D, Minkovich L, Tait G, Beattie WS. Hyperchloremia after noncardiac surgery is independently associated with increased morbidity and mortality: a propensity-matched cohort study. *Anesth Analg* 2013; **117**: 412-421 [PMID: 23757473 DOI: 10.1213/ANE.0b013e318293d81e]

24 **Yunos NM**, Kim IB, Bellomo R, Bailey M, Ho L, Story D, Gutteridge GA, Hart GK. The biochemical effects of restricting chloride-rich fluids in intensive care. *Crit Care Med* 2011; **39**: 2419-2424 [PMID: 21705897 DOI: 10.1097/CCM.0b013e31822571e5]

25 **Shaw AD**, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012; **255**: 821-829 [PMID:

22470070 DOI: 10.1097/SLA.0b013e31825074f5]
26 **Wilcox CS**. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; **71**: 726-735 [PMID: 6826732 DOI: 10.1172/JCI110820]
27 **Salomonsson M**, Gonzalez E, Kornfeld M, Persson AE. The cytosolic chloride concentration in macula densa and cortical thick ascending limb cells. *Acta Physiol Scand* 1993; **147**: 305-313 [PMID: 8386427 DOI: 10.1111/j.1748-1716.1993.tb09503.x]
28 **Hashimoto S**, Kawata T, Schnermann J, Koike T. Chloride channel blockade attenuates the effect of angiotensin II on tubuloglomerular feedback in WKY but not spontaneously hypertensive rats. *Kidney Blood Press Res* 2004; **27**: 35-42 [PMID: 14679313 DOI: 10.1159/000075621]
29 **Bullivant EM**, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. *Am J Physiol* 1989; **256**: F152-F157 [PMID: 2912160]
30 **Zhou F**, Peng ZY, Bishop JV, Cove ME, Singbartl K, Kellum JA. Effects of fluid resuscitation with 0.9% saline versus a balanced electrolyte solution on acute kidney injury in a rat model of sepsis*. *Crit Care Med* 2014; **42**: e270-e278 [PMID: 24335444 DOI: 10.1097/CCM.0000000000000145]
31 **Aksu U**, Bezemer R, Yavuz B, Kandil A, Demirci C, Ince C. Balanced vs unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation. *Resuscitation* 2012; **83**: 767-773 [PMID: 22142654 DOI: 10.1016/j.resuscitation.2011.11.022]
32 **Chowdhury AH**, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; **256**: 18-24 [PMID: 22580944 DOI: 10.1097/SLA.0b013e318256be72]
33 **Drummer C**, Gerzer R, Heer M, Molz B, Bie P, Schlossberger M, Stadaeger C, Röcker L, Strollo F, Heyduck B. Effects of an acute saline infusion on fluid and electrolyte metabolism in humans. *Am J Physiol* 1992; **262**: F744-F754 [PMID: 1590419]
34 **Stenvinkel P**, Saggar-Malik AK, Alvestrand A. Renal haemodynamics and tubular sodium handling following volume expansion with sodium chloride (NaCl) and glucose in healthy humans. *Scand J Clin Lab Invest* 1992; **52**: 837-846 [PMID: 1488621 DOI: 10.3109/00365519209088389]
35 **Young P**, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015; **314**: 1701-1710 [PMID: 26444692 DOI: 10.1001/jama.2015.12334]
36 **Reddy SK**, Young PJ, Beasley RW, Mackle DM, McGuinness SP, McArthur CJ, Henderson SJ, Weinberg L, French CJ, Orford NR, Bailey MJ, Bellomo R. Overview of the study protocols and statistical analysis plan for the Saline versus Plasma-Lyte 148 for Intravenous Fluid Therapy (SPLIT) research program. *Crit Care Resusc* 2015; **17**: 29-36 [PMID: 25702759]
37 **Lobo DN**, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: con. *Kidney Int* 2014; **86**: 1096-1105 [PMID: 24717302 DOI: 10.1038/ki.2014.105]
38 **Ince C**, Groeneveld AB. The case for 0.9% NaCl: is the undefendable, defensible? *Kidney Int* 2014; **86**: 1087-1095 [PMID: 25007167 DOI: 10.1038/ki.2014.193]
39 **Nadra A**, Hodzovic I. Incompatibility between blood and Hartmann's solution. *Anaesthesia* 2007; **62**: 639 [PMID: 17506764 DOI: 10.1111/j.1365-2044.2007.05119.x]
40 **Murney P**. To mix or not to mix - compatibilities of parenteral drug solutions. Australian Prescriber. [accessed 2015 Feb]. Available from: URL: http://www.australianprescriber.com/magazine/31/4/98/101/
41 **Morgan TJ**, Venkatesh B. Designing 'balanced' crystalloids. *Crit Care Resusc* 2003; **5**: 284-291 [PMID: 16563119]
42 **Omron EM**, Omron RM. A physicochemical model of crystalloid infusion on acid-base status. *J Intensive Care Med* 2010; **25**: 271-280 [PMID: 20622258 DOI: 10.1177/0885066610371633]
43 **Eliahou HE**, Feng PH, Weinberg U, Iaina A, Reisin E. Acetate and bicarbonate in the correction of uraemic acidosis. *Br Med J* 1970; **4**: 399-401 [PMID: 5481517 DOI: 10.1136/bmj.4.5732.399]
44 **Watten RH**, Gutman RA, Fresh JW. Comparison of acetate, lactate, and bicarbonate in treating the acidosis of cholera. *Lancet* 1969; **2**: 512-514 [PMID: 4184837 DOI: 10.1016/S0140-6736(69)90215-3]
45 **Thaha M**, Yogiantoro M. Correlation between intradialytic hypotension in patients undergoing routine hemodialysis and use of acetate compared in bicarbonate dialysate. *Acta Med Indones* 2005; **37**: 145-148 [PMID: 16138418]
46 **Schrander-vd Meer AM**, ter Wee PM, Kan G, Donker AJ, van Dorp WT. Improved cardiovascular variables during acetate free biofiltration. *Clin Nephrol* 1999; **51**: 304-309 [PMID: 10363631]
47 **Coll E**, Pérez-García R, Rodríguez-Benítez P, Ortega M, Martínez Miguel P, Jofré R, López-Gómez JM. Clinical and analytical changes in hemodialysis without acetate. *Nefrologia* 2007; **27**: 742-748 [PMID: 18336105]
48 **Böttger I**, Deuticke U, Evertz-Prüsse E, Ross BD, Wieland O. On the behavior of the free acetate in the miniature pig. Acetate metabolism in the miniature pig. *Z Gesamte Exp Med* 1968; **145**: 346-352 [PMID: 5675250 DOI: 10.1007/BF02044224]
49 **Fournier G**, Potier J, Thébaud HE, Majdalani G, Ton-That H, Man NK. Substitution of acetic acid for hydrochloric acid in the bicarbonate buffered dialysate. *Artif Organs* 1998; **22**: 608-613 [PMID: 9684700 DOI: 10.1046/j.1525-1594.1998.06205.x]
50 **Davies PG**, Venkatesh B, Morgan TJ, Presneill JJ, Kruger PS, Thomas BJ, Roberts MS, Mundy J. Plasma acetate, gluconate and interleukin-6 profiles during and after cardiopulmonary bypass: a comparison of Plasma-Lyte 148 with a bicarbonate-balanced solution. *Crit Care* 2011; **15**: R21 [PMID: 21235742 DOI: 10.1186/cc9966]
51 **Kirkendol PL**, Starrs J, Gonzalez FM. The effects of acetate, lactate, succinate and gluconate on plasma pH and electrolytes in dogs. *Trans Am Soc Artif Intern Organs* 1980; **26**: 323-327 [PMID: 7245507]
52 **Kirkendol PL**, Robie NW, Gonzalez FM, Devia CJ. Cardiac and vascular effects of infused sodium acetate in dogs. *Trans Am Soc Artif Intern Organs* 1978; **24**: 714-718 [PMID: 716087]
53 **Veech RL**, Gitomer WL. The medical and metabolic consequences of administration of sodium acetate. *Adv Enzyme Regul* 1988; **27**: 313-343 [PMID: 2854950 DOI: 10.1016/0065-2571(88)90024-6]
54 **Quebbeman EJ**, Maierhofer WJ, Piering WF. Mechanisms producing hypoxemia during hemodialysis. *Crit Care Med* 1984; **12**: 359-363 [PMID: 6705543 DOI: 10.1097/00003246-198404000-00004]
55 **Selby NM**, Fluck RJ, Taal MW, McIntyre CW. Effects of acetate-free double-chamber hemodiafiltration and standard dialysis on systemic hemodynamics and troponin T levels. *ASAIO J* 2006; **52**: 62-69 [PMID: 16436892 DOI: 10.1097/01.mat.0000189725.93808.58]
56 **Jacob AD**, Elkins N, Reiss OK, Chan L, Shapiro JI. Effects of acetate on energy metabolism and function in the isolated perfused rat heart. *Kidney Int* 1997; **52**: 755-760 [PMID: 9291197 DOI: 10.1038/ki.1997.392]
57 **Nitenberg A**, Huyghebaert MF, Blanchet F, Amiel C. Analysis of increased myocardial contractility during sodium acetate infusion in humans. *Kidney Int* 1984; **26**: 744-751 [PMID: 6521259 DOI: 10.1038/ki.1984.211]
58 **Traverso LW**, Lee WP, Langford MJ. Fluid resuscitation after an otherwise fatal hemorrhage: I. Crystalloid solutions. *J Trauma* 1986; **26**: 168-175 [PMID: 3080602 DOI: 10.1097/00005373-198602000-00014]
59 **Kveim M**, Nesbakken R. Utilization of exogenous acetate during canine haemorrhagic shock. *Scand J Clin Lab Invest* 1979; **39**: 653-658 [PMID: 43582 DOI: 10.1080/00365517909108870]
60 **Watanabe I**, Mayumi T, Arishima T, Takahashi H, Shikano T, Nakao A, Nagino M, Nimura Y, Takezawa J. Hyperlactemia can predict the prognosis of liver resection. *Shock* 2007; **28**: 35-38 [PMID: 17510606 DOI: 10.1097/shk.0b013e3180310ca9]
61 **Jansen TC**, van Bommel J, Bakker J. Blood lactate monitoring in critically ill patients: a systematic health technology assessment.

Crit Care Med 2009; **37**: 2827-2839 [PMID: 19707124 DOI: 10.1097/CCM.0b013e3181a98899]
62 **Bakker J**, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996; **171**: 221-226 [PMID: 8619454 DOI: 10.1016/S0002-9610(97)89552-9]
63 **Mudge GH**, Manning JA, Gilman A. Sodium acetate as a source of fixed base. *Proc Soc Exp Biol Med* 1949; **71**: 136-138 [PMID: 18151504 DOI: 10.3181/00379727-71-17109]
64 **Hamada T**, Yamamoto M, Nakamaru K, Iwaki K, Ito Y, Koizumi T. The pharmacokinetics of D-lactate, L-lactate and acetate in humans. *Masui* 1997; **46**: 229-236 [PMID: 9071107]
65 **Ekblad H**, Kero P, Takala J. Slow sodium acetate infusion in the correction of metabolic acidosis in premature infants. *Am J Dis Child* 1985; **139**: 708-710 [PMID: 4014095 DOI: 10.1001/archpedi.1985.02140090070032]
66 **McCague A**, Dermendjieva M, Hutchinson R, Wong DT, Dao N. Sodium acetate infusion in critically ill trauma patients for hyperchloremic acidosis. *Scand J Trauma Resusc Emerg Med* 2011; **19**: 24 [PMID: 21486493 DOI: 10.1186/1757-7241-19-24]
67 **Skutches CL**, Holroyde CP, Myers RN, Paul P, Reichard GA. Plasma acetate turnover and oxidation. *J Clin Invest* 1979; **64**: 708-713 [PMID: 468985 DOI: 10.1172/JCI109513]
68 **Akanji AO**, Bruce MA, Frayn KN. Effect of acetate infusion on energy expenditure and substrate oxidation rates in non-diabetic and diabetic subjects. *Eur J Clin Nutr* 1989; **43**: 107-115 [PMID: 2651106]
69 **Akanji AO**, Hockaday TD. Acetate tolerance and the kinetics of acetate utilization in diabetic and nondiabetic subjects. *Am J Clin Nutr* 1990; **51**: 112-118 [PMID: 2153334]
70 **Arai K**, Kawamoto M, Yuge O, Shiraki H, Mukaida K, Horibe M, Morio M. A comparative study of lactated Ringer and acetated Ringer solution as intraoperative fluids in patients with liver dysfunction. *Masui* 1986; **35**: 793-799 [PMID: 3747125]
71 **Thomas DJ**, Alberti KG. Hyperglycaemic effects of Hartmann's solution during surgery in patients with maturity onset diabetes. *Br J Anaesth* 1978; **50**: 185-188 [PMID: 626700 DOI: 10.1093/bja/50.2.185]
72 **Naylor JM**, Forsyth GW. The alkalinizing effects of metabolizable bases in the healthy calf. *Can J Vet Res* 1986; **50**: 509-516 [PMID: 3024796]
73 **Murthi SB**, Wise RM, Weglicki WB, Komarov AM, Kramer JH. Mg-gluconate provides superior protection against postischemic dysfunction and oxidative injury compared to Mg-sulfate. *Mol Cell Biochem* 2003; **245**: 141-148 [PMID: 12708753]
74 **Morgan TJ**, Power G, Venkatesh B, Jones MA. Acid-base effects of a bicarbonate-balanced priming fluid during cardiopulmonary bypass: comparison with Plasma-Lyte 148. A randomised single-blinded study. *Anaesth Intensive Care* 2008; **36**: 822-829 [PMID: 19115651]
75 **Yunos NM**, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566-1572 [PMID: 23073953 DOI: 10.1001/jama.2012.13356]
76 **Mahler SA**, Conrad SA, Wang H, Arnold TC. Resuscitation with balanced electrolyte solution prevents hyperchloremic metabolic acidosis in patients with diabetic ketoacidosis. *Am J Emerg Med* 2011; **29**: 670-674 [PMID: 20825879 DOI: 10.1016/j.ajem.2010.02.004]
77 **Chua HR**, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, Kruger P, Bellomo R. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. *J Crit Care* 2012; **27**: 138-145 [PMID: 22440386 DOI: 10.1016/j.jcrc.2012.01.007]
78 **Chioléro R**, Mavrocordatos P, Burnier P, Cayeux MC, Schindler C, Jéquier E, Tappy L. Effects of infused sodium acetate, sodium lactate, and sodium beta-hydroxybutyrate on energy expenditure and substrate oxidation rates in lean humans. *Am J Clin Nutr* 1993; **58**: 608-613 [PMID: 8237864]
79 **Drummond GB**. Is Hartmann's the solution? *Anaesthesia* 1997; **52**: 918-920 [PMID: 9349084]
80 **Jenssen T**, Nurjhan N, Consoli A, Gerich JE. Dose-response effects of lactate infusions on gluconeogenesis from lactate in normal man. *Eur J Clin Invest* 1993; **23**: 448-454 [PMID: 8404995 DOI: 10.1111/j.1365-2362.1993.tb00789.x]
81 **Ahlborg G**, Hagenfeldt L, Wahren J. Influence of lactate infusion on glucose and FFA metabolism in man. *Scand J Clin Lab Invest* 1976; **36**: 193-201 [PMID: 1273497 DOI: 10.3109/00365517609055248]
82 **Smith I**, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED. Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med* 2001; **27**: 74-83 [PMID: 11280677 DOI: 10.1007/s001340051352]
83 **Shin WJ**, Kim YK, Bang JY, Cho SK, Han SM, Hwang GS. Lactate and liver function tests after living donor right hepatectomy: a comparison of solutions with and without lactate. *Acta Anaesthesiol Scand* 2011; **55**: 558-564 [PMID: 21342149 DOI: 10.1111/j.1399-6576.2011.02398.x]
84 **Weinberg L**, Pearce B, Sullivan R, Siu L, Scurrah N, Tan C, Backstrom M, Nikfarjam M, McNicol L, Story D, Christophi C, Bellomo R. The effects of plasmalyte-148 vs. Hartmann's solution during major liver resection: a multicentre, double-blind, randomized controlled trial. *Minerva Anestesiol* 2015; **81**: 1288-1297 [PMID: 25407026]
85 **McFarlane C**, Lee A. A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. *Anaesthesia* 1994; **49**: 779-781 [PMID: 7978133 DOI: 10.1111/j.1365-2044.1994.tb04450.x]
86 **Weinberg L**, Pearce B, Bellomo R. Plasma-Lyte or Hartmann's for major liver resection: which is the best solution? *Minerva Anestesiol* 2016; **82**: 123-124 [PMID: 25971284]
87 **Hadimioglu N**, Saadawy I, Saglam T, Ertug Z, Dinckan A. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. *Anesth Analg* 2008; **107**: 264-269 [PMID: 18635497 DOI: 10.1213/ane.0b013e3181732d64]
88 **Kim SY**, Huh KH, Lee JR, Kim SH, Jeong SH, Choi YS. Comparison of the effects of normal saline versus Plasmalyte on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods. *Transplant Proc* 2013; **45**: 2191-2196 [PMID: 23953528 DOI: 10.1016/j.transproceed.2013.02.124]
89 **Potura E**, Lindner G, Biesenbach P, Funk GC, Reiterer C, Kabon B, Schwarz C, Druml W, Fleischmann E. An acetate-buffered balanced crystalloid versus 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial. *Anesth Analg* 2015; **120**: 123-129 [PMID: 25185593 DOI: 10.1213/ANE.0000000000000419]
90 **Khajavi MR**, Etezadi F, Moharari RS, Imani F, Meysamie AP, Khashayar P, Najafi A. Effects of normal saline vs. lactated ringer's during renal transplantation. *Ren Fail* 2008; **30**: 535-539 [PMID: 18569935 DOI: 10.1080/08860220802064770]
91 **O'Malley CM**, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg* 2005; **100**: 1518-1524, table of contents [PMID: 15845718 DOI: 10.1213/01.ANE.0000150939.28904.81]
92 **Shackford SR**, Zhuang J, Schmoker J. Intravenous fluid tonicity: effect on intracranial pressure, cerebral blood flow, and cerebral oxygen delivery in focal brain injury. *J Neurosurg* 1992; **76**: 91-98 [PMID: 1727174 DOI: 10.3171/jns.1992.76.1.0091]
93 **Tommasino C**, Moore S, Todd MM. Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. *Crit Care Med* 1988; **16**: 862-868 [PMID: 2456893 DOI: 10.1097/00003246-198809000-00009]
94 **Zornow MH**, Scheller MS, Shackford SR. Effect of a hypertonic lactated Ringer's solution on intracranial pressure and cerebral water content in a model of traumatic brain injury. *J Trauma* 1989; **29**: 484-488 [PMID: 2709456 DOI: 10.1097/00005373-198904000-00011]
95 **Zornow MH**, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *Anesthesiology* 1987; **67**: 936-941 [PMID: 2446535 DOI: 10.1097/00000542-198712000-00010]

96 **Walsh JC**, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. *J Surg Res* 1991; **50**: 284-292 [PMID: 1999918 DOI: 10.1016/0022-4804(91)90192-O]
97 **Kaieda R**, Todd MM, Cook LN, Warner DS. Acute effects of changing plasma osmolality and colloid oncotic pressure on the formation of brain edema after cryogenic injury. *Neurosurgery* 1989; **24**: 671-678 [PMID: 2716975 DOI: 10.1227/00006123-198905000-00003]
98 **Hyodo A**, Heros RC, Tu YK, Ogilvy C, Graichen R, Lagree K, Korosue K. Acute effects of isovolemic hemodilution with crystalloids in a canine model of focal cerebral ischemia. *Stroke* 1989; **20**: 534-540 [PMID: 2467410 DOI: 10.1161/01.STR.20.4.534]
99 **Smith CA**, Duby JJ, Utter GH, Galante JM, Scherer LA, Schermer CR. Cost-minimization analysis of two fluid products for resuscitation of critically injured trauma patients. *Am J Health Syst Pharm* 2014; **71**: 470-475 [PMID: 24589538 DOI: 10.2146/ajhp130295]
100 **Smith CA**, Gosselin RC, Utter GH, Galante JM, Young JB, Scherer LA, Schermer CR. Does saline resuscitation affect mechanisms of coagulopathy in critically ill trauma patients? An exploratory analysis. *Blood Coagul Fibrinolysis* 2015; **26**: 250-254 [PMID: 25803514 DOI: 10.1097/MBC.0000000000000154]
101 **Song JW**, Shim JK, Kim NY, Jang J, Kwak YL. The effect of 0.9% saline versus plasmalyte on coagulation in patients undergoing lumbar spinal surgery; a randomized controlled trial. *Int J Surg* 2015; **20**: 128-134 [PMID: 26123384 DOI: 10.1016/j.ijsu.2015.06.065]
102 **Young JB**, Utter GH, Schermer CR, Galante JM, Phan HH, Yang Y, Anderson BA, Scherer LA. Saline versus Plasma-Lyte A in initial resuscitation of trauma patients: a randomized trial. *Ann Surg* 2014; **259**: 255-262 [PMID: 23732264 DOI: 10.1097/SLA.0b013e318295feba]
103 **Story DA**, Lees L, Weinberg L, Teoh SY, Lee KJ, Velissaris S, Bellomo R, Wilson SJ. Cognitive changes after saline or plasmalyte infusion in healthy volunteers: a multiple blinded, randomized, cross-over trial. *Anesthesiology* 2013; **119**: 569-575 [PMID: 23598288 DOI: 10.1097/ALN.0b013e31829416ba]
104 **Noritomi DT**, Pereira AJ, Bugano DD, Rehder PS, Silva E. Impact of Plasma-Lyte pH 7.4 on acid-base status and hemodynamics in a model of controlled hemorrhagic shock. *Clinics* (Sao Paulo) 2011; **66**: 1969-1974 [PMID: 22086530]

P- Reviewer: DeSousa K, Higa K, Kvolik S **S- Editor**: Gong XM
L- Editor: A **E- Editor**: Wu HL

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com