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REVIEW

Anticoagulant modulation of inflammation in severe sepsis

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Abstract

Inflammation and coagulation are so tightly linked that the cytokine storm which accompanies the development of sepsis initiates thrombin activation and the development of an intravascular coagulopathy. This review examines the interaction between the inflammatory and coagulation cascades, as well as the role of endogenous anticoagulants in regulating this interaction and dampening the activity of both pathways. Clinical trials attempting to improve outcomes in patients with severe sepsis by inhibiting thrombin generation with heparin and or endogenous anticoagulants are reviewed. In general, these trials have failed to demonstrate that anticoagulant therapy is associated with improvement in mortality or morbidity. While it is possible that selective patients who are severely ill with a high expected mortality may be shown to benefit from such therapy, at the present time none of these anticoagulants are neither approved nor can they be recommended for the treatment of sepsis.

Key words: Inflammation; Protein C; Heparin; Tissue factor pathway inhibitor; Thrombomodulin; Antithrombin; Sepsis; Coagulation; Neutrophil extracellular traps

Core tip: The interaction between the coagulation and inflammatory cascade contributes to the overall pathophysiology of severe sepsis. These processes become unchecked and thus can lead to significant morbidity and mortality. Many anticoagulants have been studied in clinical trials as a means to modulate the inflammatory and coagulation cascade with the aim to improve outcomes for septic patients *via* modulation of these cascades. This article outlines the pathophysiology and interaction between inflammation and coagulation in severe sepsis and also reviews the anticoagulants previously studied for modulation.

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INTRODUCTION

Sepsis is a leading cause of mortality in the United States responsible for more than 200000 deaths each year. The overall mortality is estimated to be approximately 28.6% for all age groups with mortality increasing in the elderly[1]. Furthermore, the incidence of sepsis is increasing secondary to increased use of immunosuppression therapy, invasive procedures,

transplantation, and chemotherapy. Mortality in sepsis is frequently due to organ failure and the risk of mortality increases with the number of failing organs. Individuals with sepsis and three or more failing organs have a 70% mortality rate compared to a mortality rate of 15% without organ failure[2].

Much of the organ failure in sepsis is thought to be caused by microvascular thrombosis. Local thrombus formation is protective when an infection is localized as it works to prevent bacteria spread systemically to other organs. However, once the infection spreads to the blood stream and sepsis develops, the formation of thrombi within the microvasculature acts counterproductively and increases organ damage which may lead to organ failure. Significant coagulation disturbances are thought to complicate approximately 35% of all severe sepsis cases[3]. Small and medium size vessels show fibrin deposition that has been found during autopsy studies of patients with DIC and sepsis. Fibrin is also found in many organs under pathological examination following sepsis[4]. Measures of coagulation activation in patients with sepsis show that some amount of clotting is present in all patients with septic shock regardless of the presence of overt disseminated intravascular coagulation (DIC)[4-6].

Inflammation and coagulation are frequently partners in crime in severe sepsis. Studies in the 1990s showed the complex relationship between these two systems in patients with sepsis or a traumatic insult. The inflammatory mediators were shown to activate coagulation and vice versa as inflammation may be induced by activation of the coagulation cascade[7]. The two are linked through similar activation mechanisms *via* a variety of pathways. Ultimately it is thought the uncontrolled systemic expression of both systems which plays a key role in the pathogenesis of multi-organ failure in sepsis. In this review article we will outline the role of inflammatory markers and coagulation in sepsis as well as the intricate relationship between the two. Subsequently, we will then review the results of clinical trials attempting to modulate this inflammation in patients with severe sepsis.

INFLAMMATION AND COAGULATION CASCADE RESPONSE TO SEVERE SEPSIS

The innate immune system responds to bacterial infections initiated by cells which detect pathogen associated molecular patterns (PAMPs) that are expressed on invading bacteria. The damaged tissue and cells from the host in sepsis will release intracellular proteins commonly known as alarmins[8]. Together alarmins and PAMPs are termed damage-associated molecular patterns (DAMPs). The initial immune response to a pathogen or DAMPs is driven by pattern recognition receptors (PRRs) that are expressed on immune cells. PRR, however, can also be found on other cells which are primary involved in hemostasis as these are highly conserved receptors. In humans PRRs are mainly reported on platelets as toll-like receptors[9]. This serves as a key link between the immune and coagulation systems as these cells are also then able to recognize and initiate the inflammatory response. Both toll-like receptors and complement receptors are PRRs which can initiate a complex cellular inflammatory response to pathogen invasion. These PRRs further activate the coagulation system through increased production of tissue factor and impairment of anticoagulation and fibrinolysis[10].

Activation of the coagulation cascade and thrombus in sepsis are generally thought of as adverse events occurring as a result of pathogen invasion. However, the recently described process of immunothrombosis suggests that some local thrombosis in response to microorganisms may actually be an independent line of host defense against pathogens[11]. This theory suggests that small amount of clot formation actually is beneficial for the host as bacteria and DAMPs are trapped and kept away from the host circulation, preventing systemic spread of infection and inflammatory cytokines or DAMPs to other organs. The immune system and coagulation systems work closely together *via* cross signaling to produce immunothrombosis. The innate immune cells, particularly monocytes and neutrophils, are recruited to sites of intravascular thrombosis in response to DAMPs at the site. In turn these cells express activated intravascular tissue factor (TF) which enhances clot formation *via* the extrinsic pathway of coagulation[11].

Although immunothrombosis may have a beneficial effect for the host in localized infection, this is not true in profound system wide infections. Severe sepsis, septic shock, and DIC occur together when the control mechanisms of inflammation and coagulation and the intricate relationship between these to two breaks down and each proceeds unchecked. The crosstalk between each system may actually perpetuate this process in severe systemic infection. There are several key aspects of the coagulation cascade which, when up-regulated, have a significant impact and are then in turn influenced by the immune system; these include TF, thrombin, and platelets. Likewise, cells which are part of the inflammatory response, particularly neutrophils, and the complement system link inflammation to coagulation during sepsis. Furthermore, the regulation of the coagulation system fails during DIC, endogenous anticoagulant proteins including; tissue factor pathway inhibitor (TFPI), anti-thrombin (AT), and activated protein C (APC) fail to regulate coagulation[9,11].

TF is thought to have a key role in the connection of sepsis and coagulation. It is up-regulated in sepsis through both activation by inflammatory cytokines and failure of control mechanisms like TFPI[10]. The cytokine triggers that cause TF to be expressed include; tumor necrosis factor (TNF), interleukin-1 (IL-1), and other inflammatory mediators including complement[12]. TF is part of the extrinsic pathway of coagulation and in the healthy state, is not exposed on peripheral blood or

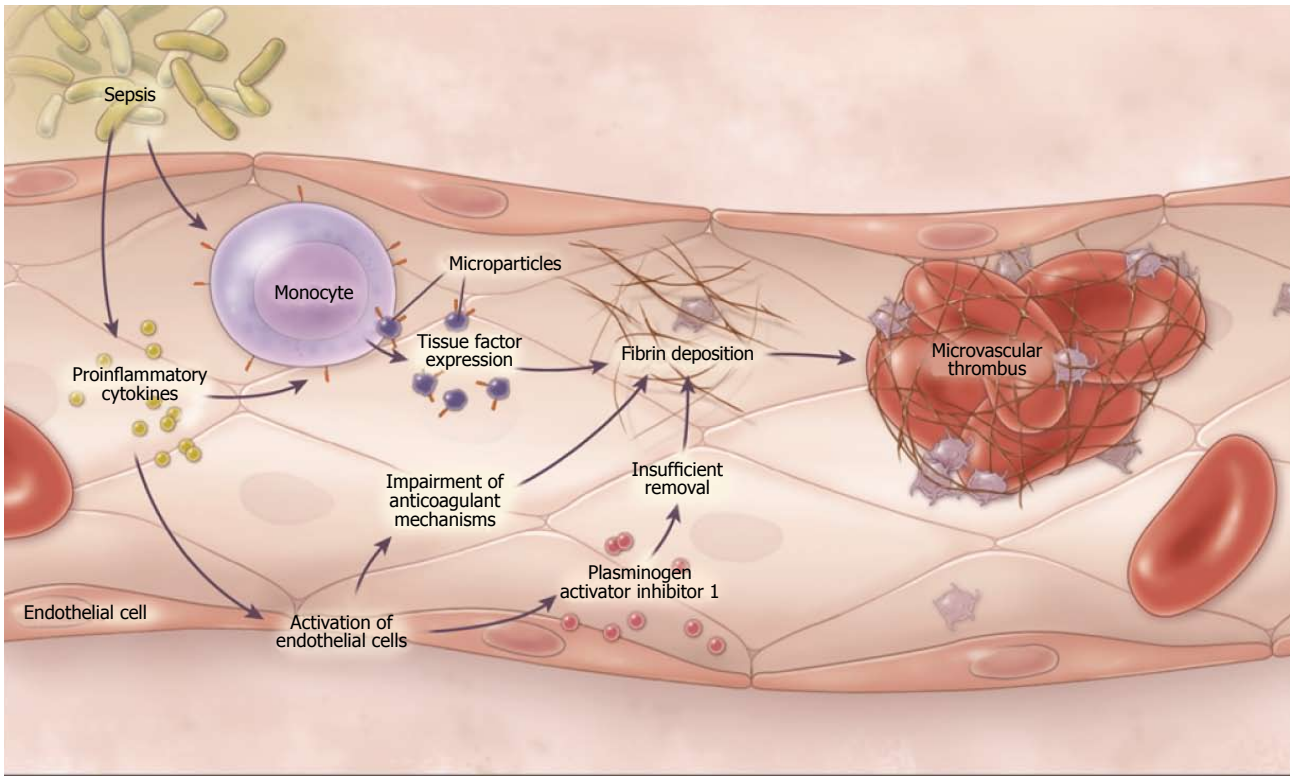

Figure 1 Pathogenesis of disseminated intravascular coagulation in sepsis[10]. Through the generation of proinflammatory cytokines and the activation of monocytes, bacteria cause the up-regulation of tissue factor as well as the release of microparticles expressing tissue factor, thus leading to the activation of coagulation. Proinflammatory cytokines also cause the activation of endothelial cells, a process that impairs anti-coagulant mechanisms and down regulates fibrinolysis by generating increased amounts of plasminogen activator inhibitor. Copyright © 2014 Massachusetts Medical Society (used with permission).

endothelial cells although it has a significant presence on extravascular cells[13]. The physiologic activation of the extrinsic pathway occurs through disruption of the endothelium and exposure of blood to extravascular cells which express TF or in the intravascular space through triggers that cause circulating monocytes, leukocytes, and neutrophils to expose TF on their cell membranes. The latter is through to be the more common pathway for enhanced expression of TF during pathogen invasion, as the recognition of PAMPs and/or DAMPs by cells of the innate immune system directly enhances TF expression[11] (Figure 1).

The initiation of coagulation by TF does not always lead to overt DIC in sepsis. Much of the impact of TF on the host response to sepsis may also be due to increasing the inflammatory response. The main inhibitor of TF is TFPI which tightly regulates the interaction of TF with other factors of the extrinsic pathway. TFPI has been studied as a method to modulate the host response to sepsis and through these studies it has become clear that TF has a strong inflammatory contribution during sepsis. Studies have shown that various levels of coagulation are noted in response to sepsis and the effectiveness of TFPI on host survival can be unrelated to differences in coagulation which suggests that much of the beneficial effects of TFPI are from an anti-inflammatory property it can exert on inhibiting TF augmentation of inflammation[14].

Thrombin, like TF, has a large role in coagulation but also exerts some influence on inflammation during sepsis. Thrombin is the central serine protease mediator of hemostasis. It is activated by Factor Xa and, once active, creates an active feedback loop for continued activation of Factor X. Thrombin also converts soluble fibrinogen to insoluble strands of fibrin for clot formation[11,15]. Activated thrombin can promote activation of several pro-inflammatory cytokines including, TNF-α, IL-β, and IL-6 as well as generate C5a (part of the complement response to infection) independent of C3. This activity of thrombin is crucial and demonstrates the complex relationships that exist as it shows the crosstalk that occurs between the coagulation system and components of both the inflammatory and complement systems[15].

Thrombin further actively participates in the inflammatory cascade that occurs during sepsis through specific receptors on platelets, endothelial cells, and white blood cells. These receptors are called protease activated receptors (PARs) and they are responsible for inducing TF emergence from cells and release of plasmin activator inhibitor I or *via* PARs, which inhibits fibrinolysis as well as decreasing thrombomodulin (TM) (a thrombin co-factor that decreases clot formation)[16]. Thrombin promotes platelet aggregation and activation. The activated platelets express P-selectin after being exposed to thrombin. P-selectin is critical for attachment of white blood cells to endothelial cells and thus initiating

white blood cell activation which contributes to diffuse microvascular injury[17].

Thrombin is regulated by AT, which is a serum protein with significant enzymatic activity to prevent coagulation and with its broad spectrum of activity it is considered a central inhibitor of the coagulation system. AT forms a complex with thrombin and inactivates it in addition to inhibiting other factors within the coagulation cascade (including the generation of Factors XIIa, XIa, IXa, and Xa). It acts on both the intrinsic and common coagulation pathways *via* inhibiting the action of Factors IXa and Xa respectively[7]. AT may also have direct anti-inflammatory actions during sepsis beyond its anti-coagulation properties. AT has the ability to inhibit the function of lipopolysaccharide (LPS) signaling on macrophages. This acts to decrease the level of inflammation through blocking macrophage activation. AT may also compete with bacterial pathogens for binding sites on endothelial surfaces and thus prevent endothelial damage by pathogens[18].

In septic patients with organ failure AT activity is reduced and the degree of reduction is proportional to the severity of sepsis, DIC and organ failure[16]. Part of this fall in AT levels is likely related to the decreased half- life of AT during sepsis. Typically the half-life of AT is between 36-48 h but decreases to less than 18 h during sepsis[7]. Additionally, part of the decrease in half-life for AT is related to neutrophil actions. Activated neutrophils release elastase which destroys AT, and therefore significantly decreases natural regulation of the coagulation system.

APC is another endogenous anticoagulant that has additional anti-inflammatory properties as well. Overall the function of protein C is reduced in sepsis and DIC which results in significant compromise of in regulation of coagulation. APC is down-regulated during the host response to sepsis through cytokines and TM loss on the endothelium as well as a decrease in its primary co-factor protein S[3]. This down-regulation may reflect a conserved part of immunothrombosis and theoretically may be protective in localized tissue infection. However, in sepsis the down-regulation of APC prevents it from actively controlling the host inflammatory response.

APC actually has been found to have an antiinflammatory role during sepsis that may serve partly to keep host response to pathogen invasion in check. APC can decrease apoptosis of endothelial cells and lymphocytes during infection thus reducing DAMPs in the bloodstream which serve to perpetuate further inflammatory reactions. APC also decreases the inflammatory response of key cells; including monocytes, leukocytes and neutrophils. APC decreases NF-κB signaling which decreases monocyte response to inflammation. APC further acts closely with endothelial cells in an anti-inflammation manner. APC specifically decreases TF up-regulation *via* leukocytes and decreases neutrophils adherence to endothelial cells in response to pathogen invasion[19].

Thrombin is further regulated by TM which is physiologically found in the intravascular space on vessel endothelial walls. TM plays a key role in preventing intravascular clot formation under normal physiological conditions. Thrombin binds with TM in a high affinity complex that prevents thrombin from activating fibrinogen to fibrin. The TM-thrombin complex also works as an anti-coagulant and activates protein C which then inactivates Factors Va and VIIIa[18]. The Thrombin-TM activation of protein C further also acts to decrease the overall inflammatory response to infection by suppressing monocyte-dependent cytokine production[19].

The Thrombin-TM complex has further influence on the anticoagulation and inflammatory systems. Thrombin activatable fibrinolysis inhibitor (TAFI) activity is increased three-fold by the Thrombin-TM complex formation. TAFI enhances fibrin clot stabilization leading to better control of inflammation as part of immunothrombosis. The activity of TAFI also has systemic anti-inflammatory properties. TAFI inactivates endogenous pro-inflammatory mediators, including bradykinin, osteopontin, and some elements of the complement system (C3 and C5)[19].

Platelets, like AT and APC, are also frequently decreased in any host response to insult including pathogen invasion. The decrease in platelets is not fully explainable by overt DIC, but rather more likely related to platelet consumption from immunothrombosis and the role platelets play in the inflammatory response. Thrombocytopenia is in fact, a predictor of poor outcome in sepsis and septic shock. This includes severity of thrombocytopenia as well as overall duration of low platelet count indicates poor outcomes[20].

Platelets have a key role in coagulation and clot formation. Platelets also recognize pathogens *via* PRRs and therefore, stimulate the host inflammatory response. An important example of cross-linkage between inflammation and coagulation *via* PRRs is toll-like receptor 4 (TLR4) (a subfamily of PRRs) on platelet cells, which recognize DAMPs and play an intricate role in activating neutrophils in the immune response[15]. TLR4 on platelets recognizes PAMPs of pathogens specifically LPS of gram negative bacteria. These receptors also recognize endogenous DAMPs which include heat shock proteins and fibronectin[21]. Platelets are further able to present microorganisms to neutrophils other immune cells, activating a portion of the innate immune system.

In addition to pathogen recognition, platelets up-regulate and alter the host immune response to pathogens. Platelets, for example, assist in recruiting and enhancing the microbicidal activity of leukocytes by releasing multiple mediators in the bloodstream. Platelets also act to recruit innate immune cells at the site of infection. In addition to recognizing DAMPs, platelets also release DMAPs which promotes additional TF and likely increases thrombosis intravascularly. This process was likely conserved in host immune response as part of the concept of immunothrombosis. Finally, platelets directly bind to neutrophils during the host

response to bacterial infection which subsequently stimulates the formation of neutrophil extracellular traps, although the exact methodology behind this is not known[11,22].

Neutrophils are terminally differentiated cells that are involved in the early immune response to invading microbes. Neutrophils are directed by cytokines to infected tissue where the cell is activated and may engulf a pathogen for intracellular killing. Neutrophils may also act though extracellular traps or NETs. NETs are composed of chromatin complexes with granular proteins which bind both Gram negative and positive bacteria and effectively kill microbes in an extracellular matrix. The NET releases cellular components that have antibacterial properties including DNA, myeloperoxidase and elastase and histones. The release of these components into the circulation can have unintended harmful effects on the host during sepsis through activation of the coagulation cascade[8].

NETs can activate coagulation *via* multiple mechanisms. NETs deliver TF to the extracellular surface and thus activate the extrinsic coagulation pathway. The NET surface is polyanionic and can activate certain contact phase proteins like Factor XII. They further stimulate platelet activation *via* histones H3 and H4 specifically. These histones also promote the extrinsic pathway through damage to the endothelial wall. Finally, NETs inactive TFPI and TM through a complex enzyme pathway. The inactivity of these endogenous anticoagulants further leads to uncontrolled coagulation during DIC. Much of the coagulation function of NETs is proposed to be protective of the host as immunothrombosis to contain pathogens at an infectious site. However, in systemic infection the protective process becomes destructive through unchecked inflammation and coagulation[11].

The complicated and complex interactions between the traditional coagulation system and the inflammatory system are further complicated by the role of complement during sepsis and DIC. Complement can be viewed as an "alarm system" which can recognize DAMPs and respond to both infectious and non-infectious changes within the host[23]. The complement system is crucial to host defense against invading microbes. It is well known that deficiency in some components of complement can make an individual susceptible to increased risk of infection. For example, deficiency in opsonization contributes to increased susceptibility to infections by pyogenic bacteria including *Haemophilus influenza* and *S. pneumonia*. However during multi-organ failure secondary to sepsis, complement is thought to have a detrimental effect on the host and contribute to organ failure[24].

Complement and in particular C5a can have harmful effects during sepsis that act through both inflammation and coagulation dis-regulation. High levels of C5a act to decrease the effectiveness of neutrophils by blocking the NADPH formation of superoxide anions essential for killing gram negative bacteria. Then in turn C5a can increase the function of macrophages causing increased or overproduction of cytokines which contribute to the cytokine storm of sepsis. C5a further enhances the expression of TF therefore disrupting the coagulation balance further. Finally C5a increases the apoptosis of thymocytes decreasing B cell production and leading to an immunodeficiency state in late sepsis[25]. Sepsis and the resulting multi-organ failure are clearly much more complex of a process to be explained by unregulated inflammation or coagulation alone. Instead, it is an intricate web with multiple cross-talk interactions between the various components of each system. This intricate web is the over-riding etiology that leads to sustained multi-organ failure which causes host demise. These are numerous targets within these systems that may be targeted as therapy to augment the overall host response to overwhelming sepsis. Many of the initial clinical trials in sepsis focused on blocking various components of the inflammatory cascade in sepsis. When these trials failed to show a significant improvement in morbidity or mortality it was natural to turn to modifying the coagulant response in an attempt to influence the outcome. Key clinical trials which investigate anticoagulants in an attempt to improve outcomes in septic patients will be reviewed in the following sections.

ANTICOAGULANT EFFECTS ON SEVERE SEPSIS

Antithrombin

AT is an endogenous anticoagulant synthesized by the liver. As its name implies, AT inhibits thrombin as well as factors Xa, IXa, VIIa, XIa, and XIIa. In addition to its anticoagulant effect, AT also has an anti-inflammatory effect at high serum levels. AT binds to glycosaminoglycans on the endothelial cell surface and enhances the microvascular production of prostacyclin I2, a potent vasodilator and inhibitor of platelet function[26].

AT levels are decreased in patients with severe sepsis, and this is associated with a worse prognosis. Several small studies initially suggested that AT administration could have a beneficial effect on organ function and survival in patients with severe sepsis. AT was subsequently studied in the phase 3 KyberSept trial. This study was a large (n = 2314) double blind, placebo controlled, multicenter trial, to determine if high dose AT would provide a survival advantage in patients with severe sepsis[27]. There was no significant effect on the overall mortality at 28 d, 38.9% in the AT group *vs* 38.7% in the placebo group. However, these results may have been complicated as the concurrent use of low dose heparin for venous thromboembolism prophylaxis was allowed in this study (Table 1).

The simultaneous use of heparin competitively inhibits the binding of AT to other glycosaminoglycans and may have affected the efficacy of AT. Also, AT must

bind to glycosaminoglycans on endothelial surfaces to promote local anticoagulant and anti-inflammatory activity[16]. In the subgroup of patients who did not receive concomitant heparin during the treatment phase, the 28 d mortality was lower in the AT group (37.8%) than in the placebo group (43.6%) but this difference did not reach statistical significance (P = 0.08). This mortality trend, however, became significant after 90 d, 44.9% in the AT group *vs* 52.5% in the placebo group, suggesting that there might be a role for AT therapy in the absence of heparin.

The KyberSept trial examined the results of high dose AT on patient with severe sepsis irrespective of DIC status. Wiedermann *et al*[28] in a subsequent analysis evaluated patients in the KyberSept trial with DIC and noted an absolute reduction in 28 d mortality of 14.6% compared to placebo (P = 0.02), whereas no effect on 28 d mortality of patients without DIC was seen[28]. A systematic review by Wiedermann suggested that the administration of AT to septic patients with DIC may increase overall survival. AT is approved and is currently being used for the treatment of DIC (including sepsis related DIC) in Japan.

Several studies from Japan have showed positive outcomes from AT use in severe sepsis. A recent small randomized controlled, multicenter trial by Gando *et al*[29], evaluated the efficacy of a supplemental dose of AT for septic patients with DIC. They enrolled septic patients with DIC and AT levels of 50%-80% normal. The patients were randomly assigned to receive supplemental doses of AT or placebo for 3 d. They noted that AT treatment resulted in significantly decreased DIC scores and better recovery rates from DIC compared with a control group without an increased incidence of bleeding complications. Tagami *et al*[30] identified 9075 patients with severe pneumonia and sepsis related DIC in a nationwide Japanese database[30]. Using propensity matching to account for confounding factors, they identified 2194 pairs of matched patients who did or did not receive AT treatment. They noted a beneficial effect of AT on 28 d mortality (confidence interval 40.6% *vs* 44.2%) and adjusted odds ratio favoring AT use. A prospective multicenter study from Japan compared 1500 IU/d *vs* 3000 IU/d supplemental dose of AT in septic DIC patients. It noted that the AT dose of 3000 IU/d improved survival. AT has been studied extensively and is widely used for the treatment of sepsis related DIC in Japan, however, it remains unavailable for the treatment of severe sepsis or sepsis related DIC in other countries.

Protein C

Protein C has multiple actions within both the coagulation and inflammation pathways. Low levels of protein C are associated with a poor outcome in patients with severe sepsis, suggesting repletion of protein C may benefit these patients. Protein C is converted by thrombin into APC which is an endogenous anticoagulant that inhibits activated cofactors Ⅴ and Ⅷ, thereby reducing thrombin generation. In addition to its ability to reduce thrombin generation, APC also has anti-inflammatory properties that are independent of its effect on thrombin generation.

Numerous basic science research studies have demonstrated potentially advantageous effects of APC. Extracellular histones released in response to an inflammatory challenge contribute to endothelial dysfunction, organ failure and death during sepsis. APC enhances histone degradation of histones[31], which may account for the cytoprotective activities of APC which include anti-apoptotic activity, ant-inflammatory activity, and endothelial barrier stabilization[32]. Protein C levels are decreased in patients with sepsis and recovery of protein C levels is associated with improved survival. Thus it would seem logical to examine its efficacy as a therapeutic agent.

The Prospective Recombinant Human APC Worldwide Evaluation in Severe Sepsis (PROWESS) trial evaluated the effects of recombinant APC (rhAPC) in patients with severe sepsis[33]. This was the first phase 3 clinical trial to demonstrate improved survival in patients with severe sepsis. PROWESS was a randomized, double blind placebo-controlled multicenter trial which was stopped early because of the improved survival observed in the treated group. The overall mortality rate was 30.8% in the placebo group and 24.7% in the APC group, a reduction of 6.1% (relative risk reduction of 19.4%). The survival benefit was greatest in the sickest patients, those with the most organ failures and highest APACHE Ⅱ scores. Patients with overt DIC had an absolute reduction in mortality from 40.3% to 30.5%, which is a relative risk reduction of 29.1%[34]. The bleeding event rate was only 3.4%. Subgroup analysis indicated that the mortality benefit was limited to patient with increased illness severity. Based on this study, rhAPC was approved by the Food and Drug Administration in 2001 for the treatment of severe sepsis in patients with an APACHE Ⅱ of 24 or greater, the median APACHE Ⅱ score in the PROWESS study.

A subsequent open label trial (ENHANCE) confirmed the mortality rate of approximately 25% in patients with severe sepsis but left open the question of whether rhAPC would be beneficial in less sick patients[35]. The ADDRESS trial randomized 2640 patients with severe sepsis and a single organ failure or APACHE Ⅱ < 25 to either rhAPC or placebo[36]. There was no difference in survival in these less severely ill patients, but the rate of serious bleeding with rhAPC was 2.4%, double that of the control patients. A subsequent trial focusing on the severely ill patient with septic shock (PROWESS - SHOCK) failed to confirm the improved outcomes noted in the original PROWESS trial, and in 2011 rhAPC was withdrawn from the world market[37].

The mortality rates in the PROWESS-SHOCK trial were substantially lower the expected given the inclusion criteria of septic shock, 26.6% *vs* 24.2% in the APC and control groups respectively. APC did not reduce

Table 1 Previous trials of anticoagulant therapy in severe sepsis

Ref.	Year	Inclusion criteria	*n*	Design	Therapy	Primary outcome	Treatment	Control	*P* value
AT									
Warren *et al*[27] (Kybersept)	2001	Severe sepsis	2314	Phase 3 RCT	AT 30000 IU × 96 h or placebo	Mortality	450/115 (38.9%)	446/1157 (38.7%)	0.94
Gando *et al*[29]	2013	Sepsis	60	Prospective randomized	AT 30 IU/kg × 72 h or placebo	DIC recovery (%) on day 3	16/30 (53.3%)	6/30 (20%)	0.015
Tagami *et al*[30]	2014	Sepsis-associated DIC in severe pneumonia	4388	Retrospective, propensity matched	AT 1500 IU/d	Mortality	890/2194 (40.6%)	270/2194 (44.2%)	0.02
rAPC									
Bernard *et al*[33] (Prowess trial)	2001	Severe sepsis	1690	Phase 3 RCT	APC 24 μg/kg per hour × 96 h or placebo	Mortality	210/850 (24.7%)	259/840 (30.8%)	0.005
Vincent *et al*[35] (Enhance trial)	2005	Severe sepsis	2378	Prospective single arm multicenter	APC 24 μg/kg per hour × 96 h	Mortality	25.30%	NA	NA
Abraham *et al*[36] (Address trial)	2005	Severe sepsis with APACHE < 25	2613	Phase 3 RCT	APC 24 μg/kg per hour × 96 h or placebo	Mortality	243/1316 (18.5%)	220/1297 (17%)	0.34
Ranieri *et al*[37] (Prowess shock)	2012	Septic shock	1680	Phase 3 RCT	APC 24 μg/kg per hour × 96 h or placebo	Mortality	223/846 (26.4%)	202/834 (24.2%)	0.31
Rimmer *et al*[38]	2012	Severe sepsis with septic shock	933	Retrospective, 2:1 propensity matched	APC 24 μg/kg per hour × 96 h	Mortality	180/311 (34.7%)	254/622 (40.8%)	0.05
Thrombomodulin									
Saito *et al*[43]	2007	DIC associated with hematologic malignancy or infection	234	Phase 3 RCT	Thrombomodulin 0.06 mg/kg × 6 d or heparin 8 U/kg per hour × 6 d	DIC recovery (%) on day 7	74/112 (66.1%) (thrombomodulin)	56 (49.9%) (heparin)	0.027
Vincent *et al*[44]	2013	Sepsis with DIC	741	Phase 2 RCT	Thrombomodulin 0.06 mg/kg × 6 d or placebo	Mortality	66/371 (17.8%)	80/370 (21.6%)	0.273
Heparin									
Jaimes *et al*[47] (HETRASE study)	2009	Sepsis	317	RCT	Heparin 500 U/h × 7 d or placebo	LOS	12 d (median)	12.5 d (median)	0.976
rTFPI									
Abraham *et al*[49]	2001	Severe sepsis	210	Phase 2 RCT	rTFPI 0.025 or 0.05 mg/kg per hour × 96 h or placebo	Mortality	43/141 (30%)	26/69 (38%)	0.3
Abraham *et al*[50] (OPTIMIST trial)	2003	Severe sepsis	1754	Phase 3 RCT	rTFPI 0.025 mg/kg per hour × 96 h or placebo	Mortality	301/880 (34.2%)	296/874 (33.9%)	0.88
Wunderink *et al*[52] (CAPTIVATE trial)	2011	Severe sepsis with community acquired pneumonia	2102	Phase 3 RCT	rTFPI 0.025 mg/kg per hour × 96 h or placebo	Severity adjusted 28 d mortality	185/955 (19.4%)	178/914 (19.5%)	0.56

RCT: Randomized controlled trial; LOS: Length of stay; APC: Activated protein C; DIC: Disseminated intravascular coagulation; TFPI: Tissue factor pathway inhibitor; AT: Anti-thrombin; NA: Not available.

mortality at 28 or 90 d, as compared with placebo, but was associated with increased bleeding risks in patients with severe sepsis and septic shock[37]. A subsequent retrospective multicenter cohort study of patients with septic shock, early use of APC was associated with 6.1% absolute reduction in 30 d mortality[38]. Another meta-analysis by Kalil *et al*[39], noted a significant reduction in hospital mortality (18%), and increased bleeding rate (5.4%) with the real life use of APC compared with controls.

Although rhAPC is no longer accessible, plasma derived APC is available in Japan. A randomized double blind trial compared the efficacy and safety of plasma derived APC with unfractionated heparin in the treatment of DIC by a Japanese group[40]. No significant difference in the rate of complete recovery from DIC was seen between the 2 groups. The rate of death from any cause within 28 d after treatment was 20.4% in the APC group, significantly lower than the 40% death rate observed in the heparin group ($P < 0.05$). There were no severe adverse events in either group. These findings suggests that plasma derived APC as a remarkably reduced dose compared to rhAPC can improve DIC, without increasing bleeding and its effects should be evaluated in future

trials.

TM

TM is an endogenous anticoagulant located on the surface of the endothelial cell that acts by inhibiting thrombin mediated clot formation and enhancing protein C activation at the site of clotting. In addition to its anticoagulant activity, TM also has anti-inflammatory properties, including interfering with the activation of complement and inactivating high-mobility group protein B1, a mediator associated with mortality in late sepsis[41]. TM expression on the endothelial surface is down regulated in patients with sepsis and may contribute to the development of DIC. Replacement of TM, therefore, may offer therapeutic value[42].

Saito *et al*[43], evaluated the efficacy of recombinant TM in treating DIC in a randomized, multicenter, double blind controlled trial. Recombinant TM or unfractionated heparin was administered to patients with DIC due to either malignancy or sepsis and resolution of DIC was assessed after 7 d[43]. DIC resolved in 66.1% of the group that received recombinant TM, as compared with 49.9% of the heparin groups, respectively ($P < 0.05$). The incidence of bleeding related adverse events was lower in the recombinant TM group 43.1% as compared to 56.5% in the heparin group. Based on this study, recombinant TM was approved for the treatment of DIC in Japan in 2008.

Subsequently a phase 2 trial evaluated the safety and efficacy of TM in patient with sepsis and DIC[44]. In this trial, DIC was diagnosed by a modified scoring system based on the platelet counts and prothrombin time and international normalized ratio (INR). Patients (371) randomized to TM and patients (370) who received placebo were similar at baseline. Twenty eight day mortality was 17.8% in the TM group and 21.6% in the placebo group. There were no significant differences between the two groups in organ dysfunction, inflammatory markers, bleeding thrombotic events or in the development of new infections during the study. In a post hoc analysis, the greatest benefit from TM was seen in patients with at least one organ dysfunction and an INR of greater than 1.4 at baseline. Based on the results of this encouraging study, a phase 3 trial of recombinant TM in patients with sepsis induced DIC and either shock or acute respiratory failure is currently in progress.

Heparin

Heparin is a sulfated polysaccharide with a heterogeneous structure and complex polymerization (MW, 357 kDa). Heparin binds to AT, causing a conformational change that increases the flexibility of the reactive site loop, activating AT. The activated AT then inactivates thrombin and other proteases, including factor Xa. Heparin also binds platelets to inhibit platelet aggregation, resulting in a strong anticoagulant effect. Heparin at high concentrations prevents histone interactions with platelets, which is a possible therapeutic target to modulate inflammation in severe sepsis. Fuchs *et al*[45], noted that heparin is highly sulfated and rich in negative charges, and electrostatic interactions with histones, are responsible for its histone-neutralizing effects, which suggests heparin could prevent cytotoxicity and collateral organ damage from histones.

Interest in heparin as a therapeutic agent in sepsis was spurred by the observation of Doshi *et al*[46], that the use of low dose prophylactic heparin in the placebo arms of KyberSept (phase 3 AT trial) and PROWESS (phase 3 rhAPC trial) was associated with a trend for reduced mortality which was not statistically significant. Heparin use was not randomized in either study and a subsequent study designed to show the safety of concomitant heparin and rhAPC use observed neither benefit nor an increase in bleeding risk. A subsequent retrospective study of 695 propensity matched pairs of patients with septic shock who did or did not receive high dose therapeutic heparin therapy suggested potential reduction in morbidity and mortality with heparin. In the prospective randomized double blind HETRASE Study, 319 patients were randomized to intravenous heparin or placebo. Heparin treatment was safe as there was no increased risk of bleeding. However, there was no significant difference in the primary endpoint, length of hospital stay. Moreover, the heparin treated patients failed to demonstrate a more rapid improvement in organ failure score or increase in survival[47]. Thus, while heparin is readily available, inexpensive, and widely used for DVT prophylaxis in septic patients, its role in the treatment of sepsis remains undetermined.

TFPI

TF is the major initiator of the blood coagulation process during sepsis and TFPI, an endogenous serine protease inhibitor which is synthesized and secreted by endothelial cells, acts to inhibit both the factor Ⅶa/TF catalytic complex in a Ⅹa dependent fashion as well as factor Xa directly[46]. TFPI may also play a role in maintaining endothelial cell integrity[48].

The initial trial results of recombinant TFPI (rTFPI) administration to patients with severe sepsis were encouraging. A multicenter, randomized placebo controlled, single-blind, dose escalation study enrolled 210 patients who received a continuous infusion of either placebo or rTFPI (dose 0.025 or 0.05 mg/kg per hour) for 4 d. Although the trial was not powered to evaluate mortality, this study noted a trend toward reduction in 28 d all-cause mortality as well as improvement in pulmonary organ dysfunction in the rTFPI group as compared with placebo. Logistic regression modeling suggested a more apparent coagulopathy, manifested by a higher baseline (INR), was associated with more pronounced beneficial TFPI effect[49].

Subsequently Abraham *et al*[50], examined this concept in a phase 3 randomized, double blind, placebo

controlled, multicenter trial which enrolled 1754 patients with severe sepsis and high INR (> 1.2) who were randomly assigned to receive either rTFPI (tifacogin) or placebo. In addition, 201 patients with a low INR (< 1.2) were randomized to receive either rTFPI or placebo. Tifacogin was effective in reducing markers of thrombin activation, but had no effect on 28 d mortality (34.2% with tifacogin *vs* 33.9% with placebo, $P = 0.88$). Tifacogin administration was associated with an increase in risk of bleeding, irrespective of baseline INR[50,51]. The most common site of infection in this study was community acquired pneumonia. A post hoc analysis suggested patients, who did not receive concomitant heparin, appeared to benefit from treatment with tifacogin. This led to a large phase 3 trial of rTFPI in patients with severe sepsis from community acquired pneumonia[53]. Again, rTFPI treated patients demonstrated a greater reduction in markers of thrombin activity, but no improvement in mortality was noted.

CONCLUSION

Inflammation and coagulation are tightly linked with each pathway capable of initiating and amplifying the activity of the other. Full blown expression of the coagulation pathway in the septic patient leads to overt DIC, overt but some degree of coagulation activation is apparent in virtually all patients with severe sepsis. Increasing coagulopathy is associated with the development of organ failures and increased mortality[53]. Simultaneous with the development of the coagulopathy there is a fall in the levels of endogenous anticoagulants including APC, AT, and TFPI as a consequence of both increased consumption and impaired production. Survivors of severe sepsis have more rapid return of this endogenous anticoagulant to normal levels. Because these endogenous anticoagulants appear to have anti-inflammatory activity independent of their ability to inhibit thrombin generation, they were administered to patients with severe sepsis in an attempt to improve outcomes. One trial of rhAPC showed an improvement in the survival of the sickest patients, but this benefit could not be replicated in subsequent studies. Phase 3 studies of AT and TFPI failed to demonstrate a clear benefit while a Phase 3 trial of TM is still in progress. Anticoagulant therapy in a patient with an underlying coagulopathy increases the risk of bleeding, which may obscure any potential benefit. At this time future trials of anticoagulant therapy for sepsis should focus on the most severely ill patients with the highest expected mortality, as this is the group in which benefit is most likely to be demonstrated. Until they can be shown to reduce morbidity and mortality, anticoagulants should not be used for the treatment of severe sepsis.

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REVIEW

Fluid and electrolyte overload in critically ill patients: An overview

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Abstract

Fluids are considered the cornerstone of therapy for many shock states, particularly states that are associated with relative or absolute hypovolemia. Fluids are also commonly used for many other purposes, such as renal protection from endogenous and exogenous substances, for the safe dilution of medications and as "maintenance" fluids. However, a large amount of evidence from the last decade has shown that fluids can have deleterious effects on several organ functions, both from excessive amounts of fluids and from their non-physiological electrolyte composition. Additionally, fluid prescription is more common in patients with systemic inflammatory response syndrome whose kidneys may have impaired mechanisms of electrolyte and free water excretion. These processes have been studied as separate entities (hypernatremia, hyperchloremic acidosis and progressive fluid accumulation) leading to worse outcomes in many clinical scenarios, including but not limited to acute kidney injury, worsening respiratory function, higher mortality and higher hospital and intensive care unit length-of-stays. In this review, we synthesize this evidence and describe this phenomenon as fluid and electrolyte overload with potentially deleterious effects. Finally, we propose a strategy to safely use fluids and thereafter wean patients from fluids, along with other caveats to be considered when dealing with fluids in the intensive care unit.

Key words: Fluid therapy; Critically Ill; Oliguria; Water-electrolyte balance; Central venous pressure; Resuscitation; Acute kidney injury; Diuretics; Multiple organ dysfunction syndrome; Systemic inflammatory response syndrome

Core tip: Fluids are a cornerstone of the management of critically ill patients with systemic inflammatory response syndrome who are at risk of multiple organ dysfunction syndrome. However, as with any therapy, fluids can be associated with harm, such as added or worsening organ dysfunctions. Therefore, patients should be weaned from fluids when possible, sometimes through an active de-resuscitation strategy.

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INTRODUCTION

Fluids have been widely used in critically ill patients to optimize hemodynamics[1], to enhance renal protection from contrast[2], globins[3], and uric acid[4], to offer caloric intake[5] and as an adjunct for medication dilution[6]. During the first hours of shock syndromes, isotonic fluids can stabilize arterial pressure and perfusion and are lifesaving at times. Furthermore, to reach physiological hemodynamic targets, a large amount of intravenous fluids may be required. Some fasting patients receive infusions of one to three liters of dextrose in water with added electrolytes, mainly sodium, chloride and potassium, to avoid hypoglycemia, dehydration and electrolyte deficiency. Renal protection in critically ill patients is of huge importance, and hyperhydration is frequently used to enhance urine output and to avoid renal tubular cell injury by the retention of toxic substances at high concentrations. Finally, many drugs require a large amount of fluids with electrolytes to be safely administered.

Fluids and electrolytes are responsible for a large amount of volume that is infused in critically ill patients and are commonly associated with reduced urine output and renal electrolyte excretion failure, particularly chloride-rich solutions. This combination is even more accentuated in the first hours of critical illness[1,7] or in the presence of acute kidney injury (AKI)[8-10]. Ultimately, the inadequate management of fluids and electrolytes in critically ill patients culminates in hydroelectrolytic overload, which causes physiological derangements and worse outcomes[11]. This manuscript describes the mechanisms, pathophysiology, and potential consequences of fluid and electrolyte overload and provides a combined bedside approach to avoid it.

ELECTROLYTE OVERLOAD

Primary electrolytes in basic human physiology

Sodium and chloride are the main determinants of colloidosmotic forces in human plasma and interstitial space because they account for 80% of the osmolality of these fluids[12]. Plasma non-permeable proteins attract positively charged ions and repel negatively charged ions, leading to a passive transmembrane distribution of anions to preserve plasma and interstitial space electroneutrality, known as the Gibbs-Donnan effect. A steady-state is achieved when the plasmatic osmolality is 1 mOsm/L greater than the interstitial space, and the capillary hydrostatic pressure opposes the osmotic movement of the water into the intravascular space[13].

Even at a constant interstitial space osmolality, to maintain cell volume, the transport of osmotically active substances across the cell membrane (mainly sodium and potassium) counterbalances the intracellular osmotic forces imposed by high-molecular-weight anionic proteins (Double-Donnan effect)[14].

One of the main roles of electrolytes and their homeostasis is the distribution of fluids throughout the human body. Colloidosmotic and hydrostatic pressures are the main forces influencing the fluid distribution between intravascular and interstitial spaces, whereas changes in intra or extracellular osmolality are in general followed by water movement and determine the changes in cell volume[14].

Sodium overload

Sodium is the main cation of solutions infused into critically ill patients. The 0.9% saline solution has 154 mEq/L of sodium, that is, one liter of 0.9% saline infusion carries 3.4 g of sodium, which represents approximately eight 100 g packages of commercially available potato chips, a huge amount of the electrolyte[15]. Nevertheless, sodium renal excretion is largely impaired in critically ill patients,[10] particularly in patients with AKI[8].

In a sample of septic patients, for instance, the mean isotonic fluid intake was 5000 mL during the first 24 h in the ICU, with a urine output of 2000 mL during the same period and a mean sodium urinary concentration of 55 mEq/L[16]. In this casuistic, the total amount of sodium infused was 770 mEq in the 24 h period analyzed with a concomitant sodium excretion of 110 mEq, resulting in a positive fluid and sodium balance of 3000 mL and 660 mEq, respectively. Because of the large sodium distribution volume in adults (49 L to 70 kg), the expected effect of the remaining 660 mEq of sodium and 3000 mL of water in patients with a pre-infusion sodium concentration of 145 mEq/L is approximately 4.0 mEq/L[17]. Notably, patients with established kidney injuries were excluded from the Stelfox *et al*[18] study, and consequently the sodium overload effect in patients with AKI is expected to be even more striking. To exemplify this finding, Table 1 shows a water and electrolyte cumulative evolution of a mono-compartment mathematical model of a post-resuscitation phase with low urinary sodium and chloride, similar to the septic patients of Noritomi's study.

Other groups have also described resuscitation fluids as a contributing factor to ICU-acquired hypernatremia with a dose-response effect: the greater the saline infusion, the worse the hypernatremia condition[19]. However, other sources of saline contribute to sodium loading in critically ill patients and may be a modifiable risk factor, such as normal saline used to dilute parenteral drugs and to keep catheters open[20]. Finally, in Australia and New Zealand, a point-prevalence study demonstrated that sodium administration in excess

Table 1 Closed mono-compartment mathematical marginal model simulating the body water space of distribution

Variables	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Patient's resulting variables						
Na^+ (mEq/L)	140	142	148	151	146	144
Cl^- (mEq/L)	100	108	114	117	113	111
Fluid balance (mL)	-	6000	0	800	800	0
Cumulative fluid balance (mL)	-	6000	6000	6800	7600	7600
Distribution water volume and electrolyte data						
Vd (L)	36	42	42	43	44	44
Total mass of Na^+ (mEq)	5040	5964	6216	6493	6424	6336
Total mass of Cl^- (mEq)	3600	4536	4788	5031	4972	4884
Fluids output						
Diuresis (mL)	-	2000	1200	1200	1200	2000
Urinary Na^+ (mEq/L)	-	30	50	70	90	110
Urinary Cl^- (mEq/L)	-	30	50	70	90	110
Fluids input						
Volume	6000	2000	2000	2000	2000	2000
Na^+ (mEq/L)	154	154	154	0	0	0
Cl^- (mEq/L)	154	154	154	0	0	0

The main assumptions of this model are the absence of feces, sudoresis, renal replacement therapy, and the absence of Gibbs-Donnan effect. This patient was resuscitated with 4000 mL of 0.9% saline and received additional 2000 mL of 0.9 fluids during the Day 0. He received an amount of 0.9% saline during day 1 and day 2, afterwards the same 2000 mL of volume was infused without electrolytes due to hypernatremia. Vd: Denotes distribution volume.

of recommended daily requirements (*i.e.*, 1-2 mmol/kg) was fairly common, with the major sources being maintenance fluids (30.9%), fluid boluses (16.3%) and drug boluses (12.3%)[21].

Hypernatremia is present at hospital admission and at ICU admission in 2% and 7% of patients, respectively[22,23]. By contrast, up to 27% of patients in the ICU develop hypernatremia during their ICU stay[18]. In a speculative view, this higher incidence of hypernatremia in critically ill patients might be explained by sodium overload. Critical illness related hypernatremia is associated with disease severity, kidney injury and dysfunction, mechanical ventilation and ICU length-of-stay[18]. Finally, hypernatremia is associated with higher in-hospital mortality[18,22,24,25] and it has been considered in several ICUs as a quality-of-care marker[26,27]. Recently, a group also retrospectively noted that correcting this abnormality ultimately resulted in better survival[28].

Chloride overload

Chloride is the main anion of fluids used in critical care settings, and its concentration is well correlated to the sodium concentration to maintain the electroneutrality of solutions[29]. The 0.9% saline solution, Ringer's lactate solution, and Plasmalyte contain 154, 109 and 98 mEq/L of chloride, respectively[15]. Because the serum chloride concentration is approximately 100 mEq/L, it is expected that a 0.9% saline infusion potentially increases the serum chloride concentration. In septic patients, Park *et al*[30] showed that 2000 ± 300 mL of a 0.9% saline infusion promptly resulted in a disproportionate elevation of serum chloride in comparison to the sodium concentration (Figure 1). Of note, this disproportionate elevation occurred in spite of equal chloride and sodium concentrations in the 0.9% saline solution that was infused[15,30].

The principle of the unequal chloride and sodium concentration elevations is based on the fact that the initial serum chloride concentration is lower than the initial sodium concentration. Therefore, the same infused amount in mEq/L of sodium and chloride is expected to have a greater effect on the ion with the lower serum concentration - in this case, chloride (Figure 2).

Kellum *et al*[31] demonstrated in a canine model of endotoxemia that only one-third of the post-volume infusion of chloride associated acidosis could be explained by exogenous chloride. The authors attributed this fact to an extravascular to intravascular chloride shift that was driven by differences in the transmembrane potential and the Gibbs-Donnan effect secondary to the fluid challenge. This same finding of chloride elevation was observed in humans with severe sepsis and septic shock[16]. Therefore, one can expect an intrinsic chloride elevation in patients with systemic inflammation, which is amplified by a chloride-rich fluid infusion, such as the many previously described sources of normal saline that are infused in critically ill patients.

In addition to these sources of chloride, the renal excretion of chloride is also impaired, similarly to sodium excretion, during the initial phase of critical illness[9,10], particularly in patients with AKI[8]. The net result is a positive balance of chloride (Table 1), and an increased serum chloride concentration results in a hyperchloremic metabolic acidosis[16,32]. This is also called "SID acidosis" and is not related to outcomes in mixed critically ill patients[33]. However, specifically in septic patients, initial hyperchloremic acidosis is associated with a higher mortality[16].

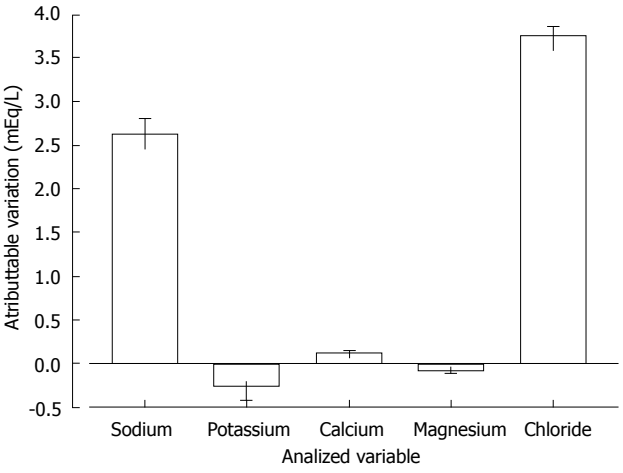

Figure 1 Variation of plasma electrolytes concentration immediately after 2000 ± 300 mL infusion of 0.9% saline in septic patients. Adapted from Park *et al*[30].

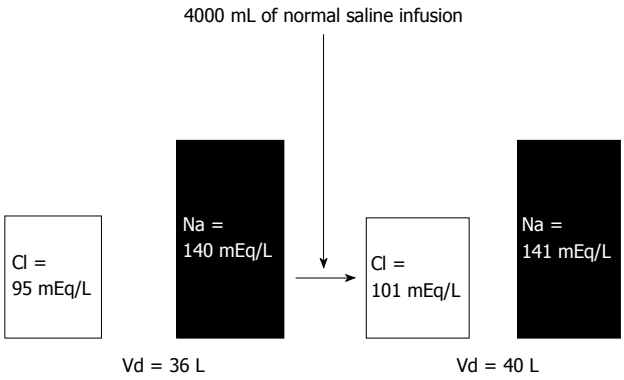

Figure 2 A monocompartimental model of intravascular 0.9% saline infusion, simulating the extracellular volume modification. To the initial distribution volume (Vd) = 36 L (approximately 60% of body mass of 60 kg), the total AMMOUNT of Cl^- and Na^+ were 3420 and 5040 mEq respectively. The infusion of 4000 mL of 0.9% saline results in additional 616 mEq of Cl^- and Na^+ to the total QUANTITY of extracellular electrolytes, that is, 4036 and 5656 mEq of Cl^- and Na^+ respectively. The new total AMMOUNT of electrolytes are distributed in a new Vd of 40 (36 + 4) liters, resulting in the new concentrations, where the chloride elevation was more striking than the sodium elevation.

Pathophysiology

Renal consequences: Electrolyte overload may have detrimental effects on renal function, particularly chloride overload. Animal studies suggest that chloride may influence renal blood flow (RBF), which is mediated primarily by its effects on afferent and intrarenal arterial vessels[34,35]. In canine experiments, the renal infusion of solutions containing chloride, such as 0.9% saline or NH_4Cl, led to reductions in the total RBF and GFR in both denervated and *in situ* kidneys[34]. In an animal model of sepsis, unbalanced solutions worsened sepsis-induced AKI[36]. Other experiments confirmed that extracellular chloride is essential for contraction in renal afferent arterioles[37,38]. In humans, an infusion of 2 L of 0.9% saline over 1 h was associated with a reduction in the RBF velocity and renal cortical tissue perfusion measured by magnetic resonance imaging (MRI); these changes were not observed after a similar infusion of a balanced crystalloid[39]. Moreover, studies in healthy volunteers have shown a delayed urine output with saline compared to a balanced solution[40].

An infusion of hypertonic solutions containing chloride into the renal artery causes a biphasic response in renal vascular resistance[34]. Hyperosmolality leads to an abrupt renal vasodilatation and consequent increase in RBF. After 1-5 min, vasodilation is reversed, and RBF and GFR decrease below pre-infusion levels. The second phase is absent in hypertonic solutions that do not contain chloride.

In vitro, the entry of chloride from elevated tubular chloride concentrations into epithelial renal cells causes the depolarization of the basolateral membrane[41]. Increased NaCl concentrations in the macula densa stimulate ATP release, resulting in the extracellular formation of adenosine, which is involved in the signal transmission of the tubule-glomerular feedback response, increasing afferent arteriolar resistance and reducing GFR[35,42].

Clinically, Yunos *et al*[43] translated this experimental knowledge to a large population of critically ill patients in a prospective open-label sequential period pilot study. After a control period and a wash-out phase, the use of chloride-rich intravenous fluids was restricted; this resulted in decreased chloride administration (694 to 496 mmol/patient) and led to better renal outcomes even after adjustment for covariates, including less high-severity AKI [OR = 0.52 (95%CI: 0.37-0.75); $P < 0.001$] and the reduced use of renal replacement therapy [OR = 0.52 (95%CI: 0.33-0.81); $P = 0.004$][43].

Acid-base consequences: Large volume resuscitation is commonly required in patients with sepsis and trauma. These patients may receive crystalloid infusions of many times their plasma volumes. Because the chloride concentration in 0.9% saline is approximately 50% higher than the plasma values, the chloride load associated with these volumes is significant. As previously described in this review, the chloride load associated with normal saline, which is a solution with a strong ion difference (SID) of 0, may be one of the main determinants of acidosis induced by fluids, along with chloride shifts that may occur in patients with sepsis (and other inflammatory states) and the Gibbs-Donnan effect after fluid challenges. These chloride loads and shifts interact with the patient's renal function, leading to both more AKI and subsequently lower chloride excretion, which might affect the kidney's recovery.

In surgical patients, when 0.9% saline was used as the primary intraoperative solution, significantly more acidosis was observed on completion of the surgery. These patients required larger amounts of bicarbonate to achieve predetermined measurements of base deficit and were associated with the use of larger amounts of blood products[44]. In another trial, a 0.9% saline infusion was compared to a balanced electrolyte and glucose solution. Two-thirds of the patients in the 0.9% saline

group but none of the patients in the balanced fluid group developed hyperchloremic metabolic acidosis, and the hyperchloremic acidosis was associated with reduced gastric mucosal perfusion on gastric tonometry[45].

Although the effects of chloride are well studied, little is known about the potential contributions of sodium to the metabolic acid-base state. In a sample of 51 critically ill patients, a rise in serum sodium levels during the development of hypernatremia was accompanied by an increasing pH, serum bicarbonate, and standard base excess, and consequently metabolic alkalosis[46]. In addition, the development of metabolic alkalosis correlated with the SID but not with the absolute serum sodium concentrations, indicating that the increase in the serum sodium-to-chloride ratio led to the development of metabolic alkalosis[47].

Inflammatory response: Fluid and electrolyte overload may also influence cytokine production and the inflammatory response. In an animal model of hyperchloremic acidosis induced by dilute HCl infusion, moderate (SBE, - 5 to - 10) and severe (SBE, - 10 to - 15) acidosis significantly increased cytokine expression in a dose-dependent fashion in normotensive septic rats[48]. These results are consistent with *in vitro* studies showing that HCl influences cytokine production in LPS-stimulated cells[49], and pH interferes in nitric oxide[50] and tumor necrosis-α production[51] by macrophages in cell models. Interestingly, acidosis etiology may determine the inflammatory response pattern. Hyperchloremic acidosis is essentially pro-inflammatory as assessed by the increased NO release and the IL-6-to-IL-10 ratio, whereas lactic acidosis is associated with an anti-inflammatory pattern[49].

Hemodynamic consequences: Chloride overload and its consequent hyperchloremic acidosis may have direct and independent deleterious effects on hemodynamics and survival. In an endotoxic shock model in rats, moderate and severe acidosis that was generated by HCl infusion induced a significant drop in blood pressure. This change in blood pressure was correlated with increases in plasma chloride concentrations and to a lesser degree with a decrease in pH[52]. Furthermore, saline solution resuscitation was associated with a significantly shorter survival time compared to a balanced electrolyte solution containing starch in a similar animal model. Survival time was negatively correlated with both the decrease in pH and the increase in serum chloride following the initial resuscitation. The decrease in pH appeared to have been brought on by changes in chloride, lactate, and $PaCO_2$. However, lactate values were not different between the groups, and the changes in $PaCO_2$ were not correlated with survival time. Thus, hyperchloremic acidosis, rather than acidosis in general, was strongly and independently associated with early mortality in these animals[53].

FLUID OVERLOAD

Pathophysiology

The renal compartment syndrome: The human body is composed of different organ systems. Lungs are, perhaps, the most affected organs by fluid overload, followed by encapsulated organs such as the kidneys. Experimental and clinical evidence from more than 30 years ago links the development of renal edema with oliguria and the perpetuation of ischemic AKI[54]. This could be explained by reduced perfusion pressure through the kidneys as a result of higher central venous pressure, which has been better described in the context of cardiorenal syndromes[55,56]. In addition to heart failure, patients with systemic inflammatory response syndrome (SIRS) may also develop interstitial edema and subsequently increases in interstitial pressure, leading to lower perfusion pressure, particularly in encapsulated organs such as the kidney[57].

In animal models, Burnett *et al*[58] also demonstrated that an increase in renal venous pressure associated with volume expansion led to higher interstitial pressures and decreased sodium excretion in association with a decreased RBF and glomerular filtration rate. Recently, Cruces *et al*[59] experimentally described a model that provided even more support of the existence of a renal compartment. In their work, pressure had a nonlinear dependence on volume in the intact kidney, whereas the decapsulated kidney followed a linear pressure-volume curve, thus corroborating the hypothesis that kidney hypoperfusion might be explained by a reduced perfusion pressure. Clinical evidence supporting the role of interstitial edema to worse kidney outcomes will be discussed later in this review.

Pulmonary consequences: Derangements in the capillary permeability, which occurs in SIRS, combined with an increased hydrostatic pressure, as induced by aggressive fluid resuscitation, results in major interstitial edema that can lead to important clinical consequences.

Fluid overload increases hydrostatic pressure, leading to fluid accumulation in the lungs. Studies in mice have shown that the leakage occurs in the bronchiole, and the backflow of fluids leads to alveolar edema[60]. There is a reabsorption of fluids in the interstitial space and, because the accumulated fluids are drained across the lymphatic vessels to the thoracic duct and superior vena cava, alterations in systemic venous pressure, which occurs during fluid overload, result in impaired lymphatic drainage and consequently pulmonary edema[61], leading to a gas exchange impairment.

The high hydrostatic pressure not only causes fluid leakage but also generates mechanical stress injury to capillary walls, leading to the impairment of the mechanisms of fluid reabsorption[62] and alveolo-capillary barrier damage[63,64]. This damage causes

ultrastructural changes in the capillary, altering permeability to proteins and activating the inflammatory response[65], which compromises gas exchange[66].

Hypoxemia resulting from impaired gas exchange leads to lung regional blood flow redistribution. As demonstrated by Ruff *et al*[67], fluid overload leads to an inversion of the pulmonary perfusion pattern, with decreased blood flow to the pulmonary dependent regions and increased blood flow to the non-dependent regions, most likely because of hypoxic vasoconstriction.

The clinical features of pulmonary edema are not restricted to oxygenation but are a result of decreased pulmonary ventilation as well. In 1922, Drinker had described a tidal volume reduction of 40%-70% in an induced pulmonary edema animal model[68], and a subsequent study has shown that a negative fluid balance strategy improved lung compliance and arterial oxygenation[69].

Considering Starling's equation in which pulmonary edema is a result of colloidosmotic and hydrostatic forces, one approach to this clinical problem is to lower filling pressures. Despite concerns regarding lowering cardiac output and oxygen delivery, current evidence shows that a conservative fluid strategy improves the oxygenation index and number of ventilation-free days without compromising hemodynamics or other organ functions[11,70].

Other organ consequences: Other organs might be affected by fluid overload in addition to the lungs and kidneys. Worse outcomes of the skin and the recovery of soft tissue wounds after surgery have been described, and the trial of Brandstrup *et al*[71] showed that a more conservative approach on fluids achieved better outcomes, particularly regarding surgical complications.

Gastrointestinal complications, such as ileum and anastomotic leakages, can also be increased because of interstitial edema associated with accumulated fluids during critical illness or major surgeries[72]. This might lead to delays in the administration of nutritional needs and worsen the possibility of achieving an adequate enteral nutrition intake.

The liver is also an encapsulated organ, and interstitial edema could lead to a sort of compartment syndrome. In shock states, in addition to hypoperfusion, a high central venous pressure is required for the development of ischemic hepatitis[73]. High venous pressures are usually secondary to a low cardiac output in patients with congestive heart failure, but it can also occur in fluid overloaded patients with SIRS who develop myocardial dysfunction.

From a broader perspective, abdominal compartment syndrome can be seen as another preventable complication of fluid overload. This syndrome would be an extreme situation regarding fluid overload states and can be either primary or secondary. In this case, fluid overload contributes to the development of abdominal compartment syndrome, leading to deleterious effects on many organ systems, including hemodynamic (as a result of reduced venous return), renal (as a result of increased renal venous pressure) and even respiratory system mechanics (by reducing the thoracic wall compliance)[74].

Other organ systems have more limited evidence associating fluid overload with worse outcomes. Although the brain could be considered an encapsulated organ, in general ICU patients whose blood-brain barrier is considered intact, fluid overload will most likely not lead to a significant cerebral edema that will develop into intracranial hypertension. However, it might be associated with an increased incidence of delirium[75], which is associated with worse outcomes.

Acid-base water effect: Despite the effect of electrolytes on acid-base status, water itself might influence the acid-base status. Some experimental evidence from *in vitro* studies suggests that the dilution of plasma with distilled water changes many electrolyte concentrations, but because the ensuing proportions are maintained regarding the SID, $PaCO_2$ and weak anions, there is no significant difference in the pH[76]. However, in a mathematical modeling approach validated thereafter with human plasma, Gattinoni *et al*[77] demonstrated that water itself, when in an open system, leads to acidosis, mainly because of the reaction of CO_2 with H_2O. The same group later described a possible rule that would regulate pH changes during crystalloid infusion, with interesting results. Mainly, the baseline [HCO_3^-] values would dictate the pH response to a crystalloid solution whose (SID) would be the main determinant of the direction of the pH change[78]. As an example, giving a patient both 0.9% saline [(SID) = 0] or dextrose in water [(SID) = 0] can lead to worsened acidemia, depending on the patient's renal function and pulmonary function to counteract these effects. However, 0.9% saline comes with an added cost, which is that of electrolyte overload, as we have discussed.

Observational evidence correlating fluid overload with worse outcomes

Fluid overload or cumulative fluid balances have been associated with worse outcomes in many scenarios, including in patients with sepsis[79], cancer[80], and surgical patients[81], and during weaning from mechanical ventilation[82] and at discharge from the ICU[83].

A sub analysis of the VASST trial, which included patients with septic shock who were on vasopressors, reported that a positive fluid balance at both 12 h and 4 d after the onset of shock was associated with worse outcomes. Interestingly, the patients with CVP values below 8 mmHg at 12 h after septic shock onset had improved survival compared to patients with higher values of CVP[79], which are recommended by the surviving sepsis campaign during the first hours of resuscitation[84]. More provocative are the findings of Murphy *et al*[85], who studied a cohort of patients with septic shock who thereafter developed acute respiratory distress syndrome (ARDS), in which they hypothesized whether an adequate initial

fluid resuscitation strategy and a conservative late fluid management strategy were associated with improved survival[85]. In this cohort, the patients who achieved both adequate initial fluid resuscitation and conservative late fluid management had the lowest mortality. Interestingly, the patients who achieved a conservative late fluid management but not adequate initial fluid resuscitation had lower mortality rates than those who achieved adequate initial fluid resuscitation but not conservative late fluid management. This appears to provide a lesson regarding this population: trying to optimize hemodynamics later in the course of the disease is most likely deleterious, whereas achieving negative fluid balances, *i.e.*, actively de-resuscitating patients even if the initial resuscitation was not deemed adequate, appears to be successful, particularly for patients with ARDS[11]. In patients with ARDS, a large observational cohort also demonstrated that more positive fluid balances are associated with worse outcomes[86].

In patients being weaned from mechanical ventilation, data demonstrate that a 24-h negative fluid balance on the day of the spontaneous breathing trial and a cumulative negative fluid balance were associated with better weaning outcomes[82]. In another cohort of elderly patients, both negative fluid balances and decreasing values of central venous pressure were associated with better weaning outcomes[87]. A higher cumulative fluid balance, even after ICU discharge, was also associated with worse outcomes during hospitalization[83].

In patients with AKI, positive fluid balances have also been associated with worse outcomes. In a sub analysis of a European cohort of general ICU patients who developed AKI, a positive mean fluid balance was an independent risk factor for 60-d mortality[88]. In a sub analysis of the RENAL study, the authors investigated the effect of fluid balance on the outcomes of patients with many different statistical approaches, and they consistently found an association between negative mean daily fluid balances and improved clinical outcomes[89].

Many of these conditions in which fluid overload has been shown to be deleterious share a common feature: the presence of SIRS and the risk of multiple organ dysfunction syndrome, which can manifest clinically as shock along with AKI, ARDS and many other possible organ dysfunctions, septic or non-septic in origin[90]. What remains to be established is whether fluid overload is only a biomarker[91] that puts patients under an increased risk of death or an iatrogenic condition from critical care that should be considered in daily care and actively treated and avoided. This is a question to be answered with randomized controlled trials.

Randomized controlled trials correlating fluid overload with worse outcomes

Some randomized controlled trials in critically ill patients attempted to address whether a conservative fluid management approach would result in better outcomes for patients instead of a liberal approach, testing the hypothesis that fluid overload is not only a biomarker but is also a modifiable risk factor for worsening organ dysfunctions and death. In each trial, the fluid-restrictive protocols were different; however, the greatest objective in all of the studies was to withdraw fluids from the patients and/or to avoid giving unnecessary fluids.

In patients admitted to an intensive care unit who required a pulmonary artery catheter, Mitchell *et al*[70] compared an extravascular lung-water based strategy against a wedge pressure-based strategy for the treatment of 101 patients. Regardless of the protocol used, in the extravascular lung-water based strategy, the cumulative fluid balance was 142 ± 3632 mL compared to 2239 ± 3695 mL in the other group. The conservative strategy led to better outcomes in this group although mortality was unchanged.

In patients undergoing high-risk colorectal surgery, Brandstrup *et al*[71] also tested another conservative strategy for fluid management during the perioperative state and achieved a significantly lower fluid balance in these patients, yielding a lower rate of complications after surgery, many of which included surgical wound repair and cardiopulmonary complications.

In the landmark FACTT trial, which included two different protocols for the fluid management of patients with ARDS, patients in the conservative group achieved a negative fluid balance throughout the course of the disease, whereas patients in the liberal group progressively accumulated more fluids during their ICU stay. The primary outcome (mortality) was not different between the groups. However, the conservative group achieved a higher number of ventilator-free days and ICU-free days but had less vasopressor free-days, along with a slight trend towards a lower dialysis requirement through day 60 (P = 0.06)[11]. This trial demonstrated an interesting point: when using a conservative fluid management strategy, one will likely require vasopressors for a longer period but paradoxically at the benefit of being able to breathe without the ventilator sooner and being discharged from the ICU sooner. The cumulative fluid balance of both arms of the FACTT study is shown in Figure 3, as is the fluid balance of the ALVEOLI[92] and ARMA[93] studies about protective mechanical ventilation in ARDS patients.

Finally, during weaning from mechanical ventilation in a mixed ICU population, it has been demonstrated that a brain natriuretic peptide-driven strategy for fluid withdrawal resulted in more negative cumulative fluid balances [median, - 180 (-2556; 2832) *vs* - 2320 (-4735 to 738), P < 0.001], resulting in more ventilator-free days, although without impact on mortality[94].

These trials, although conducted in different clinical scenarios, share an interesting feature. In the population of patients at risk of developing new organ failures (such as patients during high-risk surgery) or with ongoing organ failures (such as patients with ARDS) or even

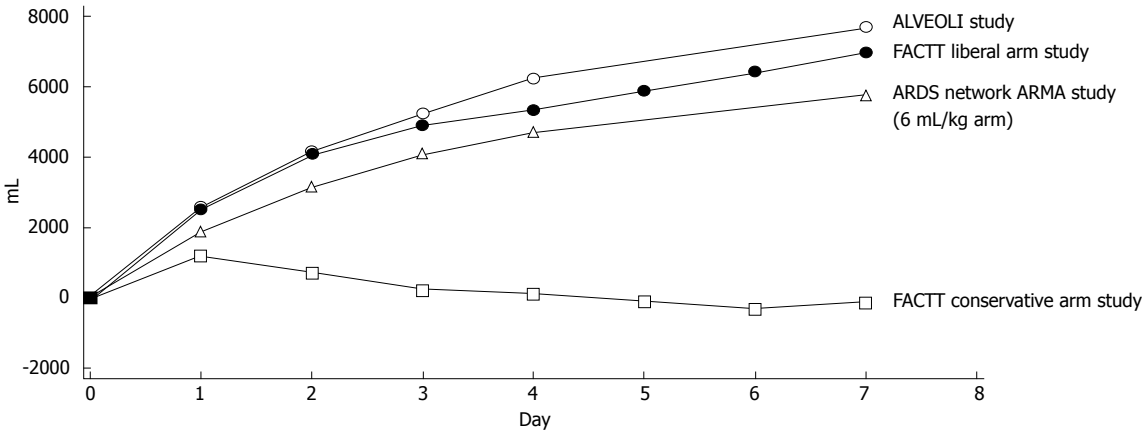

Figure 3 Cumulative fluid balances of the acute respiratory distress syndrome network group studies. The FACTT conservative fluid strategy arm returned to the neutral fluid balance within the first three days after randomization. The former strategy did not result in better survival, however patients were ventilated for less time and spent less time in the ICU in the conservative group. Adapted from Wiedemann *et al*[11]. ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

during recovery of the critical illness, a conservative strategy led to better outcomes. Whether this can be extrapolated to all clinical scenarios remains to be answered.

The kidney paradox (oliguria worsened by fluid challenge)

Oliguria is usually considered a marker of decreased cardiac output, and a fluid challenge is often considered in an attempt to increase the cardiac preload and enhance cardiac output, which would ultimately enhance organ perfusion. However, after the optimization of hemodynamic parameters, some patients will still develop AKI and may have persistent oliguria on the ensuing days. Hence, after the first hours of resuscitation, oliguria should be interpreted as a marker of organ dysfunction but should not be seen as a marker of low cardiac output and does not necessarily indicate the need for volume expansion.

In this context of oliguria and a high risk of fluid overload, an added fluid challenge may worsen urine output and even renal function, as we have discussed previously in this review; most of the time, this will contribute to fluid and electrolyte overload. Clinically, Van Biesen *et al*[95] demonstrated in a cohort of septic patients with AKI that additional fluid therapy failed to improve renal function, and other studies have shown an association between a positive fluid balance and worse outcomes in patients with AKI[91], in addition to a decreased likelihood of renal recovery[88,96]. Another implication of increasing cumulative fluid balances in this context is the potential underestimation of the diagnosis or severity of AKI because of an increased creatinine distribution volume[97].

Therefore, this kidney paradox should be avoided in which clinicians attempt to enhance urinary output through repeated fluid challenges to avoid worsening kidney injury; these actions may in fact lead to more fluid accumulation and ultimately a worse outcome.

A BEDSIDE PATIENT-TAILORED APPROACH

To avoid potentially deleterious complications associated with fluid and electrolyte overload (Table 2), a patient-tailored approach is necessary to result in better outcomes for the individual patient. This will involve some aspects of fluid resuscitation, maintenance fluids, other sources of electrolytes and water and, ultimately, an active de-resuscitation strategy that may aim at the fluid balance and, if performed adequately will also remove the excessive loads of sodium and chloride. Here we describe how clinicians can address this situation at the bedside.

Judicious resuscitation

During the acute phase of resuscitation, fluids should be used judiciously to achieve an adequate perfusion. This encompasses four distinct aspects of fluid resuscitation: timing, type, amount and avoidance of the kidney paradox[98].

Resuscitation with fluids should be performed during the appropriate timing for this action, which occurs during the onset of the injury (intra-operative states) or soon after it (first hours after septic shock, major surgery or other acute physiological insults)[1]. There is no evidence that fluid resuscitation after these first moments will lead to better results. In fact, as we have discussed so far, the evidence points in the opposite direction.

In general, balanced solutions should be the fluids of choice in patients with shock states because they carry a lower chloride load, lead to less acid-base disturbances and most likely to better organ dysfunction outcomes, particularly for the kidneys, as shown in the study by Yunos *et al*[43].

The proper amount of fluid for acute care resuscitation is another critical component of judicious resuscitation. A recently published cohort of septic patients from

Table 2 Potential complications of fluids and electrolytes overload

Organ system	Complication	Main modifiable risk factor	Pathophysiological mechanism
Central nervous system	Delirium	Hypernatremia	Excessive sodium load Kidneys inability to excrete excess sodium load
Renal/ metabolic	Worse recovery of renal function	Cumulative fluid balance/higher CVP	Renal edema, reduced perfusion pressure
	Worsening acute kidney injury	Unbalanced solutions	Chloride-induced renal vasoconstriction
	Worsening acidemia	Unbalanced solutions	Solution SID relative to plasma SID Kidneys inability to excrete excess chloride load
Respiratory	Impaired gas exchange Altered pulmonar and chest wall mechanics Increased work of breathing	Cumulative fluid balance/higher CVP/higher EVLW	Lung edema
Gastrointestinal	Ileum	Cumulative fluid balance	Bowel edema
	Hepatic congestion	Higher CVP	Hepatic congestion
	Increased intra-abdominal pressure (may induce by itself more organ dysfunctions)	Cumulative fluid balance	Visceral edema (bowel, renal, *etc.*), ascites
Hemostasis	Increased bleeding	Unbalanced solutions	Acidemia secondary to chloride load
Wound healing	Impaired wound healing	Cumulative fluid balance	Local edema
Hemodynamics	Worse microcirculatory blood flow	Higher CVP	Reduced perfusion pressure

CVP: Central venous pressure; SID: Strong ion difference; EVLW: Extravascular lung water.

Australia and New Zealand, which yielded impressive mortality outcomes, demonstrated that patients received approximately 3 L of fluids during the first hours of resuscitation[99]. Furthermore, in the recently published PROCESS trial, in patients who received more fluids (approximately 1 L more) in one of the three study arms, there were more cases of new onset renal failure than the usual care group[7]. With this in mind, particularly in cases of septic shock, after an initial fluid challenge of 20-30 mL/kg, we favor an earlier use of vasopressors and the avoidance of repeated fluid expansion in patients with vasodilatatory states, particularly in those with adequate perfusion parameters who are no longer fluid-responsive[100].

Another issue to be considered is to avoid the "kidney paradox". In oliguric patients, one should strongly consider avoiding repeated volume expansions after the first hours of resuscitation because this will most likely lead to higher filling pressures and more fluid accumulation despite a possibly increased urine output. In patients who further develop anuria, fluid challenges might be even more deleterious.

Acid-base monitoring during resuscitation

During the resuscitation phase of critical illness, in addition to usual hemodynamic monitoring, it is important to monitor potentially deleterious effects of fluids and electrolytes on the acid-base status. As previously discussed, both fluid composition and quantity can influence acid-base status[98]. Through acid-base monitoring, one can identify at an earlier stage metabolic complications occurring during resuscitation. If possible, one should attempt to quantify which component of metabolic acidosis is worse during acute resuscitation because they carry different prognostic significances[16].

Active de-resuscitation

After a judicious resuscitation strategy, active de-resuscitation should be considered to avoid the deleterious effects of continuous fluid accumulation when the patient does not passively excrete the excess amount of water and electrolytes. This can be achieved both with diuretics, which have been shown to be safe in the context of AKI, or with an earlier indication of hemodialysis, as defended by some authors, when the former cannot control fluid overload[101]. To achieve a safe withdrawal of fluids and electrolytes, some factors must be considered:

Fluid removal rate: either with dialysis or diuretics, the fluid removal rate should be titrated to the patient hemodynamic status to avoid underfilling during this phase[102]. If tolerated, there will likely be no deleterious effects of fluid withdrawal, even in the presence of vasopressors or inotropic drugs.

Intermittent *vs* continuous infusion of diuretics: in critically ill patients, the continuous infusion of diuretics was not extensively studied. Better evidence from other clinical situations has not demonstrated any consistent advantage of one way of administering diuretics over another, except for higher doses of diuretics in intermittent therapy for the same fluid balance achievement compared to continuous infusion diuretic therapy[103,104]. As long as a target diuresis is achieved, there will likely be no differences among these treatments.

Association of albumin to furosemide: although albumin was not associated with better outcomes in patients with septic shock[105] or for fluid resuscitation in general ICU patients[106], in patients with ARDS, a better hemodynamic tolerance during fluid withdrawal was achieved with the combination of albumin and furosemide[107] and could be a useful adjunct during the active de-resuscitation phase.

Monitoring and treating metabolic complications: the use of diuretics is associated with more metabolic disturbances, including hypernatremia, hypokalemia and metabolic alkalosis[11]. To counteract these disturbances,

we favor the use of acetazolamide if the patient develops metabolic alkalosis, thiazide diuretics and increases in free water reposition if hypernatremia ensues and the aggressive reposition of electrolytes to avoid extreme electrolyte disturbances. We refer the reader to the trial by Mekontso Dessap *et al*[94], which proposed a method to do this safely with a combination of diuretics.

Consideration for an earlier indication of renal replacement therapy in oliguria should be part of an active de-resuscitation strategy because some patients will develop stage Ⅲ AKI[108], will be unresponsive to diuretics and, during this process, will accumulate fluids progressively, which has been consistently shown to be associated with worse outcomes in this specific population[88,89,96].

Although pulmonary edema is a common trigger for fluid withdrawal, it is a late and potentially deadly consequence of fluid overload. Hence, during this phase of active fluid withdrawal, some very simple monitoring strategies can be used.

Central venous pressure, although recently receiving discredit as a guide to fluid loading[109], was used in the largest randomized controlled trial on conservative fluid strategies[11]. In this regard, although there are many physiological states that can influence its isolated value, higher CVP values have been associated with worse outcomes in many conditions, including septic shock[79], likely not only because of fluid overload but also because of the associated significant effect of heart dysfunction on its values. Therefore, it can be an adjunct for active de-resuscitation strategies, and a goal towards lower CVP values (*e.g.*, down to < 4 mmHg in adequately perfused patients without vasopressors) is a simple way to monitor this strategy.

An even simpler solution is to focus on fluid balance. Although daily weights would potentially be better, these values are also prone to error when measuring patients on ICU beds[110], and we believe that fluid balance, although imperfect, appears to be a simple bedside target of active de-resuscitation. Therefore, reaching even to negative fluid balances during the first days of critical illness onset and, as soon as possible, aiming at more negative fluid balances until reaching a cumulative fluid balance of approximately zero during the ICU stay appears to be a good approach.

In addition to active fluid withdrawal, one should avoid the unnecessary entrance of fluids and electrolytes in the form of electrolyte reposition, drugs dilution and as caloric intake on a daily basis because as we have previously discussed, these are important sources of sodium, chloride and water. In this regard, we favor using hypertonic glucose solutions if deemed necessary for minimum caloric intake (when the enteral route is not available for feeding) and the avoidance of maintenance fluids when there are no clinically relevant fluid losses (*e.g.*, ileostomy). Finally, electrolytes, antimicrobials and other drugs should be diluted in the minimum necessary amount of fluids and preferentially in 5% dextrose in water[20].

With all this evidence combined, it appears that a judicious initial fluid resuscitation followed by a conservative fluid management approach will lead to better outcomes in patients in many different shock states, including in patients with sepsis and patients with other causes of non-septic SIRS. As we have discussed, hypernatremia is associated with worse outcomes, along with hyperchloremic acidosis in some scenarios and also progressive cumulative fluid balances. Many of the studies in this regard examined these issues separately, whereas these may be different aspects of the same problem: that of fluid and electrolyte overload.

CONCLUSION

Although there are no adequate prospective experimentally designed studies that have shown that fluids are essential in the treatment of critically ill patients, fluids are used liberally among ICU patients, and fluid accumulation is very common throughout the course of a patient's ICU stay. In this review, we provided evidence of the potentially deleterious effects of fluids and electrolytes on many organ systems, how to monitor for these complications and how to manage this increasingly recognized clinical problem. Currently, we favor a more conservative approach regarding fluid management strategies in general ICU patients, although a randomized controlled trial addressing this issue is mandatory to shed light on this discussion, along with deeper mechanistic studies to understand the relative contributions of each component of fluid therapy.

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MINIREVIEWS

Tumor lysis syndrome: A clinical review

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Abstract

Tumor lysis syndrome is an oncometabolic emergency resulting from rapid cell death. Tumor lysis syndrome can occur as a consequence of tumor targeted therapy or spontaneously. Clinicians should stratify every hospitalized cancer patient and especially those receiving chemotherapy for the risk of tumor lysis syndrome. Several aspects of prevention include adequate hydration, use of uric acid lowering therapies, use of phosphate binders and minimization of potassium intake. Patients at high risk for the development of tumor lysis syndrome should be monitored in the intensive care unit. Established tumor lysis syndrome should be treated in the intensive care unit by aggressive hydration, possible use of loop diuretics, possible use of phosphate binders, use of uric acid lowering agents and dialysis in refractory cases.

Key words: Cancer; Arrhythmia; Seizure disorder; Tumor lysis syndrome; Acute kidney injury

Core tip: Tumor lysis syndrome (TLS) is characterized by a massive tumor cell death leading to the development of metabolic derangements and target organ dysfunction. TLS can occur as a result of cancer treatment or spontaneously. Blood cancers constitute the vast majority of TLS cases because of the sensitivity to therapy and rapid division rates. Solid cancers comprise the minority of cases and are usually advanced if complicated by TLS. Prophylaxis is the mainstay of management and should be routinely implemented in high and intermediate risk patients. Management of established TLS includes intravenous hydration, urate lowering therapies, management of hyperkalemia and hemodialysis in refractory cases.

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INTRODUCTION

Cancer disorders constitute a diverse group of pathologies in which abnormal metabolism and life cycle lead to the profound derangement of a host's metabolism. These cancers differ in their cellular origin, pathogenesis, clinical presentation, and management. Furthermore, cancer has been found by the Centers for Disease Control and Prevention to be the second leading cause of death among United States residents in 2011[1]. Thus, because of the high prevalence of malignant neoplasms,

Table 1 Cairo-Bishop definition of laboratory tumor lysis syndrome for adults

Variable	Value	Change from baseline value
Uric acid	⩾ 8 mg/dL (476 mmol/L)	25% increase
Potassium	⩾ 6.0 mEq/L (or 6 mmol/L)	25% increase
Phosphorus	⩾ 4.5 mg/dL (1.45 mmol/L) for adults and ⩾ 6.5 mg/dL (2.1 mmol/L) for children	25% increase
Calcium	⩽ 7 mg/dL (1.75 mmol/L)	25% decrease

Adapted from Cairo *et al*[2].

Table 2 Cairo-Bishop grading of clinical tumor lysis syndrome for adults

Variable	Grade 0	Grade Ⅰ	Grade Ⅱ	Grade Ⅲ	Grade Ⅳ	Grade Ⅴ
Creatinine	None	1.5 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 1.5-3.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 3.0-6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	> 6.0 times ULN. Rise in creatinine is not attributable to chemotherapeutic agent(s)	Death
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated. Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Symptomatic and incompletely controlled medically or controlled with device (*e.g.*, defibrillator). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Life-threatening (*e.g.*, arrhythmia associated with HF, hypotension, syncope, shock). Cardiac arrhythmias not attributable to chemotherapeutic agent(s)	Death
Seizures	None	-	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (*e.g.*, status epilepticus, intractable epilepsy)	Death

Adapted from Cairo *et al*[2]. ADL: Activities of daily living; HF: Heart failure; ULN: Upper limits of normal.

it is essential that clinicians are aware of the major complications of cancer itself and its management. Furthermore, it is likely that physicians will manage a greater number of cancer patients in future in the future, due to the improved survival rates of patients with cancer, ageing and growing population.

Tumor lysis syndrome (TLS) is a major oncometabolic entity requiring emergent recognition and management. TLS comprises a clinicolaboratory derangement of cellular metabolism, which can lead to severe renal impairment, cardiac arrhythmias, seizures, and death[2]. Cellular death mediated by treatment targeted at cancer (chemotherapy or another pharmacological antitumor intervention, embolization of tumor or radiation therapy) or spontaneous cellular death in rapidly dividing cancer cells (which is known as spontaneous TLS) leads to an efflux of cellular material rich in potassium, phosphorus, and uric acid into the bloodstream. However, serum calcium levels typically decrease in patients with TLS because of its binding to excess phosphorus. These key metabolic derangements mediate the acute impairment of renal function, cardiac arrhythmogenicity, central nervous system toxicity, and ultimately death.

The most widely used diagnostic criteria are those proposed by Cairo *et al*[2] in 2004. Based on this classification, TLS can be defined as laboratory TLS, when TLS is clinically silent and only detected through laboratory work up, and clinical TLS, when laboratory TLS is complicated by the clinical manifestations mentioned above. The diagnostic criteria proposed by Cairo *et al*[2] are presented in Tables 1 and 2. It is necessary to note that laboratory TLS is defined as the presence of at least two or more biochemical variables within the 3 d before chemotherapy or 7 d after chemotherapy in the face of adequate hydration and use of uric acid lowering agent. Clinical TLS is defined as the presence of at least one clinical criterion that is not believed to be attributable to the chemotherapy agent[2]. However, our group has recently mentioned that this definition is imperfect since radiation therapy may lead to TLS as well, and TLS can occur spontaneously in rapidly proliferating and bulky malignancies[3,4].

This manuscript summarizes the current state knowledge on TLS for clinicians involved in the care of critically ill patients: first, we briefly discuss the relevant pathobiology of TLS; second, we review and discuss which patients with cancer should be deemed to be at high risk; third, we go through the clinical presentation and diagnosis of TLS, including making an appropriate differential diagnosis; fourth, the information on TLS prevention is discussed; and finally, the treatment options for full blown TLS are provided.

SEARCH STRATEGY

We searched PubMed/Medline, Scopus, Embase, and the Web of Science for articles focused on TLS from 1950 to June 2014. The search terms were: tumor lysis syndrome, tumor lysis syndrome and renal impairment, tumor lysis syndrome and cardiac arrhythmias, tumor lysis syndrome and cardiac toxicity, tumor lysis syndrome and central nervous disease, and tumor lysis syndrome and seizures, as well as combinations of these. The reference lists of the identified articles were further screened for potentially relevant articles that could have been overlooked by an electronic search. The search methodology was adapted from the scientific search guidelines published in 2011[5].

PATHOPHYSIOLOGY OF TLS

The basic understanding of the pathogenesis of TLS lies in the fact that cells and cancer cells in particular are rich in potassium, phosphorus, and uric acid. As mentioned previously, TLS can be either spontaneous when cancer cells die without the preceding chemotherapy, embolization, or radiation therapy, or secondary to cancer targeted treatment. In either case, the release of the above mentioned intracellular substances mediates the pathobiology of TLS and its complications.

Hyperkalemia is one of the key laboratory manifestations of TLS. Increased serum concentrations of potassium can adversely affect the skeletal muscle and cardiac myocardium[6,7]. Indeed, hyperkalemia can mediate severe skeletal muscle dysfunction and weakness and induce various electrocardiogram (ECG) abnormalities including peaked narrow T waves, prolongation of the PR interval, prolongation of the QRS interval, as well as sine wave morphology[8]. Ultimately, the cardiac effects of excess potassium can lead to ventricular tachyarrhythmias and death.

Uric acid is a byproduct of the purine nucleotides adenine and guanine, which constitute the backbone of nucleic acids[9]. Put simply, purines are metabolized initially to hypoxanthine and xanthine *via* enzyme xanthine oxidase to uric acid, which is a final byproduct in humans. However, some mammals have an additional enzyme called urate oxidase that converts uric acid to the much more water soluble allantoin, which is easily removed by renal system. Given a high cellular turnover in cancer for whatever reason, huge amounts of nucleic acids, purines, and eventually uric acid are released and formed. Uric acid can crystalize and obstruct the flow in the renal tubules, leading to acute kidney injury[2-4,10]. However, there are other mechanisms for uric acid mediated kidney impairment such as endothelial dysfunction and local ischemia, proinflammatory and proxidative states, and impairment of local renal repair mechanisms[10,11]. It is important to note that calcium phosphate crystals facilitate the deposition of uric acid in renal tissue[2].

It is relevant to mention that in the contemporary era most individuals at risk of TLS (at least in developed countries) or with a full-blown TLS are treated with hypouricemic agents, which minimize the impact of uric acid on the occurrence of acute kidney injury. An increase in serum phosphorus from cellular death can mediate acute kidney injury *via* similar mechanisms. When in excess, phosphorus tends to bind to calcium, forming the so-called calcium phosphorus product or calcium phosphate[2-4]. This product can be deposited in kidneys, mediating acute kidney injury, as well as in cardiac tissue, leading to arrhythmia. Furthermore, a secondary decrease in free calcium concentration (due to phosphorus binding) is manifested by indications of central nervous toxicity such as seizures and psychiatric complaints, prolongation of the QT interval on ECG, and muscle tetany[12]. It is interesting to observe that patients with spontaneous TLS may have lower rates of hyperphosphatemia due to phosphate uptake into rapidly dividing tumor cells[3,4]. An increase in lactate dehydrogenase (LDH) is typically seen in patients with TLS, probably because of anaerobic glucose metabolism. However, the elevation of LDH is not included in the laboratory definition of LDH and it is important to note that LDH is a very sensitive but quite nonspecific marker for TLS.

In conclusion, it is important to note that preexistent renal disease and the characteristics of certain patients increase the risk of full-blown clinical TLS. These factors will be discussed in more detail in the next section.

POPULATION AT RISK

When assessing the risk of TLS in a particular patient, it is essential to bear in mind both the general and tumor-related predictors of risk.

An older age is associated with a reduction in the glomerular filtration rate[13]. It is likely that advanced age predisposes to TLS *via* a decrease in the renal reserve, and may complicate volume replacement therapy due to higher rates of cardiac dysfunction. However, it is important to keep in mind that the impact of age on the occurrence of TLS has not been specifically studied. Other general patient characteristics such as volume depletion should be assessed and corrected if present. Patients afflicted with cancer often have decreased oral intake due to the decrease in appetite and nausea. Furthermore, cancer patients often suffer from vomiting and diarrhea, which can significantly diminish their volume status. Another important aspect which we routinely assess in our patients is the use of medications capable of detrimentally affecting renal function such as non-steroidal anti-inflammatory drugs, inhibitors of the angiotensin converting enzyme, and angiotensin receptor blockers, especially in patients with decreased volume status[4]. The medication list of every patient should be reviewed and medications with a nephrotoxic renal profile should be discontinued wherever possible. It is important to consider that baseline kidney disease is a well-established risk factor for TLS[4,14]. In addition,

a baseline increase in serum uric acid, phosphorus, potassium, and LDH also portends a greater risk of TLS[4]. Other general comorbid conditions such as cardiac disease, diabetes mellitus, and renal disease should be considered prior to hydration since patients with these medical problems might easily develop symptomatic volume overload.

Another aspect of the risk stratification which we use is the type and burden of malignancy. We agree with the clinical risk stratification proposed by Cairo *et al*[15] who stratified cancers into three risk groups: a high risk group, an intermediate risk group, and a low risk group. The high risk group of cancers include advanced Burkitt's lymphoma/leukemia or early stage disease with elevated baseline LDH, acute lymphocytic leukemia (ALL) with white blood cell (WBC) count $\geqslant$ 100000 or less if the baseline elevation of LDH is twice the upper limit of normal (ULN), acute myeloid leukemia (AML) with WBC count $\geqslant$ 100000, diffuse large B-cell lymphoma with an elevated baseline LDH of twice ULN, and bulky disease. Intermediate risk malignancies include AML with a WBC between 25000 and 100000, ALL with WBC < 100000 and an LDH of less than twice ULN, early stage Burkitt lymphoma/leukemia with an LDH of less than twice ULN, and diffuse large B-cell lymphoma with a baseline increase in LDH of twice ULN but non-bulky disease. Low risk diseases include indolent lymphomas, chronic lymphocytic leukemia, chronic myeloid leukemia in the chronic phase, AML with WBC count < 25000 and an LDH elevated to less than twice ULN, multiple myeloma, and solid cancers. Therefore, during our risk stratification we paid extra attention to patients with Burkitt's lymphoma/leukemia, ALL, AML, and diffuse large B cell lymphoma. Furthermore, we have recently reported that TLS in patients with solid malignancies may be higher than previously thought, and certain cancers with a sensitivity to therapy may be at higher risk for TLS, such as small cell lung cancer[4].

In summary, it is recommended that both general and cancer-related factors are included in the risk assessment of every patient. Certain patient factors such advanced age and the presence of preexistent renal and cardiac diseases warrant a closer follow up during preventive hydration.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation and symptomatology is directly linked to the biochemical derangements observed in this disorder. As discussed earlier, the biochemical evidence of TLS includes hypocalcemia, hyperkalemia, hyperphosphatemia, and hyperuricemia[2]. Therefore, the presentation of these biochemical disorders is typically represented by a clinical constellation of symptoms. For example, patients with TLS who have hypocalcemia may present with such symptoms as nausea, vomiting, muscular hyperactivation such as spasms and tetany, seizures, prolongation of QT interval on the ECG, cardiac dysrhythmias, and alterations of mental status[12]. Hyperphosphatemia may actually be a key mediator of acute kidney impairment as well as cardiac rhythm disturbances. Patients with hyperkalemia, if symptomatic, present with generalized fatigue, ECG abnormalities[8], and serious cardiac arrhythmias including cardiac arrest. Elevations of uric acid can lead to acute renal insult manifested as an increase in serum creatinine and decrease in urine output.

Therefore, it is essential to be highly suspicious if any of the above symptoms arise in patients with cancer, especially those with tumors in a high risk group In rare instances (at least in developed countries), TLS may present prior to the diagnosis of cancer. Nevertheless, a clinician should differentiate TLS from other causes of acute kidney injury such as sepsis, obstructive renal disease, medication toxicities (including those of chemotherapeutic agents), use of contrast dye for imaging studies, and rhabdomyolysis, as well as other rarer conditions such as vasculitis and primary glomerulopathies in appropriate clinical scenarios[16]. Thus, a thorough clinical history is of paramount importance when dealing with a cancer patient who has presented with an acute decline in kidney function. The minimum amount of testing should include urinalysis and urine microscopy, comprehensive metabolic panel, uric acid, LDH, complete blood count, and renal ultrasound. The Cairo-Bishop criteria for the diagnosis of laboratory and clinical TLS are presented in Tables 1 and 2, respectively.

In conclusion, the clinical presentation of TLS is based on the constellation of individual metabolic derangements in a particular patient.

PREVENTION

It is essential to remember that the prevention of disease is always more cost-effective than the treatment of an established disease. Therefore, it is important to address and target any underlying kidney disease and possible hypovolemia before the start of cancer targeted therapies. Patients' management should be focused on the basis of the type of cancer and certain biochemical parameters such as LDH, phosphorus, uric acid, and potassium and serum creatinine, as discussed above. Subjects at intermediate and high risk of TLS should be monitored in a hospital setting and possibly in an intensive care unit (especially individuals at high risk of TLS). Potassium and phosphorus should be eliminated from the diet and intravenous (IV) fluids.

Several features are the mainstay of treatment for the prevention of TLS in patients undergoing active therapy. First, all patients at intermediate and high risk should be actively hydrated with IV fluids. Coiffier *et al*[17] recommended patients should be hydrated to

maintain urine output of at least 2 mL/kg per hour to minimize the risk of acute kidney injury. The choice of the fluid varies and some recommend the use of dextrose in one quarter normal saline as the initial fluid of choice[17]. However, normal saline or lactated Ringer's solution are alternative choices, especially if the patient has other conditions such as dehydration, hypovolemia, and hyponatremia (it is essential to remember that lactated Ringer contains potassium and normal saline is associated with hyperchloremic metabolic acidosis)[17]. Also, it is prudent to limit the calcium and potassium content of the IV fluids in such patients. Nevertheless, it is essential to note that some patients with cancer have underlying cardiorenal disease, which puts them at high risk of fluid overload and pulmonary edema. Such patients should be followed in closely monitored settings and there should be a low threshold for initiating loop diuretics if signs of fluid overload appear (shortness of breath, crackles on physical examination, desaturation, *etc.*). Loop diuretics are preferably used in clinical practice because of their potent diuretic properties as well as their hypokalemic effect, which can be of benefit in patients at risk of TLS. However, to the best of our knowledge there are no published scientific studies assessing the role of diuretics in the treatment of TLS.

Second, individuals at intermediate risk of TLS should be started on allopurinol at least 24 to 48 h prior to chemotherapy or radiation therapy to reduce the risk of uric acid nephropathy[17]. Patients who do not tolerate oral medication such as those with severe nausea, vomiting, or altered function of the gastrointestinal tract can be given allopurinol IV. The recommended dose of allopurinol is up to 800 mg a day orally or 100 mg per square meter, and up to 600 mg a day for IV formulation[17]. Allopurinol works by blocking the xanthine oxidase enzyme. In rare instances, allopurinol can lead to hypersensitivity reactions manifested as skin rashes, liver transaminitis, and acute kidney injury in the form of acute interstitial nephritis[18]. Another important aspect of allopurinol use is the fact that the dose should be reduced in the event of chronic kidney disease[19]. In such patients (intermediate risk, underlying renal disease, and/or history of allopurinol intolerance) the use of febuxostat may be considered, which is a relatively new xanthine oxidase inhibitor. Febuxostat does not require dose modification in patients with renal disease and does not seem to have allergy cross-reactivity with allopurinol[20]. However, febuxostat has not been specifically studied for the population at risk of TLS or in patients with established TLS. Therefore, lack of specific data on febuxostat in patients with TLS should be mentioned during the management plan discussion with the patient and significant others, whenever appropriate.

Nevertheless, despite the availability of allopurinol, there is a significant number of patients who still develop significant kidney damage due to uric acid toxicity. As discussed above, some mammals (but not humans) possess urate oxidase or uricase enzyme, which is capable of converting xanthine into allantoin. This is an important step since allantoin is easily excreted substance. A medication mimicking urate oxidase named rasburicase was approved by Food and Drug Association in 2012 for use in subjects at risk of TLS[21]. Coiffier *et al*[22] enrolled 100 patients with aggressive non-Hodgkin lymphoma to investigate whether the use of rasburicase is a safe and effective method of preventing TLS in a high risk group. Indeed, this investigation showed that rasburicase led to the normalization of uric acid within four hours of its administration, and it was well tolerated. Rasburicase provides much better control of uric acid than allopurinol (87% compared to 66%, respectively) as demonstrated in a study by Cortes *et al*[23]. However, on the development of clinical TLS, no change between rasburicase and allopurinol was demonstrated[23]. Similarly, in a recent meta-analysis published by Lopez-Olivo *et al*[24], rasburicase was found to be effective in reducing uric acid levels, but it is unclear whether it led to better outcomes for clinical TLS.

Rasburicase should be used in individuals who are at high risk of developing TLS and in patients whose baseline uric acid is higher than 7.5 mg/dL (446 mmol/L)[17]. The dosage of rasburicase is based on the underlying risk of TLS. Thus, in patients at high risk the recommended dose is 0.2 mg/kg daily and in patients with intermediate risk and whose baseline uric acid level is $\leqslant$ 7.5 mg/dL the suggested dose of rasburicase is 0.15 mg/kg daily[17]. However, it is essential to mention that several small studies, most of which are retrospective in nature, have demonstrated that a single dose of rasburicase was effective[25-27]. The dose of the rasburicase administered varies, but 6 mg of rasburicase has been shown to be effective[27] and has provided uric acid control for 48 h after administration[26]. Given the high cost of rasburicase, this may decrease the cost of treatment. This approach should be reserved for subjects at intermediate risk of TLS and allopurinol should usually be started simultaneously with rasburicase, unless contraindicated. Purine metabolism and the sites of action of allopurinol, febuxostat, and rasburicase are presented in Figure 1.

Despite being a safe agent, rasburicase should not be used in pregnant or lactating patients due to limited data on safety (pregnancy category C drug) and excretion into breast milk. Furthermore, it should not be used on patients with glucose 6 phosphate dehydrogenase deficiency due to the high risk of hemolysis and methemoglobinemia[24,28].

Urine alkalization is another way of managing patients at risk of TLS. The rationale for this approach lies in the fact that an alkaline urine pH promotes uric acid solubility and its removal[29]. Typically, a carbonic anhydrase inhibitor acetazolamide or sodium bicarbonate are used to reach a urine pH of at least 6.5. However, this approach has not been shown to be superior to the administration of normal saline alone[29]. Furthermore, as

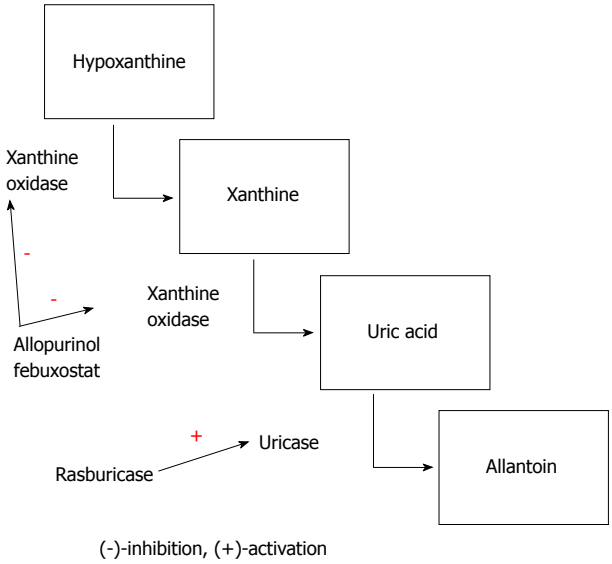

Figure 1 Purine metabolism and sites of action of allopurinol, febuxostat and rasburicase.

mentioned above, in the current era of the widespread use of uric acid lowering agents for TLS prevention, the role of calcium phosphate toxicity increases as a mediator of kidney damage in patients with TLS. In contrast to uric acid crystal deposition in acidic pH, the crystals of calcium phosphate more readily precipitate in alkaline pH, making this approach to alkalization potentially dangerous[30]. Also, an alkaline pH promotes calcium binding to albumin, which can be very dangerous in patients with TLS who tend to have lower calcium levels at baseline, leading to neuromuscular and cardiac toxicity. Therefore, the current role of urine alkalization is of limited value and not recommended for routine use in patients at risk of TLS. It is also important to note that the use of phosphate binders in the prevention of TLS was not specifically studied in the literature. The decision to start phosphate binders should be decided on a case by case basis and always discussed with the patient prior to its initiation. The interested reader is referred to a recently published review on phosphate binders[31].

Certain parameters should be monitored in individuals at high risk for TLS such as uric acid, phosphorus, potassium, and LDH 4 h after the initiation of chemotherapy or radiation therapy. The discontinuation of prophylaxis should be considered after the completion of cancer-related treatment when serum markers (uric acid, potassium, phosphorus, calcium, LDH, and creatinine) are within normal limits for at least two consecutive measurements several hours apart. It is reasonable to monitor patients for at least 24 h after discontinuation of TLS prophylaxis to ensure no development of TLS.

PRINCIPLES OF MANAGEMENT OF ESTABLISHED TLS

The treatment of fully blown TLS is based on the same principles as its prevention. Patients with laboratory TLS and cardiorenal comorbid conditions, as well as patients with clinical TLS, should be admitted to an intensive care unit (ICU). Patients with TLS, unless anuric, should receive aggressive IV fluids with the goal of a urine output of at least 2 mL/kg per hour, as described above. Individuals deemed to be at increased risk of fluid overload, such as patients with cardiac and baseline renal disease, we consider the administration of IV loop diuretics such as furosemide to decrease the risk of pulmonary edema and augment urine output. Administration of loop diuretics may also improve control of hyperkalemia in patients with TLS. However, the role of loop diuretics is not based on solid data; thus, it should be approached on an individual basis.

As described above, the clinical spectrum of TLS includes laboratory abnormalities such as hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia, which present clinically as cardiac arrhythmias, tetany, seizures, and acute kidney injury. We will briefly discuss the management of each laboratory abnormality one at a time. Hyperkalemia is a dangerous abnormality which may lead to muscle fatigue and cardiac toxicity and arrest[8,32]. The reader is referred to a detailed review on the management of hyperkalemia[32]. However, the management of hyperkalemia should always start from a 12-lead ECG. As discussed above, hyperkalemia may present with peaked narrow-based T waves, prolongation of the PR interval, loss of P waves, prolongation of the QRS interval, and the appearance of so called sine waves[8]. Certain therapies are available for the management of hyperkalemia such as IV calcium products, IV insulin +/- dextrose, inhalational beta 2 agonists, IV sodium bicarbonate, cation exchange resins, and hemodialysis[32]. Calcium in the form of gluconate or chloride should be administered IV (a typical dose is either 1 g of calcium gluconate and 500 mg to 1 g of calcium chloride) with certain ECG changes such loss of P waves and prolongation of the QRS interval[32]. It is important to note that calcium chloride contains more calcium than calcium gluconate and should preferably be administered *via* a central line. IV calcium works by blocking the potassium effect on the cardiac cell membrane. However, it is essential to mention that in subjects with TLS calcium should be administered cautiously and ideally only in patients with severe ECG changes, malignant cardiac dysrhythmias, and cardiac arrest, and also in patients with severe neurological dysfunction such as seizures due to the possibility of forming a calcium phosphate product, which may lead to acute kidney injury[33]. Furthermore, calcium products do not lower potassium levels and they must be used in conjunction with modalities which lower the serum concentration of potassium.

Albuterol, the most commonly used beta 2 agonist, which works by driving potassium into the cells, should be administered by a dose of 10 mg to 20 mg diluted in 4 mL of normal saline and nebulized during 10

min with a peak effect 90 min after administration[32]. Generally, albuterol should be combined with IV insulin, with or without dextrose. Usually, 10 units of regular insulin should be administered, and if the serum glucose is < 250 mg/dL 50 mL of 50% dextrose should be administered [32]. If the serum glucose is > 250, the administration of 50% dextrose is not necessary. IV insulin drives potassium into the cells in a similar way to albuterol and starts working 10 min after administration, peaks in 1 h, and lasts up to 6 h[32]. A drop of potassium should be expected of up to 1.5 mmol/L after administration of both insulin and albuterol combined[32]. The third option for reducing potassium is the administration of IV sodium bicarbonate in a dose of 50 mEq, which works by pushing potassium into the cells in exchange for hydrogen ions[32]. However, it is necessary to remember that IV sodium bicarbonate is a weak agent with the best possible effect observed in patients with hyperkalemia and metabolic acidosis[32]. Sodium bicarbonate should not be used as a sole agent in reducing elevated potassium. Furthermore, there are at least two factors that should be considered when using sodium bicarbonate in patients with TLS: first, alkalization may further decrease the free calcium concentration due to the greater binding of calcium to albumin, which might further decrease the physiologically active calcium; and second, urine alkalization might facilitate the deposition of calcium phosphate crystals in the kidney. Therefore, the general use of sodium bicarbonate in patients with hyperkalemia in the TLS setting is not recommended.

Another option for reducing potassium is the use of cation exchange resins such as sodium polystyrene sulfonate[32]. Sodium polystyrene sulfonate works in the intestinal tract by binding potassium and exchanging it with sodium[32]. The clinical effect of cation exchange resins typically starts within 2 h of administration and lasts up to 6 to 8 h. Sodium polystyrene sulfonate can be administered orally or as enema. The oral dose ranges from 15 to 45 g and can be repeated every 6 h as needed, while the enema is administered as 50 g of sodium polystyrene sulfonate mixed with water as a tap water enema. It is essential to note that sodium polystyrene sulfonate should not be used in patients with intestinal ileus or obstruction, and in post-operative patients due to higher risk of intestinal ischemia and necrosis[32]. Also, whenever possible, patients with TLS should receive aggressive IV hydration (as with patients without end-stage renal disease who produce urine), and if needed with loop diuretics to minimize the chances of fluid overload as this will also promote the normalization of serum potassium. However, patients with refractory hyperkalemia should be strongly considered for renal replacement therapy, typically hemodialysis. In emergent cases where there is no permanent dialysis access, a short term dialysis catheter should be inserted.

One aspect of the management of elevated phosphorus in patients with TLS includes the restriction in phosphorus intake, both in diet and IV fluids. It is necessary to mention that phosphate binders may be used in patients with hyperphosphatemia in the TLS setting. Phosphate binders include calcium containing medications such as calcium acetate and calcium carbonate, as well as non-calcium phosphate binders such as sevelamer and lanthanum[31]. Phosphate binders should be taken with each meal and work by reducing the intestinal absorption of phosphorus[31]. Calcium containing phosphate binders should theoretically be the first choice given the frequent presence of hypocalcemia in patients with TLS. However, there are no published scientific studies investigating the role of phosphate binders in the TLS setting. Hemodialysis or renal replacement therapy should be considered in patients with refractory hyperphosphatemia, in patients with symptomatic hypocalcemia, and with an elevated calcium phosphorus product of at least 70 mg^2/dL^2. The calcium phosphorus produced is calculated simply by multiplying the serum calcium and the phosphorus concentration. As discussed above, patients with TLS who have hypocalcemia should not be generally treated with calcium supplementation, given the higher risk of calcium phosphate crystallization and organ injury. However, calcium should be administered in the case of malignant cardiac arrhythmia (such as ventricular tachycardia or fibrillation), cardiac arrest, and seizure disorder. In the cardiac arrest setting, it is important to follow the advanced cardiac life support (ACLS) guidelines for its management and to exclude other possible causes of cardiac arrest such as hyperkalemia (common in TLS), hypokalemia, hypovolemia, acidosis (common in TLS, and which may be an indication for renal replacement therapy), hypothermia, tension pneumothorax, cardiac tamponade, thrombosis of the coronary and/or pulmonary circulation, as well as toxin exposure[34]. In the same way, the approach to seizure in the TLS setting should include exclusion of hypoglycemia (and corrected if present), other metabolic abnormalities (hypo- or hypernatremia, hypomagnesemia), brain vascular abnormalities (hemorrhagic and ischemic strokes, subarachnoid hemorrhage, *etc.*), brain tumors or metastatic disease, toxin exposure (such as amphetamines, cocaine, tricyclic antidepressants, *etc.*), alcohol withdrawal, benzodiazepine withdrawal, brain infection, and others[35].

Briefly, elevated levels of uric acid should be treated with rasburicase, unless contraindicated, in doses of at least 0.2 mg/kg once or twice a day. Allopurinol should only be considered if rasburicase is contraindicated or unavailable. Furthermore, it is essential to remember that allopurinol may actually increase the risk of acute kidney injury, given the increased production of xanthine, which is a poorly soluble bypass uric acid metabolite, as discussed above. In such patients early consideration of renal replacement therapy is advisable.

In conclusion, hemodialysis or other forms of renal replacement therapy should be considered in patients who are anuric, who have refractory hyperkalemia, symptomatic hypocalcemia, and with a calcium pho-

sphorus product of at least 70.

CONCLUSION

TLS is an oncometabolic emergency resulting from rapid cell death. TLS can occur as a consequence of tumor targeted therapy (chemotherapy, embolization therapy, and radiation therapy) or spontaneously. Clinicians should stratify every hospitalized cancer patient, especially those receiving chemotherapy, for the risk of TLS. Some aspects of prevention include adequate hydration, use of uric acid lowering therapies, use of phosphate binders, and the minimization of potassium intake. Patients at high risk for the development of TLS should be monitored in the ICU.

Treatment of established TLS should be taken in the ICU and includes aggressive hydration, the possible use of loop diuretics (especially for the patients prone to fluid overload), use of phosphate binders, use of uric acid lowering agents (preferably rasburicase), and dialysis in refractory cases.

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MINIREVIEWS

Designing drug regimens for special intensive care unit populations

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Abstract

This review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions. The data sources included a literature search of MEDLINE and EMBASE with reviews of reference lists of retrieved articles. Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy. Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients were extracted. Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses. Critically ill patients with changes in body size, habitus and composition require special consideration when designing medication regimens, but there is a paucity of literature on which to make drug-specific, high-level evidence-based recommendations. Based on the evidence that is available, general recommendations are provided for drug choice or dosing in special critically ill populations.

Key words: Drug dosage calculations; Pharmacokinetics; Critical care; Body composition; Obesity; Pregnancy

Core tip: Special populations of intensive care units patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

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INTRODUCTION

What are special populations?

The term "special populations" does not have a uniform definition. For example, within the National Institutes of Health (NIH) there is an Office for Special Populations within the National Institute of Mental Health (http://www.nimh.nih.gov/about/organization/od/office-for-special-populations-osp.shtml) that refers to "the mental health needs of women and minority populations". On the other hand, there is an Office of Special Populations within the National Institute on Aging (http://www.nia.nih.gov/about/offices/office-special-populations) refers to "older women, minorities, and persons with disabilities" and the National Institute on Alcohol Abuse and Alcoholism (http://www.niaaa.nih.gov/alcohol-health/special-populations-co-occurring-disorders) that refers to "Special populations are groups who face particular risks from drinking alcohol based on personal characteristics such as age or gender". The overarching theme to these definitions is that they try to focus on the special populations of particular importance to each institute. Along those lines, this review is intended to help clinicians design drug regimens for special populations of critically ill patients with extremes of body size, habitus and composition that make drug choice or dosing particularly challenging due to the lack of high-level evidence on which to make well-informed clinical decisions.

LITERATURE STUDY

Data sources

Searches of MEDLINE and EMBASE were performed. The search strategies were developed in cooperation with a medical librarian with training in the performance of systematic reviews. The initial search strategy for MEDLINE was: (((((“critical care” (MeSH Major Topic) or “critically ill patients” or “critically ill” or “critical patients” or “critical patient”) and ((((“physiological phenomena” (MeSH Terms)) or “body composition” (MeSH Terms) or “body size descriptors” or “body weight changes” or “body weight change” or “body size” or “body composition” or “physical body change” or “body change”))) and English (lang))))). For EMBASE the initial search strategy was: “intensive care”/exp or “critical care”: ab,ti or “critically ill patients”: ab,ti or “critically ill”:ab,ti or “critical ill”:ab,ti or “critical patient”:ab,ti and (“body weight”/exp or “weight change”/exp or “weight fluctuation”/exp or “weight, mass and size”/exp or “body composition”/exp or “body weight change”:ab,ti or “body weight changes”:ab,ti or “body size”:ab,ti or “body composition”:ab,ti or “physical body change”:ab,ti) and (English)/lim and [(embase)/lim or (embase classic)/lim]. Subsequent searches were performed looking at more specific special populations. For example for MEDLINE: (((“critical care” (MeSH Terms) or “critically ill patients” or “critically ill” or “critical patients” or “critical patient”) and (“body composition” (MeSH Terms) or “body size descriptors” or “body weight changes” or “body weight change” or “body size” or “body composition” or “physical body change” or “body change” or “Overweight” (Mesh) or “Obesity” (Mesh) or “overweight” or “obese” or “obesity” or “Thinness” (Mesh) or “underweight” or “Amputation Stumps” (Mesh) or “short limbs” or “missing limbs” or “Pregnant Women” (Mesh) or “Pregnancy” (Mesh) or “pregnant patients” or “pregnant women” or “Extracorporeal Membrane Oxygenation” (Mesh) or “Plasma Exchange” (Mesh))) and (“Treatment Outcome” (Mesh) or “Pharmaceutical Preparations” (Mesh) or “medication regimen” or “medication regimens” or “Patient Care Planning” (Mesh) or “Patient Care Management”(Mesh) or “Therapeutics” (Mesh) or “Drug Therapy” (Mesh) or “Drug Delivery Systems” (Mesh))).

Study selection

Abstracts of original research investigations and review papers were reviewed for their relevance to drug choice or dosing in the following special critically ill populations: patients with more severe forms of bodyweight or height, patients with amputations or missing limbs, pregnant patients, and patients undergoing extracorporeal membrane oxygenation (ECMO) or plasma exchange. Relevant papers were retrieved and evaluated, and their associated reference lists were reviewed for citations that may have been missed through the electronic search strategy.

Data extraction

Relevant original research investigations and review papers that could be used to formulate general principles for drug choice or dosing in special populations of critically ill patients.

Data synthesis and analysis

Randomized studies with clinically relevant endpoints were not available for performing quantitative analyses (Table 1). For this reason, it was decided to focus this review on general principles related to drug choice or dosing in special populations of critically ill patients, rather than trying to provide specific dosing recommendations for every medication that might be used in the intensive care units (ICU) setting[1]. Selected medications will be discussed to provide examples of dosing issues, but most of the references will list review articles and guidelines of particular relevance to the special population under consideration. Recommendations that are provided are done so under the assumption that there are no concomitant therapies or co-morbidities that would alter the parameter of interest. It is also presumed that additional expertise, such as that of a clinical pharmacist, will be sought when dealing with these difficult therapeutic decisions.

This paper will be divided into 2 parts beginning in Part 1 with an overview of body composition and how various size descriptors such as body weight that are used for drug dosing reflect changes in body

Table 1 Results of search strategies for randomized controlled trials

	Number of citations
MEDLINE	
Initial search strategy as described in text	5316
Search strategy limited to "clinical trial" and "humans"	726
Of the 725 citations, the number of RCTs with clinically relevant endpoints	0
MEDLINE	
Focused search strategy as described in text	2586
Search strategy limited to "clinical trial" and "human"	176
Of the 176 citations, the number of RCTs with clinically relevant endpoints	0
EMBASE	
Initial search strategy as described in text limited to terms indexed as major focus	1898
Search strategy limited to "human" or "clinical trial"	1431
Search strategy limited to "article"	870
Of the 871 citations, the number of RCTs with clinically relevant endpoints	0

RCT: Randomized controlled trial.

composition. The remaining sections of Part 1 deal with pharmacokinetic and therapeutic drug monitoring considerations when selecting and dosing drugs in special populations. Part 2 of this paper will highlight specific populations with changes in body size, habitus and composition that require special consideration when designing drug regimens: obese patients, patients who are underweight, amputated or missing limbs, pregnant patients, and patients undergoing ECMO or plasma exchange.

PART 1

Body composition

Body size and shape (also known as habitus) refer to physical attributes of individuals such as height, weight, and body proportions. Anthropometry is the measure of such attributes. Epidemiological studies conducted in the United States have demonstrated not only an increase in attributes such as weight but also increased variability in anthropometric indicators with implications for drug dosing[2]. Table 2 lists body composition changes that frequently occur in critically ill patients during more prolonged ICU stays.

There are a number of techniques for assessing body composition that have been used to assess tissue differences such as fat *vs* fat-free mass, but have yet to receive widespread use in the clinical arena[3]. While much of this research has focused on the nutritional aspects of body composition measurements[4], the metabolic aspects of the measurements have implications for the pharmacokinetics and pharmacodynamics of medications[5]. Approximately 25% of weight gain or loss is fat free mass[6]. Further, different types of adipose

Table 2 Changes in body composition during intensive care units stay that may affect drug disposition

Lean *vs* adipose tissue changes during more prolonged stay
Loss of lean tissue
Gain of adipose tissue
Distribution of adipose tissue (*e.g.*, subcutaneous *vs* visceral)
Gains or losses of total body water throughout stay
Distribution of retained fluid (*e.g.*, intracellular *vs* extracellular, interstitial *vs* intravascular)

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Table 3 Weight descriptors commonly used in adult patients in the clinical setting

Ideal body weight (IBW)
IBW in kg for men = 50 kg + 2.3 kg for each inch in height over 60 inches
IBW in kg for women = 45.5 kg + 2.3 kg for each inch in height over 60 inches
Adjusted body weight (ABWadj)
ABWadj in kg = IBW + 0.4 (actual weight - IBW)
Lean body weight (LBW)
LBW (men) = (1.10 × weight in kg) – {120 × [(weight in kg)/(height in cm)]^2}
LBW (women) = (1.07 × weight in kg) – {148 × [(weight in kg)/(height in cm)]^2}
Body mass index (BMI)
BMI = actual body weight (ABW) in kg divided by (height in m)^2
Body surface area (BSA) in m^2
BSA = square root [(height in cm × ABW in kg)/3600]

Various methods have been used for estimation - inclusion in this table should not be interpreted as support for a particular method. Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

tissue have differing metabolic activity. Brown adipose tissue has been investigated as an anti-obesity tissue[7].

Size descriptors

Since sophisticated technologies for assessing body composition are not typically employed in the ICU setting, most prognostic and drug dosing information based on physical attributes is derived from basic size descriptor information such as height, weight, sex or some combination of these variables (see Table 3). In particular, body mass index has been studied as an indicator of morbidity and mortality in critically ill patients. The relationship between body mass index and mortality is not linear and there appears to be a so-called obesity paradox in which obese patients as defined by a BMI range between 30 and 39.9 kg/m^2 have a lower ICU mortality compared to patients of more extreme weights[8,9].

While commonly used to categorize and stratify patients by height and weight, body mass index is used less frequently as a size descriptor for drug dosing. The choice of size descriptor for drug dosing is between actual body weight or some type of adjusted

Table 4 Estimates and measurements of size descriptors such as height and weight

Strive for consistency and standardization within and between all healthcare professionals and staff involved in size descriptor estimates and measurements. Examples include:
Method of estimates including formulas and equations used for calculations
Instruments used for measurement and how utilized (*e.g.*, clothes off or on for weight recordings)
Recording and use of units of estimates and measurements (*e.g.*, centimeters *vs* inches, pounds *vs* kilograms)
Terminology related to size descriptors (*e.g.*, ideal weight, adjusted weight)
Ensure proper communication and documentation of method (*e.g.*, patient *vs* provider, estimate *vs* measurement) used to obtain estimates and measurements of size descriptors
Have ongoing education with evaluation of all personnel involved in the determination and documentation of estimates and measurements
Have periodic evaluation of compliance by area (*e.g.*, ICU *vs* emergency department)
Ensure that age-appropriate instruments are available and have regularly scheduled calibration
Use technology (*e.g.*, automated infusion devices, dosing calculators) when available to reduce chance of medication errors

Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc. ICU: Intensive care units.

Table 5 Pharmacokinetic considerations in the critically ill patient

Data from pharmacokinetic studies are no substitute for clinical monitoring of the individual patient's response to therapy
Pharmacokinetic parameters derived from studies involving normal volunteers or less severely ill patients are not directly applicable to the critically ill patient
Average parameters for volume of distribution and clearance are larger and have much greater variability in critically ill patients compared with less severely ill patients
The duration of action of single or isolated IV doses of more lipophilic drugs used in the ICU is a function more of distribution than of clearance
The values for volume of distribution and clearance frequently change from baseline with prolonged drug administration because of factors such as accumulation or altered elimination
For drugs with active metabolites, the pharmacokinetics of the metabolites as well as the parent compound must be considered
Drug absorption is important not only with oral or enteral administration but also with intramuscular and subcutaneous injections

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body weight. Clearly, there are implications for body composition differences on medications dosed based by body weight even when weight is appropriately measured[10]. Table 4 describes some of the more important issues to consider relative to size descriptor measurements.

Pharmacokinetic considerations and therapeutic drug monitoring

Volume of distribution is the pharmacokinetic parameter of most importance for giving loading doses of drugs and it is expected that more lipophilic drugs would have more extensive distribution. Lean body weight appears to be more predictive of renal clearance than actual body weight for obese patients, but there is substantial variation in clearance in critically ill patients[11,12]. Further, critically ill patients may have augmented measured creatinine clearance values[13].

An understanding of the concept of dose proportionality is important for deciding how to apply pharmacokinetic data from patients with near-normal body size and shape to patients with more extreme forms of size, shape and body composition. Basically, dose proportionality suggests that pharmacokinetic parameters change in the same direction and same degree as changes in body weight. Tables 5 and 6 describe important considerations when evaluating pharmacokinetic and dose proportionality issues in critically ill patients.

Because drug dosing based on pharmacokinetic parameters is often insufficient to accurately predict pharmacologic effects in individual patients, therapeutic drug monitoring may help to provide additional information about the body's handling of a drug. Unfortunately, in most clinical settings, only a limited number of drugs have assays for assessing concentrations of the drugs in the body; even when such assays are available, they do not always have a clear-cut correlation with the pharmacodynamic and pharmacological properties of a particular drug (Table 7). Importantly, this discussion of pharmacokinetics and therapeutic drug monitoring is based on generalizations and should not be used to guide dosing regimens of specific drugs. Instead, drug dosing regimens in patients of more extreme body compositions should be based on evidence from a variety of sources as exemplified by the approach used in Table 8 for obese patients.

PART 2

Drug dosing in obese patients

It is not surprising that epidemiological studies continue to track the prevalence and markers (*e.g.*, body mass index) of obesity and associated health outcomes. What is surprising is the relative lack of data on drug dosing in obesity, particularly in patients with more extreme forms of obesity[14]. Currently, there is no mandate that

Table 6 Assessment of possible dose proportionality in studies with obese subjects[1]

Did the study involve a comparator group of normal weight subjects of similar demographics (*e.g.*, age, height, gender) and co-morbidities as the obese subjects?
Did the values of pharmacokinetic parameters unadjusted for bodyweight (*e.g.*, volume of distribution in mL and clearance in mL/min) increase proportionally to weight in the obese *vs* the normal-weight subjects?
Were the values of pharmacokinetic parameters adjusted for actual bodyweight (*e.g.*, volume of distribution in mL/kg and clearance in mL/min per kilogram) similar in the obese and normal-weight subjects?
Did the values of pharmacokinetic parameters adjusted for ideal bodyweight (*e.g.*, volume of distribution in mL/kg and clearance in mL/min per kilogram) increase proportionally to weight in the obese *vs* the normal-weight subjects?
Was the calculated half-life based on the pharmacokinetic parameters similar in the obese and normal-weight subjects?
When actual bodyweight was used in weight-based dosing protocols were the therapeutic effects and dose-related adverse drug events similar in the obese and normal-weight subjects?

[1]If the answers to all of these questions are yes, the data suggests that dose proportionality is present, although this does not necessarily mean that actual bodyweight should be used in weight-based dosing protocols. Reprinted with permission from Erstad[15]. Copyright © by John Wiley Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Table 7 Considerations with therapeutic drug monitoring

Blood concentration measurements are not available for the majority of drugs used in critically ill patients
So-called therapeutic ranges for therapeutic drug monitoring (TDM) are typically derived from studies involving small numbers of patients
Most therapeutic ranges are based on steady-state drug concentrations, so non–steady-state concentrations can be very difficult to interpret (and often meaningless)
Disease states that affect a drug's volume of distribution or clearance often negate the presumption of steady-state conditions necessary for proper interpretation of concentrations
The minimum and maximum concentrations used to define a therapeutic range are often quite arbitrary and not necessarily applicable to a specific patient
The free or unbound form of a drug is the active form, but the total drug concentration is most commonly measured by clinical laboratories
Total drug concentrations for a drug with high protein binding (*e.g.*, > 90%) can be difficult to interpret when protein concentrations are decreased or when other drugs or diseases displace drug
Clinical response, not a TDM measurement, should be the primary driver of dosing decisions
The administration and timing of drug doses prior to TDM measurement should be verified, not presumed, because these affect the proper interpretation of the measurement
TDM is most useful when clinical indicators are misleading or not available or when the clinical indicator is a problem that the clinician is trying to prevent (*e.g.*, aminoglycoside nephrotoxicity)
Unnecessary TDM should be avoided (*e.g.*, ordering daily measurements of drug concentrations for a drug with a long half-life) because it may lead to inappropriate changes and unnecessary TDM costs

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product labeling provide information on drug dosing in obesity, or for that matter, what weight should be used for weight-based dosing of medications. Even the word "weight" as used in most product brochures is not defined, so an assumption is usually made by clinicians that the term is referring to actual body weight. For drugs that have non-weight-based dosing regimens (*e.g.*, mg per dose rather than mg/kg per dose), the clinician make elect to use the higher end of the dosing range for drugs with a rather wide therapeutic index. The issue becomes more complicated for weight-based dosing regimens in which the choice of weight is not clear.

When dosing an obese patient on a drug that does not include specific recommendations in the product labeling, the first step should be to perform a literature search looking for relevant investigations. The clinician may find that key studies involving a drug included patients with more mild to moderate forms of obesity (BMI < 35), suggesting that weight-based dosing with the use of actual body weight is applicable. When such studies with direct applicability to a particular patient are not available, the clinician will likely have to extrapolate from the evidence that does exist; often, this evidence is limited to pharmacokinetic investigations where an assessment of dose proportionality is needed. For the majority of drugs commonly used in the ICU setting, there is little evidence to suggest the use of actual body weight for weight-based dosing regimens in more severe forms of obesity[15]. The recommendation for the use of actual body weight for maintenance dosing of vancomycin is a notable exception, not the rule, for most of these drugs. This is not totally unexpected given that many of these drugs are eliminated by the kidneys and the most accurate estimations of creatinine clearance in more extreme forms of obesity have been made using equations based on lean or another form of adjusted body weight[16]. Similarly, loading doses of drugs that primarily distribute into the intravascular compartment would likely require dosing based on a lean or adjusted body weight for weight-based dosing regimens given that blood volume does not increase

Table 8 Conceptual framework for dosing medications in obese patients[1]

Step 1 Evaluate the clinical investigations involving the medication to determine the degree of obesity in the patients under study and the weight descriptor used for dosing, which is usually actual body weight (ABW) in studies leading to medication approval. Determine if the patient under consideration appears to fit the profile of the patients in the study; be particularly cautious if the patient is extremely obese. If the patient appears to fit the profile of the patients in the studies, use the weight descriptor. If not, proceed to Step 2
↓
Step 2 If the patient does not fit the profile of the patients in the clinical investigations, search the literature for pharmacokinetic studies involving the medication in obese patients. Assess whether the pharmacokinetic parameters of the medication appear to increase proportionately with increasing weight suggesting that use of ABW may be appropriate. If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 3
↓
Step 3 If the patient does not fit the profile of the patients in the clinical investigations and if no pharmacokinetic studies involving the specific medication in obese patients are available, evaluate the literature for dosing studies in obese patients with medications that have similar physicochemical and pharmacokinetic parameters (*e.g.*, medications in the same class). If the patient appears to fit the profile of the patients in the studies, consider using the weight descriptor and proceed to Step 5. If not, proceed to Step 4
↓
Step 4 If no relevant studies can be found, and particularly if the patient is extremely obese, assess whether an alternative medication (where more is known about dosing in obese patients) might be appropriate. If there is no equivalent or better medication option available, proceed to Step 5
↓
Step 5 Assess the benefits and risks of using ABW for dosing using step 5a for weight-based dosing or 5b for non-weight based dosing
Step 5a If weight-based dosing (*e.g.*, mg/kg) is being used, assess whether the potential benefits of using ABW (*e.g.*, need to reach therapeutic range quickly) are likely to exceed the potential risks of over-dosing. If the patient under consideration is substantially heavier than the patients in the investigations or if no studies are available, assess whether a lean body weight or adjusted body weight equation might be preferable, especially in medications with a narrow therapeutic range and small (*e.g.*, < 0.2 L/kg) to moderate (*e.g.*, 0.2 to 1 L/kg) volumes of distribution that are cleared primarily by glomerular filtration
Step 5b If non-weight-based dosing (*e.g.*, mg/dose) is being used, assess whether the potential benefits of using a larger dose are likely to exceed the potential risks of over-dosing if the patient under consideration is substantially heavier than the patients who were enrolled in the clinical investigations involving the medication, and if the medication has a narrow therapeutic range and a moderate (0.2 to 1 L/kg) to large (> 1 L/kg) volume of distribution

[1]Should always take into account potential co-morbidity confounders such as renal or liver dysfunction when determining dosing regimens. Reprinted with permission from Erstad[57].

proportionally to increasing fat weight; importantly, the standard variation of both creatinine clearance and plasma volume measurements become larger in more severely obese patients[17,18].

Recommendations

For patients with mild-moderate forms of obesity (BMI < 35), dosing recommendations provided in the product information and other reputable drug information sources are usually appropriate since the studies that led to drug approval likely included such patients. The issue of dosing is more complicated in patients with more extreme forms of obesity since such patients are often either excluded from studies or included in such small numbers that a sub-analysis of data is inadequately powered to provide meaningful conclusions. When dosing these patients in the ICU setting the clinician will likely need to extrapolate dosing information from other similar drugs (*e.g.*, drugs in the same structural class) when such information is available and from investigations evaluating the drug's physicochemical and pharmacokinetic properties. Finally, the benefit *vs* risk assessment of using actual body weight for weight-based dosing of a drug should take into account the fact that most renally-eliminated drugs studied to date have not exhibited dose proportionality in patients with extreme forms of obesity; in other words, renal clearance of the drug does not increase proportionately with increasing body weight suggesting that an adjusted weight would be more appropriate to use when designing weight-based dosing regimens in severely obese patients.

Drug dosing in patients who are underweight, short, or have amputations or missing limbs

Based primarily on indirect evidence, underweight or short (assuming relatively normal body weight for height) patients are usually dosed on the lower end of dosing ranges for non-weight based dosing regimens. Such dosing is predicated on the assumption that the proportion of lean or metabolically active tissue is similar to that of patients of more normal weight and stature. However, an interesting issue arises when it is decided to use ideal body weight for a drug that has weight-based recommendations. The formulas most commonly used for dosing ideal body weight are based

on calculations that assume the patient is at least 5 feet tall. For example, for a male, one ideal body weight equation is calculated by adding 2.3 kg for each inch above 5 feet tall with a 50 kg base weight for the first 5 feet. While not based on any solid evidence, some clinicians have estimated the ideal body weight for a person less than 5 feet tall by subtracting 2.3 kg for each inch below 5 feet. Others have used regression analysis, typically on older data, to derive estimations for individuals less than 5 feet. With any of these methods, the estimates are likely to be less precise the shorter the patient. Similar issues would arise when estimating ideal body weight in patients who are missing body parts such as an arm or leg.

Recommendations

For non-weight-based dosing, usual or slightly lower than usual doses likely will suffice, assuming all other factors such as body weight and renal function are near normal. For weight-based dosing, there are a couple of options. Particularly for drugs with a wide therapeutic index, one could use actual body weight with the assumption that the missing limb had metabolic activity similar to the rest of the body. Also as above, the issue arises as to which weight to use when calculating an ideal body weight. One method that has been used in this situation for nutritional assessment is based on body part proportionality[19]. With this method, different body segments are assigned a percentage of total body weight. For example, a leg with a foot might comprise 16% of the total body weight, so the ideal body weight calculation in a patient with a leg amputation would be lowered by 16%. For an obese patient with this same amputation, the ideal body weight would be calculated in the same manner. If this same obese patient was being dosed by some other adjusted body weight equation (*e.g.,* ideal weight plus 40% of the excess weight), then the ideal body weight that takes into account the missing leg would be calculated first and used in the adjusted body weight equation. It is unknown if these methods of ideal body weight correction are more accurate or appropriate than an uncorrected (and easier to calculate) ideal body weight estimation for drug dosing.

None of these methods has been validated; further, the methods for calculating ideal body weight in patients of short stature do not take into account possible fat weight associated with obesity. If used, any of these dosing estimations should have some form of verification through therapeutic drug monitoring if available and/or through pharmacologic endpoints.

Drug choice or dosing in pregnancy

In general, pregnant or postpartum women account for a relatively small percent of ICU admissions, although the numbers are dependent on the type and location of hospital[20]. Traumatic injuries occur in approximately 7% of pregnancies in the United States[21]. Apart from the direct adverse consequences of the trauma or underlying disease states in the pregnant woman, there are special considerations for drug dosing not only because of physiological changes in the mother, but also because of potential fetal risk. The current FDA labeling of drugs is based on risk categories A, B, C, D, and X, although this system is currently undergoing revision by the FDA because of confusion associated with risk/benefit interpretation. It is important to note that these categories do not represent a linear increase in risk, since categories C, D, and X each involve a risk/benefit assessment. Such an assessment should take into account the timing of drug administration is important; for example, the critical period for embryonic organ formation is during weeks 3 to 8 post-conception. It has been estimated that approximately 66% of all drugs are category C[22]. In light of these categorical limitations, other references have been developed to provide the clinician with more information for drug use in pregnancy[23]. However, the quality and usefulness of the data in such sources is a function of the method of data collection, which in the case of fetal adverse drug events in pregnancy is data from case reports and registries. Both the numerator (*i.e.,* number of subjects with a reported adverse event) and the denominator (total number of subjects receiving the drug) are unlikely to be accurate with these collection techniques, so a true incidence is unknown, assuming causality does exist. Also largely unknown is how the duration of drug exposure relates to potential fetal harm.

The assessment of drug risk *vs* benefit in critically ill pregnant women is particularly complicated since potential delays in therapy could lead to adverse outcomes for the mother and fetus. Often initial life-saving interventions are performed without knowing whether or not a critically ill woman is pregnant. There is a saying that as maternal health goes, so goes fetal health[24]. Recommendations by the American College of Obstetricians and Gynecologists specifically state that necessary medications should not be withheld to due to fetal concerns[25]. Usually, there are at least a few potential alternatives in which case the decision is made based on factors such as drug risk category, other drug toxicities and experience with the drug in pregnancy. The two examples of severe sepsis/septic shock and hypertensive crisis will be used to illustrate some of these considerations. In general, the recommendations for fluids, vasoactive agents, and antimicrobial agents in pregnant women with severe sepsis or septic shock are the same as for non-pregnant women[26,27]. In fact, the recommendations in the Surviving Sepsis Guidelines have been endorsed by respected organizations such as the Royal College of Obstetricians and Gynaecologists[28]. Prior to widespread endorsement of these guidelines, arguments for the use of specific agents such as choice of vasopressors was often made on the basis of animal models that focused on issues such as uterine blood

flow[29]. Current thinking is that the potential mortality benefits of optimal resuscitation with a more potent agent such as norepinephrine outweigh more local or regional blood flow concerns[26]. In cases where there is no clear drug of choice, as might occur with antimicrobial selection, drugs with well-described toxicities (*e.g.,* aminoglycoside nephrotoxicity) should only prescribed when similarly efficacious, but less toxic agents are not an option (as should be the case in non-pregnant women).

In contrast to severe sepsis and septic shock that have one widely accepted guideline with treatment recommendations aimed at reducing mortality, there are multiple guidelines and recommended agents for treating hypertensive crisis during pregnancy. There is no high level evidence to suggest any differences in antihypertensive agents using mortality as the outcome of interest, so the choice-of-drug decision is heavily based on toxicity considerations. In the past, IV hydralazine was routinely recommended as a first-line choice for hypertensive crises including preeclampsia, but it is increasingly be considered a second-tier agent[30,31]. Currently, IV labetalol is considered as a preferred first-line agent for hypertensive crisis in pregnant women in the majority of treatment guidelines[32], but alternatives exist for refractory cases as long as one considers potential toxicities especially with more prolonged use (*e.g.,* methemoglobinemia due to nitroglycerin)[33,34]. An example of a class of antihypertensive agents that should almost always be avoided during pregnancy is the angiotensin-converting enzyme inhibitors such as intravenous enalaprilat that have a boxed warning about potential fetal injury and death when given during the second and third trimesters of pregnancy.

There are far more questions than answers when it comes to supportive care drug (*e.g.,* analgesics, sedatives) use in the critically ill pregnant patient, and the risk/benefit assessment must include potential harm to the fetus. The difficulty in such assessments is illustrated by the choice of a sedative agent for a pregnant critically ill patient. In the not too distant past, benzodiazepines were the drugs of choice for ICU sedation. However, benzodiazepines cross the placenta and are labeled as pregnancy category D. Additionally, alternative sedative agents are now available including propofol (category B) and dexmedetomidine (category C), but there is little data on longer-term use in pregnant women. This can lead to difficult decisions in pregnant women with prolonged ICU stays[35]. Table 9 lists some of the more common drugs used in the ICU setting and their implications for use in pregnant women. This table is meant to supplement other materials including more specific recommendations in FDA-approved product information brochures (*e.g.,* the use of preservative-free heparin and low molecular weight heparin preparations).

Recommendations

The drug management principles for critically ill pregnant patients are the same as for non-pregnant patients in the sense that potentially life-saving medications should not be withheld when no similarly efficacious therapies exist. When the situation is less dire and when more than one drug option is available, the benefit *vs* risk assessment should take into account the limited information on potential maternal/fetal harm that is available. Some decisions will be more clear-cut than others. For example, there are multiple agents available for treating hypertensive episodes in the ICU, so there would rarely if ever be a need to use sustained dosing with an agent like an ACE-inhibitor that has documented potential for fetal harm. For more difficult therapeutic dilemmas, additional expertise such as that by genetic counseling experts may be helpful.

Drug choice or dosing in extracorporeal membrane oxygenation

Long-term ECMO was first used in an adult patient with respiratory failure in 1972, but initial enthusiasm was dampened when a randomized trial of ECMO for adult respiratory distress syndrome (ARDS) was stopped due to futility[36]. Enthusiasm for this technique has been renewed based on reductions in mortality noted in more recent randomized and cohort studies of patients with severe ARDS, and in particular, H1N1-related ARDS[37,38]. From a medication standpoint, much of the emphasis has been on anticoagulation strategies and monitoring, which is not surprising given that bleeding and thrombosis are important causes of ECMO-associated morbidity and mortality[39]. However, ECMO may also alter the pharmacokinetic, pharmacodynamics and therapeutic properties of medications that must be administered to patients receiving this modality - that is the focus of this discussion. One recent review of pharmacokinetic changes associated with ECMO concluded that "published literature is insufficient to make any meaningful recommendations for adjusting therapy for drug dosing"[40]. Fortunately, there are ongoing systematic studies that are investigating the actions of a variety of drugs commonly administered during ECMO procedures[41,42]. The studies involving drug administration in conjunction with ECMO fall into 3 general categories: *in vitro* studies related to physicochemical properties of drugs (*e.g.,* drug binding to ECMO circuitry); pharmacokinetic studies; and clinical trials. The *in vitro* studies are demonstrated by a recent investigation that evaluated potential drug sequestration in ECMO circuitry by 5 drugs commonly administered to critically ill patients. Equivalent doses of 2 opioids (fentanyl, morphine), 1 sedative (midazolam), and 2 antimicrobials (meropenem, vancomycin) were studied in ECMO circuits and polyvinylchloride jars with fresh human whole blood[43]. There were no substantial issues of stability or sequestration with vancomycin or morphine, but meropenem recovery was low (20% *vs* 42% in ECMO *vs* control, respectively) suggesting temperature-related stability issues, and fentanyl and midazolam recovery were significantly lower in the

Table 9 Implications of medications for the pregnant critically ill patient

Indication/class	Specific drug	FDA[3]	Comments[1]	Indication/class	Specific drug	FDA[3]	Comments[1]
Sedative	Propofol	B		Anticoagulant	Enoxaparin	B	
	Midazolam	D			Heparin	C	
	Lorazepam	D	Risk (1st and 3rd trimesters)		Fondaparinux	B	
	Dexmedetomidine	C			Argatroban	B	
Analgesic	Morphine	C	Risk (3rd trimester)	Corticosteroid	Methylprednisolone	C	
	Fentanyl	C	Risk (3rd trimester)		Hydrocortisone	C	Data suggest risk
	Hydromorphone	C	Risk (3rd trimester)	Antifungal/ antiviral	Voriconazole	D	
Delirium	Quetiapine	C	Risk (1st and 3rd trimesters)		Fluconazole	D	Data suggest risk if > 400 mg/d
	Haloperidol	C			Micafungin	C	
Pulmonary	Epoprostenol	B			Amphotericin	B	
hypertension	Treprostinil	B			Acyclovir	B	
	Iloprost	C		Antibiotic	Azithromycin	B	
Bronchodilator	Tiotropium	C			Aztreonam	B	
	Ipratropium	B			Cefazolin	B	
	Albuterol	B			Cefepime	B	
	Levalbuterol	C			Cefoxitin	B	
Vasoactive	Epinephrine	C	Data suggest risk		Ceftriaxone	B	
	Norepinephrine	C	Data suggest risk		Ciprofloxacin	C	Data suggest low risk
	Vasopressin	C			Clindamycin	B	
	Phenylephrine	C	Data suggest risk		Linezolid	C	
	Dopamine	C			Meropenem	B	
	Dobutamine	B			Metronidazole	B	Data suggest low risk
	Milrinone	C			Moxifloxacin	C	Data suggest low risk
Antiarrhythmic	Diltiazem	C	Data suggest low risk		Piperacillin/ tazobactam	B	
	Amiodarone	D	Data suggest risk		Vancomycin	C	
	Digoxin	C		Anti-seizure[2]	Levetiracetam	C	
Antihypertensive	Labetalol	C	Data suggest low risk		Phenytoin	D	
	Esmolol	C		Paralytic	Rocuronium	C	
	Hydralazine	C	Risk (3rd trimester)		Cisatracurium	B	
	Magnesium sulfate	D			Vecuronium	C	
	Nitroglycerin	C	Data suggest low risk		Succinylcholine	C	
	Sodium nitroprusside	C	Data suggest risk				
	ACE-inhibitors	D	Data suggest risk (2nd and 3rd trimesters)				
Diuretic	Furosemide	C	Data suggest low risk				
	Mannitol	C					
GI/antiemetic	Pantoprazole	B	Data suggest low risk				
	Famotidine	B					
	Ondansetron	B					
	Metoclopramide	B					
	Erythromycin (non-estolate)	B					

[1]Human data to suggest risk based on data from Briggs *et al*[23]; [2]Pregnant women exposed to AEDs should register with the North American Antiepileptic Drug Pregnancy Registry (888-233-2334); [3]Refers to FDA pregnancy rating category. FDA: Food and Drug Administration; ACE: Angiotensin converting enzyme.

ECMO groups (3% *vs* 82%, P = 0.0005 and 13% *vs* 100%, P = 0.01, respectively) suggesting lipophilic-drug sequestration. Dosing modifications based on these *ex-vivo* findings of meropenem instability requires further study, but there are potential implications for other thermo-labile medications. In contrast to these findings that suggest no stability or sequestration concerns with morphine, another *in vitro* study found that 40% of a single dose of morphine was removed by ECMO tubing or circuitry[44]. The differences in morphine disposition in these 2 studies may be a function of differing methodologies, but they illustrate the problem with excessive reliance on *in vitro* data.

Pharmacokinetic studies have the potential advantage of measuring blood drug concentrations *in vivo* but these studies require the availability of a drug assay, presume a relationship between a surrogate marker (*i.e.,* the blood concentration of the drug or its active metabolite) and therapeutic effect, and are difficult to perform in critically ill patients. Pharmacokinetic studies are commonly employed for investigations of antimicrobial agents used to treat infections associated with ECMO. For example, antiviral medications have been used in combination with ECMO for treating severe influenza infections. Pharmacokinetic studies involving the neuraminidase inhibitor oseltamivir given enterally in critically ill adult patients on ECMO suggest that normal doses of oseltamivir (*i.e.,* 75 mg twice daily) are appropriate

Table 10 Drug dosing considerations in adult patients receiving extracorporeal membrane oxygenation

Drug dosing recommendations for an adult on ECMO are unlikely to be evidenced-based
Data from neonatal case reports, case series or studies may not apply to adults
Data from one drug may not be applicable to another even from the same class
Drug regimen recommendations in critical care guidelines may not apply to patients on ECMO
Organ dysfunction apart from the lung and heart complicate interpretation of literature
The contribution of distinct physicochemical properties of drugs to sequestration is unclear
Hydrophilicity or lipophilicity appear to be important factors affecting pharmacokinetics
The therapeutic actions of drugs are not consistently predictable by pharmacokinetics
The design and properties of the equipment change over time with implications for dosing
The priming solution such as blood or blood-derived products may affect dosing

ECMO: Extracorporeal membrane oxygenation.

unless a patient has concomitant renal dysfunction in which case dose reduction may be in order[45-47]. Case report pharmacokinetic data in patients undergoing ECMO is available for other antimicrobials including the antifungal agents caspofungin and voriconazole[48]. Similar to pharmacokinetic studies, there are a few studies using laboratory parameters as surrogate markers of clinical effect. For example, in critically ill patients on ECMO who were receiving argatroban for suspected heparin-induced thrombocytopenia, argatroban requirements based on activated partial thromboplastin time monitoring were found 10-fold lower than the 2 μg/kg per minute dose recommended in product labeling[49].

There are limited clinical studies involving drug choice or dosing in patients undergoing ECMO and the data from these studies does not always seem to corroborate data from the *in vitro* and pharmacokinetic investigations. For example, one retrospective study found that morphine and midazolam requirements increased, but fentanyl requirements remained unchanged with continued dosing over time in adult patients on ECMO for cardiorespiratory failure[50]. On the other hand, neonates on ECMO required less supplemental analgesia when given morphine infusions *vs* fentanyl infusions in a historical control group[51]. The patients in the morphine group all experienced less withdrawal and were discharged earlier ($P = 0.01$ for both). Table 10 lists some of the more important considerations when evaluating published literature and devising dosing regimens in critically ill patients receiving ECMO.

Recommendations

The paucity of literature regarding drug dosing in ECMO with relevant clinical outcomes precludes any meaningful evidence-based recommendations. Therefore, the clinician must extrapolate information from the limited *ex vivo* and pharmacokinetic studies that have been conducted for selected drugs taking into account changes in ECMO technologies in recent years that may influence previous study findings. *Ex vivo* studies suggest that lipophilic drugs are particularly prone sequestration by ECMO circuitry. For drugs titrated to clinical effect such as opioids, the clinician may either choose to use less lipophilic agents such as morphine (assuming no renal failure) or use more lipophilic agents like fentanyl with the appreciation that higher than expected doses may be needed. For some drugs, therapeutic drug monitoring may be available and useful. For lipophilic or thermolabile (*e.g.,* carbapenems and ampicillin) drugs that are not titrated to clinical effect and for which therapeutic drug monitoring is usually not available, the clinician must be alert for potential therapeutic unresponsiveness or failure due to inadequate dosing. Table 11 lists the pharmacokinetic and physicochemical characteristics of drugs commonly used in critically ill patients in order to help with drug selection and dosing when data from clinical trials involving ECMO are not available.

Drug choice or dosing during plasma exchange

Plasma exchange (aka plasmapheresis) is another modality that has drug-dosing related concerns. If one assumes a normal plasma volume of approximately 4 L for an 80 kg patient, then plasma exchange at a rate of approximately 50 mL/kg over 2 h would remove 2 plasma volumes and more than 80% of all solutes[52]. Much of the experience with plasma exchange has been case report data associated with overdosing or poisonings. The AABB and the American Society for Apheresis has concluded that there is little or conflicting evidence for the latter indications and that such use represents "heroic" of "last-ditch" efforts[53]. Apart from the intended use of plasma exchange for toxicological problems, there is the unintended effect of plasma exchange on drugs being used in usual therapeutic doses.

Drugs most likely to be eliminated by plasma exchange are those with small volumes of distribution that approximate extracellular fluid stores (less than 0.2 L/kg) and those with plasma protein binding of at least 80%[54]. Since plasma proteins and bound drugs are removed in tandem with fluid in plasma exchange, there is increased drug removal with increased protein binding in contrast to hemodialysis that preferentially removes unbound drugs. The timing of drug administration relative to onset of plasma exchange is critical to the amount of drug elimination. Hydrophilic drugs with small volumes of distribution and high protein binding would be particularly susceptible to removal if initiated after plasma exchange has begun. Lipophilic drugs with larger volumes of distribution would not be expected to have substantial removal by plasma exchange, presuming

Table 11 Pharmacokinetic and physicochemical properties of drugs commonly used in the intensive care units[1]

Indication/class	Specific drug	LogP	Pb (%)	Vd (L/kg)
Sedative				
	Propofol	4.16	98	60
	Midazolam	3.33	97	2
	Lorazepam	3.53	91	1.3
	Dexmedetomidine	3.39	94	1.3
Analgesic				
	Morphine	0.9	35	3
	Fentanyl	3.82	83	5
	Hydromorphone	1.62	20	1.2
Delirium				
	Quetiapine	2.81	83	10
	Haloperidol	3.66	92	18
Antiarrhythmic				
	Diltiazem	2.37	80	5
	Amiodarone	7.64	98	70
	Digoxin	2.37	25	6
Antihypertensive				
	Labetalol	1.89	50	5
	Esmolol	1.82	55	3
	Hydralazine	0.75	87	4
GI/antiemetic				
	Pantoprazole	2.18	98	0.15
	Famotidine	-2	18	1.2
	Ondansetron	2.35	73	2
	Metoclopramide	1.4	30	4.4
	Erythromycin	2.6	85	0.6
Anticoagulant				
	Enoxaparin	-8.3	80	0.07
	Heparin	NA	NA	0.05
	Fondaparinux	-10	94	0.1
	Argatroban	-0.97	54	0.17
Corticosteroid				
	Methylprednisolone	1.56	78	1.1
	Hydrocortisone	1.28	95	0.5
Antifungal/ antiviral				
	Voriconazole	1.82	58	3
	Fluconazole	0.56	11	0.8
	Micafungin	-6.3	99	0.39
	Amphotericin	-2.3	95	1.8
	Acyclovir	-1	9-33	0.6
Antibiotic				
	Azithromycin	2.44	51	0.44
	Aztreonam	-3.1	56	0.17
	Cefazolin	-1.5	80	0.14
	Cefepime	-4.3	20	0.23
	Cefoxitin	0.29	75	0.26
	Ceftriaxone	-1.8	95	0.14
	Ciprofloxacin	-0.81	35	2.5
	Clindamycin	1.04	93	2.5
	Linezolid	0.64	31	0.64
	Meropenem	-4.4	2	0.36
	Metronidazole	-0.46	25	1
	Moxifloxacin	-0.5	50	2
	Piperacillin/ tazobactam	-0.26		0.1
	Vancomycin	-3.1	55	0.7
Anti-seizure				
	Levetiracetam	-0.59	8	0.6
	Phenytoin	2.15	90	0.7

[1]LogP is the octanol-water partition coefficient and is expressed as the ratio of the solubility of a compound in octanol (non-polar solvent) to its solubility in water (polar solvent). Some of the data from this table (particularly the log *P* values) were obtained from www.drugbank.ca. NA: Not applicable.

the plasma exchange is not initiated until after the initial distribution phase of the drug has taken place. There is case report data for some drugs that confirm these generalizations. For example, voriconazole that has a volume of distribution slightly over 4 L/kg and protein binding of approximately 58% would not be expected to have significant removal by plasma exchange and this was confirmed in a pharmacokinetic study involving a patient receiving plasma exchange in conjunction with voriconazole for an invasive aspergillosis infection[55].

Recommendations

Once it is known that a patient will undergo plasma exchange, the clinician must evaluate each of the drugs being administered to the patient and attempt to devise an optimal dosing regimen or find alternative drugs unlikely to be affected by the procedure (*i.e.*, large volume of distribution and low protein binding). The evaluation must take into account the specific plasma expander being used as a replacement fluid, since albumin or albumin-containing fluids like fresh frozen plasma influence drug binding. Additionally, the evaluation should consider the pharmacokinetics of the drug, the timing of the drug relative to the plasma exchange procedure, co-morbidities such as renal failure that might alter normal kinetics, and the limited published literature that is available. Table 11 lists pharmacokinetic and physicochemical properties of drugs commonly used in critically ill patients that can be used to help predict drug disposition in association with plasma exchange.

CONCLUSION

Special populations of ICU patients with more severe alterations in body size, shape, and composition pose unique challenges to clinicians faced with drug choice or dosing decisions. Appropriate drug choice or dosing in these populations must take into account a variety of factors from altered pharmacokinetic parameters to concomitant therapeutic interventions and co-morbidities.

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