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EDITORIAL

From bronchiolitis guideline to practice: A critical care perspective

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Abstract

Acute viral bronchiolitis is a leading cause of admission to pediatric intensive care units, but research on the care of these critically ill infants has been limited. Pathology of viral bronchiolitis revealed respiratory obstruction due to intraluminal debris and edema of the airways and vasculature. This and clinical evidence suggest that airway clearance interventions such as hypertonic saline nebulizers and pulmonary toilet devices may be of benefit, particularly in situations of atelectasis associated with bronchiolitis. Research to distinguish an underlying asthma predisposition in wheezing infants with viral bronchiolitis may one day lead to guidance on when to trial bronchodilator therapy. Considering the paucity of critical care research in pediatric viral bronchiolitis, intensive care practitioners must substantially rely on individualization of therapies based on bedside clinical assessments. However, with the introduction of new diagnostic and respiratory technologies, our ability to support critically ill infants with acute viral bronchiolitis will continue to advance.

Key words: Respiratory syncytial virus; Rhinovirus; Asthma; Hypertonic nebulized saline; Acute viral bronchiolitis

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Core tip: Pediatric acute viral bronchiolitis is characterized by small airways obstruction due to inflammatory infiltrates and debris. While this pathology has little or no overlap with asthma, the clinical presentation of wheezing may be similar. Emerging methods to distinguish asthmatics from the general bronchiolitis population, stratify patients according to illness severity, and provide more effective pulmonary clearance and respiratory support may improve outcomes for these patients in the pediatric intensive care unit.

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INTRODUCTION AND PURPOSE OF THIS PAPER

Widely recognized as the most common cause of hospitalization for infants, bronchiolitis is responsible for more than 100000 hospitalizations annually and poses a significant risk for respiratory failure requiring mechanical ventilation in infants[1]. Approximately 5% to 30% of infants hospitalized with bronchiolitis require pediatric intensive care[2-4]. To address the needs of this patient population, many institutions have established bronchiolitis order sets and pathways. A number of issues now prompt the need to update and reconsider the implementation of bronchiolitis pathways: institution of new electronic medical systems under the Meaningful Use program[5], the burgeoning pediatric hospitalist movement[6], a national trend toward protocolized and evidence-based hospital care, and the recent publication of an updated AAP bronchiolitis guideline[7].

CLINICAL PRESENTATION AND PATHOLOGY

Bronchiolitis is typically recognized clinically by the presence of wheeze, signs and symptoms of upper and lower respiratory tract infection, and respiratory distress[7]. Apnea can be a major finding, especially in younger infants[8]. Pathological studies of fatal RSV bronchiolitis have revealed multiple contributing factors to obstruction of small to large-sized airways: intraluminal debris, airway wall edema, and compression by edematous bronchial arteries and inflammatory peribronchial lymphoid follicular aggregates (Figure 1). The intraluminal debris may be composed of mucus, fibrin, epithelial cells, and inflammatory cells[9].

MICROBIOLOGY

Etiologic agents of bronchiolitis include most prominently respiratory syncytial virus (RSV) and rhinovirus[7]. Additional viruses implicated in acute bronchiolitis include parainfluenza virus, influenza virus, human metapneumovirus, bocavirus, adenovirus, and coronavirus[7,10].

What is the significance of viral identification in acute bronchiolitis? The triple mission of academic health centers is to deliver leading-edge patient care, conduct research, and educate. In the United States, more than 500 clinical laboratories, many of which are maintained by academic centers, participate in the National Respiratory and Enteric Virus Surveillance System (NREVSS). The Centers for Disease Control and Prevention (CDC) relies on NREVSS to monitor temporal and geographic patterns of relevant virus infections. These viruses significantly include RSV, human metapneumovirus, respiratory adenovirus, and human parainfluenza virus. This surveillance system constitutes an important part of the CDC's efforts to prevent and control respiratory and enteric viral diseases. For instance, an outbreak of enterovirus D68 in 2014 was identified in the Midwestern United States and subsequently spread throughout the United States. Enterovirus D68 caused unusually severe respiratory illnesses, with almost all confirmed cases confined to children. Although the disease was not reportable nationally, "laboratory detections of enterovirus… are reported voluntarily to (NREVSS)…. (Suspected) clusters or outbreaks should be reported to local or state health department"[11]. Identifying viruses that cause illnesses resembling asthma exacerbations is important for the overall scientific goal of understanding respiratory diseases in general. This leads to the philosophic question of whether microbiological investigation of bronchiolitis-causing viruses at centers participating in NREVSS should be regarded differently from nonparticipating centers. Viral identification is an important part of an academic institution's broader societal, educational, and research mission. Additionally, for the patient's family, knowledge that their hospitalized child has RSV or non-RSV virus infection may provide important prognostic information in terms of well-studied risk factors for mortality associated with RSV, potential for longer hospitalization with RSV *vs* rhinovirus[7], reduced likelihood of bacterial infection

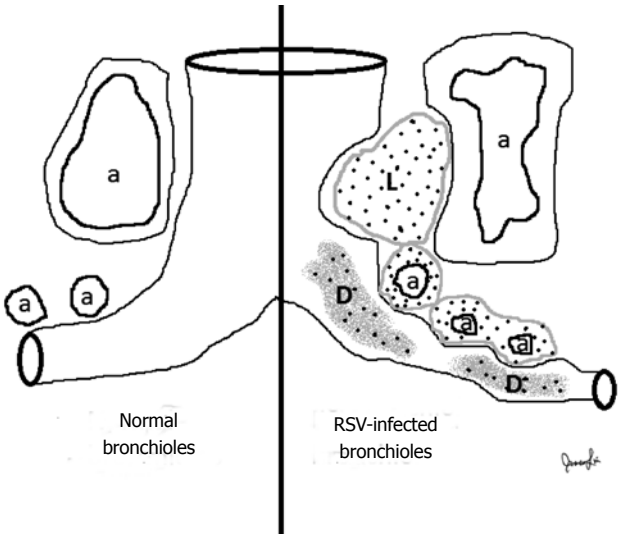

Figure 1 Respiratory syncytial virus infection is associated with vasocentric inflammation affecting bronchioles. Lymphoid aggregates (L), probably developing from bronchiolar-associated lymphoid tissue, are found between pulmonary arteries/arterioles (a) and bronchioles. Congested arterioles surrounding bronchioles contribute to airways obstruction, along with intraluminal debris (D) consisting of mucus, fibrin, epithelial cells, and inflammatory cells. While neutrophils are occasionally obtained from bronchoalveolar lavage, macrophages are the predominant inflammatory cell type in the submucosal infiltrates and intraluminal locations.

Table 1 Respiratory syncytial virus reinfection risk

Ref.	Year	*n*	Reinfection risk
Henderson *et al*[39]	1979	78	74% by age 2 if infected in 1st year of age
Glezen *et al*[40]	1986	125	76% by 24 mo age if infected before 12 mo age
Hall *et al*[15]	1991	15	50% at first challenge with RSV 2 mo after initial infection
Kawasaki *et al*[16]	2004	165	25% within a year of first RSV infection

n: Total cohort of subjects studied; RSV: Respiratory syncytial virus.

in non-critically ill patients with community-acquired pneumonia[12], and potentially increased risk of asthma associated with rhinovirus[13,14]. Finally, a virology-positive diagnosis of RSV or another well-established bronchiolitis-causing agent would possibly help to distinguish cases of bronchiolitis from asthmatics with first-time acute wheeze, although this issue remains under investigation (see section on Asthma below).

What is the risk of RSV reinfection? The most recent AAP guidelines suggest that RSV prophylaxis may be discontinued after breakthrough RSV infection[7]. We conducted a literature search to clarify the reinfection risk of RSV in infants receiving palivizumab prophylaxis who experience an acute episode of bronchiolitis. Previous literature has demonstrated that RSV infection is highly prevalent and only partially limited by acquired immunity (Table 1). Risk of reinfection may be related to serum titers of RSV-specific antibody[15,16]. These data suggest that the reinfection risk for RSV in the absence of ongoing passive immunization is high, is correlated with diminished serum titers of RSV-neutralizing antibodies, and can occur within the same RSV season. To our knowledge, neither the effective development of adaptive host immunity to RSV infection in the setting of passive immunization, nor the incidence of RSV reinfection after palivizumab withdrawal has been reported.

SCORING SYSTEM

A scoring system for bronchiolitis would help to standardize care and potentially improve outcomes. Unfortunately, no clinical scoring system has been appropriately validated for reliability, physiologic correlation, and clinical course[17]. The original basis of bronchiolitis scores was physical examination of respiratory distress using commonly assessed clinical variables[18]. Over time, continuing reassessment of bronchiolitis scoring has made apparent that the most common scoring system for bronchiolitis, the RDAI, has poor construct validity for overall respiratory status and limited discriminative ability to determine major clinical outcomes like length of stay[19]. Recent efforts have focused on modeling clinical indicators associated with worse clinical outcomes. A secondary analysis of a randomized, controlled multicenter trial in 20 emergency departments related to bronchiolitis concluded that oxygen saturation was the best predictor of hospitalization and length of stay[20]. Among previously healthy infants with RSV bronchiolitis who were admitted to a single academic center, risk factors for respiratory failure that were identified in the emergency department included lethargy, grunting, and PaCO2 $\geqslant$ 65 mmHg[4]. Prodhan and colleagues also noted that among RSV-infected infants admitted to the intensive care unit with respiratory failure, the major radiologic predictor of prolonged mechanical ventilation was atelectasis, not hyperinflation[21]. Walsh *et al*[22] validated a model to predict admission from the emergency department based on age, dehydration, work of breathing, and initial heart rate. Weisgerber *et al*[23] developed a model to predict prolonged length of stay based on need for supplemental oxygen, respiratory rate, gestation, and caloric intake. The topic of predictive modeling for bronchiolitis has recently been reviewed systematically[24]. Development of a clinical score for bronchiolitis that accurately reflects relevant indicators of bronchiolitis outcomes could potentially enable research on earlier interventions to ameliorate or prevent critical bronchiolitis disease.

ASTHMA EVALUATION IN EARLY CHILDHOOD

The key differential diagnosis when evaluating a wheezing infant with viral respiratory disease is asthma exacerbation. Viral respiratory infections - especially RSV, parainfluenza, and rhinovirus - are identified by the Expert Panel Report 3: Guidelines for Diagnosis and Management of Asthma to be "one of the most important causes of asthma exacerbation and may also contribute to the development of asthma"[25]. Approximately 40% of infants hospitalized with RSV may continue to wheeze or have asthma even into young adulthood[26]. Importantly, children who develop asthma symptoms before the age of 3 years are more likely to experience declines in lung function growth than those who develop asthma symptoms after 3 years of age[25]. Thus, efforts to predict development of childhood asthma are ongoing. While a thorough review of asthma prediction is beyond the scope of this editorial, we present as examples 3 asthma prediction tools in Table 2[27-29]. The wide range of predictive values is notable, which may be attributable to the different age ranges and clinical baseline of the analyzed patient cohorts. As efforts continue to determine whether early anti-inflammatory therapies can alter the decline in lung function growth[30] associated with early childhood asthma, it seems likely that research will return to focus on wheezing associated with preschool viral illness. The proscription against a bronchodilator trial in the latest AAP bronchiolitis guideline - regardless of history of recurrent wheeze, atopy, or family history of asthma - will need to be reconciled with both asthma biology and more long-term efforts to modify the natural history of

Table 2 Selected asthma prediction tools

Ref.	Clough *et al*[29]	Castro-Rodríguez *et al*[27]	Zhang *et al*[28]
Year	1999	2000	2014
n	107	1246	128
Cohort	Age 3 mo to 3 yr Wheeze onset < 12 wk prior Parental history of asthma or eczema Parental positive allergen skin prick test	Longitudinal healthy birth cohort	Age 2-20 mo 1st wheeze
Outcome prediction	Ongoing wheeze requiring treatment 1 yr after presentation	Active asthma during the school years 6-13	Multi-trigger wheezing after 2 yr
Prediction results	71% accuracy overall, 57% sensitivity, 84% specificity, 76% PPV, 68% NPV	42% sensitivity, 85% specificity, 59% PPV, 73% NPV	95% sensitivity, 74% specificity, 59% PPV, 94% NPV
Components of tool	Age at presentation Serum soluble interleukin-2 receptor concentration	Wheezing by parent report Major criteria: parental MD asthma, MD eczema Minor criteria: MD allergic rhinitis, Wheezing apart from colds, eosinophilia ⩾ 4%	Wheezing severity score Family or personal history of atopic disease Number of exfoliated airway epithelial cells in sputum

n: Number of subjects; NPV: Negative predictive value; PPV: Positive predictive value; ROC: Receiver operator characteristic.

childhood asthma.

BETA2-AGONISTS FOR ACUTE PEDIATRIC BRONCHIOLITIS

The relevant Cochrane review for bronchodilator therapy in bronchiolitis is directed at first-time wheezing infants receiving beta2-agonists. Exclusion criteria for studies on first-time wheezing infants generally included prior history of wheeze, previous bronchodilator or steroid use, and underlying lung or cardiac disease (including asthma). Additionally, most of the studies excluded patients requiring intensive care. Regarding bronchodilators, the AAP bronchiolitis guideline noted "variable study designs" and "inclusion of infants who had a history of previous wheezing in some studies". This is an unreferenced statement and requires clarification. Of the 33 studies included in the most recent relevant Cochrane analysis, only 4 studies included infants with prior history of wheeze. Two of those studies included only 3 or fewer infants with prior wheeze in each study arm[17]. In other words, the inclusion of infants with any prior wheeze in bronchodilator trials for bronchiolitis was extremely limited. The AAP guideline makes reference to this: "Those studies showing benefit (of bronchodilators)… include older children with recurrent wheezing…. Although it is true that a small subset of children with bronchiolitis may have reversible airway obstruction…, attempts to define a subgroup of responders have not been successful to date". Furthermore, the AAP guideline goes on to state, "Children with severe disease or with respiratory failure were generally excluded from these trials, and this evidence cannot be generalized to these situations"[7]. Therefore, significant question remains as to whether to trial a beta2-agonist in infants with prior history of wheezing, atopy, or more severe clinical presentations of acute viral bronchiolitis.

CHEST RADIOGRAPHY, ATELECTASIS AND AIRWAY CLEARANCE THERAPY

The AAP bronchiolitis guideline recommends against routine chest radiography in children with bronchiolitis, except for "cases in which respiratory effort is severe enough to warrant ICU admission or where signs of an airway complication (such as pneumothorax) are present"[7].

While mild-to-moderate presentations of bronchiolitis are unlikely to benefit from chest radiography, detection of radiographic atelectasis in more severe disease may be clinically important. In a study of 46 children with RSV-related respiratory failure, a multiple logistic regression model was developed by Prodhan *et al*[4,21] to predict length of mechanical ventilation. After excluding hyperinflation due to lack of association, the model included only age and radiologic atelectasis. On days 1 and 2 of mechanical ventilation this model correctly classified patients requiring > 8 d of mechanical ventilation in 84% of cases, and had an area under the ROC curve of 0.92[21]. This suggests that development of atelectasis in severe bronchiolitis is highly correlated with worse clinical outcome.

The cumulative literature on severe bronchiolitis and our own clinical experience in pediatric intensive care support the idea that the ability to clear obstructed airways and prevent or reverse atelectasis is directly related to an improved clinical course. That atelectasis predicts clinical outcome substantially explains why the literature on chest physiotherapy in acute bronchiolitis in infants has been uniformly negative. As reported in the relevant Cochrane review[31], patient selection for these trials did not specifically test whether patients with evidence of impaired mucus clearance would fare better with chest physiotherapy. Atelectasis, when reported at all, was in the range of 10%-25% of subjects. In one of the trials, a patient in the control

arm who developed atelectasis was withdrawn from the study in order to receive chest physiotherapy[32]. This suggests that randomized trials of chest physiotherapy may be limited by clinicians who would not allow their patients to participate if the patients were clinically likely to benefit from chest physiotherapy. Most of the chest physiotherapy trials were conducted on small numbers of subjects. The data could not be pooled because of major differences between studies in both study design and chest physiotherapy technique. To our knowledge, none of the chest physiotherapy trials in bronchiolitis tested recent pulmonary toilet devices like The Vest (pneumovest), intrapulmonary percussive ventilator, MetaNeb, or Cough Assist. A randomized trial on the use of cough assist in acute bronchiolitis is currently underway.

Currently the literature on chest physiotherapy in acute bronchiolitis should be regarded as limited to non-critically ill bronchiolitis and inadequate to make any conclusions regarding patients with suspected or radiologic atelectasis. We believe that clinicians should make individualized decisions on chest radiography and chest physiotherapy in bronchiolitis, particularly to evaluate and treat atelectasis. Although this may seem to be in contrast to the AAP guideline: "Clinicians should not use chest physiotherapy for infants and children with a diagnosis of bronchiolitis"[7], the nature of the guidelines is as "an evidence-based shared baseline…. (not to) tell you what to do in the case of every patient"[33].

THREE PERCENT OF HYPERTONIC SALINE NEBULIZER THERAPY

Nebulized hypertonic saline potentially addresses the pathophysiology of airways obstruction in acute viral bronchiolitis by reducing pulmonary edema and loosening intraluminal debris to facilitate mobilization. The most recent Cochrane review on hypertonic saline therapy for acute bronchiolitis was undertaken on 11 inpatient and outpatient studies, all of which were randomized, double-blind, parallel-group, controlled trials (RCTs) using 0.9% saline as a control. All of the trials excluded patients with prior wheeze or severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation < 85% on room air). The concentration of hypertonic saline was 3% in all but one trial, which included both 3% and 5% concentrations. The 6 inpatient trials involving 500 participants revealed a pooled reduction in length of hospital stay by 1.15 d (95%CI: -1.49 to -0.82, P < 0.0001) for children treated with hypertonic saline, with average stays ranging 3.5 to 7.4 d. All 6 inpatient trials demonstrated a benefit in reducing duration of hospitalization[34]. Subsequent to this Cochrane review, randomized trials of inhaled hypertonic saline have revealed mixed results[35-38]. Resolving the differences between the many RCTs on nebulized hypertonic saline will likely require either a meta-analysis approach or an updated Cochrane review. In the meantime, evidence in support of 3% hypertonic saline therapy for hospitalized pediatric bronchiolitis includes clinical and biologic plausibility, numerous well-designed RCT's, substantial benefit in a number of trials, and virtually no observed harm, including a notable absence of bronchospasm[34]. While the AAP guideline on hypertonic saline nebulizer for inpatient bronchiolitis appropriately balances the mostly if not uniformly positive evidence, the development of an institutional protocol could reasonably implement hypertonic saline for every admitted patient with acute bronchiolitis, especially if the institutional average length of stay for bronchiolitis exceeds three days.

ADDRESSING THE ACADEMIC MISSION OF ADVANCING HEALTH CARE

In conclusion, we applaud the 2014 revision of the AAP guideline on bronchiolitis and suggest further research to: (1) develop and validate severity scores to help guide clinical therapies; (2) incorporate early identification of childhood asthma; (3) study methods to identify and address atelectasis; and (4) consolidate the available data on inhaled hypertonic saline. Most importantly for the bedside practitioner, the pragmatic clinical setting and individualized assessment continue to guide medical care. With the development of new medical technologies and informatics, we are beginning to investigate bronchiolitis using a different set of tools and in a different way from those in the past, although constrained by the same limitations on resources and funds. In this way, academic centers can continue to fulfill our mission to educate, study, and provide the best health care to each of our patients.

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EDITORIAL

Opening the doors of the intensive care unit to cancer patients: A current perspective

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Abstract

The introduction of new treatments for cancer and advances in the intensive care of critically ill cancer patients has improved the prognosis and survival. In recent years, the classical intensive care unit (ICU) admission comorbidity criteria used for this group of patients have been discouraged since the risk factors for death that have been studied, mainly the number and severity of organic failures, allow us to understand the determinants of the prognosis inside the ICU. However, the availability of intensive care resources is dissimilar by country, and these differences are known to alter the indications for admission to critical care setting. Three to five days of ICU management is warranted before making a final decision (ICU trial) to consider keep down intensive management of critically ill cancer patients. Nowadays, taking into account only the diagnosis of cancer to consider ICU admission of patients who need full-supporting management is no longer justified.

Key words: Intensive care unit; Critical care setting; Cancer patients; Critically ill cancer patients; Organ failures

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Core tip: The number and severity of organ failures are still the most important determinants for in-hospital mortality of critically ill cancer patients. Thus, an early intensive care unit admission is crucial to impact in the short-term prognosis of this population.

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INTRODUCTION

The concept of futility was used to support either refuse of intensive care unit (ICU) admission or early treatment withdrawal decisions for critically ill cancer patients. Nevertheless, emerging of new treatments for cancer and recent advances in intensive care medicine has improved prognosis and survival.

At present, the classical comorbidity criteria used for ICU admission in this group of patients have been discouraged since the risk factors for death that have been studied, mainly the number and severity of organ failures, allow us to understand the determinants of the outcomes inside the ICU. In our center, the overall mortality was 17.5% over a four-year period, provided an appropriate selection of patients, an adequate evaluation of predictors of ICU mortality and treatment outcomes are necessary in each case evaluation[1-5].

Also, the clinician should be updated in the recent information available about prognostic factors that contribute to in-hospital mortality of critically ill patients with cancer. Furthermore, the availability of intensive care resources is dissimilar by country, and these differences are known to alter the indications for admission to critical care setting[6]. Unlike the United States and Canada, Mexico seems to have approximately 1984 ICU beds with mechanical ventilators (1.76 ICU beds per population of 100000)[7].

Also, clinicians should be hard-headed during discussions and respect the patient's will to choice an invasive treatment. We should take into account the number and severity of organ failures when evaluating patients for ICU admission, beyond the diagnosis of cancer. For this purpose Sequential Organ Failure Assessment (SOFA) or, recently, the Mexican sequential organ failure assessment are useful to evaluate number and severity of organ failures as the main prognostic factor in critically ill patients with cancer. Thus, early admission to the ICU with the lowest possible number of organ failures is recommended[8-10].

In a substudy of the Sepsis Occurrence in Acutely Ill Patients study, a large prospective cohort that included 198 participating ICUs from 24 European countries, the primary endpoint was death or hospital discharge at 60 d. In this study, Taccone *et al*[11] found that ICU and hospital mortality rates were similar in patients with solid tumors and those without cancer.

Aygencel *et al*[12] recently described a median of the SOFA score of 9 as a major contributor to mortality of critically ill cancer patients with solid tumors and a median of SOFA score of 10 in patients with hematologic malignancies. Other significant predictors for ICU mortality in patients with solid tumors were lactate dehydrogenase level on admission, sepsis or septic shock during ICU stay, and remission of the underlying cancer. In 2010, Namendys-Silva *et al*[2] described that Acute Physiology and Chronic Health Evaluation Ⅱ score and vasopressor requirement during ICU stay, were independent predictors for ICU mortality in patients with solid malignancies. Aygencel *et al*[12] also found these risk factors to be significant. In general, classic predictors of mortality are no longer relevant, and we should evaluate other characteristics of the cancer patient to decide the admission to the ICU[2,12].

In addition, age influences minimally on 6-mo survival of critically ill cancer patients[13], whereas performance status and comorbidity are much more important[13-15].

In 2013, we made recommendations and developed a management algorithm to guide ICU admission of cancer patients (Table 1)[16]. In fact, we highlight that this algorithm should not be different from admission criteria of other patients admitted to the ICU without cancer.

There is a subgroup of patients that should not be considered for admission, including those patients with a poor status performance or those who refuse to ICU admission to receive invasive treatment.

Three to five days of ICU management is warranted before making a final decision (ICU trial) to consider keep down intensive management[17].

When a doubt exists about the criteria for ICU admission, a trial of ICU management should be proposed to assert that no patients are withhold of an opportunity for recovering from their acute condition. When ICU admission is accepted, patients should be treated with a full-supporting management (ICU trial) for at least 3-5 d. By doing this, patients receive everything they need during the first few ICU days and then have their clinical status reassessed after completing this trial. This "full-code status" includes the provision of cancer chemotherapy, antibiotics, and other life-sustaining therapies. After 3 d of full intensive management, an improvement in the number and severity of organ failures indicates that additional life-supporting treatment should be continued; whereas deterioration of clinical status, evaluated by an increase in the number or severity of organ failures, should prompt a discussion of the patients suitable to be still under aggressive treatment[17].

In addition, patients with tumor lysis syndrome, neoplasm-related pulmonary or renal infiltration, sepsis related to obstructive pneumonia, or ureteral compression may require full-supporting treatment until the cancer chemotherapy becomes effective[18].

Full ICU treatment should be provided to cancer patients with particular characteristics (Table 1). However, the postoperative care of surgical oncology patients is not always mandatory in the ICU.

In addition, the mortality rate for mechanically ventilated cancer patients remains higher than that for patients with non- malignant diseases[19,20].

We studied the prognosis and ICU mortality rates for hematologic malignancies patients who required invasive mechanical ventilation (IMV) and for those with solid tumors, being 73% (65/189) and 34.3% (58/169), respectively. Although IMV in cancer patients is still associated with a very high risk of death, the mortality

Table 1 Recommendations for intensive care unit admission of critically ill cancer patients[16]

Cancer patients who benefit of ICU admission
SOFA score between 7 and 10 or less than 3 organ failures
Recent diagnosis of hemato-oncological disease
Treatment of medical emergencies related to cancer or its treatment; tumor lysis syndrome, pulmonary infiltrates in patients with leukemia or leukostasis as the initial manifestation of leukemia
The likelihood of a cure or probable disease control
Performance status (Eastern Cooperative Oncology Group scale) between 0 and 2
Postoperative intensive care for patients undergoing complex surgical procedures who require hemodynamic monitoring and/or mechanical ventilation

ICU: Intensive care unit.

rate for patients with IMV in our ICU was lower than previously reported[21-26]. Soares *et al*[25] studied prospectively 463 cancer patients on mechanical ventilation. Age > 70 years, severity of acute organ failures, poor performance status, cancer status, and older age were the main determinants of mortality.

In a large multicenter study of 1004 patients with solid or hematological malignancies and acute respiratory distress syndrome (ARDS) meeting the new operational Berlin definition, about 90% of ARDS cases were due to infections. Opportunistic organisms accounted for over one-third of all ARDS cases, with invasive aspergillosis and *Pneumocystis jiroveci* pneumonia in primary ARDS and candidemia in secondary ARDS. The authors concluded that mortality decreased significantly over time to 52%, despite adjustment for patients' ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. This highlights the relevance of optimal patient triage to ICU admission and ARDS management in ICUs that are highly experienced in managing patients with ARDS and malignancies[27].

There are some interventions well studied in non-cancer patients that could be beneficial in the critical care setting of patients with malignancies. de Almeida *et al*[28] recently found that a restrictive transfusion strategy in surgical oncology patients results in more postoperative complications compared with liberal strategy (hemoglobin trigger of 9 g/dL). The absolute risk reduction for the liberal strategy was 16% (95%CI: 3.8-28.2) and a number needed to treat of 6.2 (95%CI: 3.5-26.5) to avoid postsurgical complications.

Some studies have demonstrated the feasibility of administering chemotherapy in the ICU setting, with admissible short and long-term outcomes, as recently shown by Wohlfarth *et al*[29].

CONCLUSION

In conclusion, hesitancy to admit cancer patients to the ICU for advance life supporting therapy is no longer justified if this decision is made based only on the presence of cancer. The clinical oncologist, hematologist and surgical oncologist should be trained with clinical capabilities that will impact in short term outcomes of patients, not only requesting admission to the ICU when they already have vasopressor requirements, mechanical ventilation, multiple organ failures or palliative care is the only treatment option. Moreover, we should take into account that critically ill cancer patients should be evaluated likewise every other patient before admission to the ICU.

Our aim is to emphasize the clinical relevance of implementing preventive measures to avoid in-hospital death of cancer patients, identifying them at an earlier stage of organ failures, when offering full support to those patients who selectively are candidates to ICU admission will impact on their final outcome.

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REVIEW

Brain-lung crosstalk: Implications for neurocritical care patients

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Abstract

Major pulmonary disorders may occur after brain injuries as ventilator-associated pneumonia, acute respiratory distress syndrome or neurogenic pulmonary edema. They are key points for the management of brain-injured patients because respiratory failure and mechanical ventilation seem to be a risk factor for increased mortality, poor neurological outcome and longer intensive care unit or hospital length of stay. Brain and lung strongly interact *via* complex pathways from the brain to the lung but also from the lung to the brain. Several hypotheses have been proposed with a particular interest for the recently described "double hit" model. Ventilator setting in brain-injured patients with lung injuries has been poorly studied and intensivists are often fearful to use some parts of protective ventilation in patients with brain injury. This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

Key words: Brain-lung crosstalk; Brain injury; Lung injury; Protective ventilation; Double hit model

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Core tip: Brain lung crosstalk is a complex interaction from the brain to the lung but also from the lung to the brain. Intensivists are often fearful to use some parts of protective ventilation in patients with brain injuries but if correctly applied, mechanical ventilation could have beneficial effect on brain oxygenation, even if positive end-expiratory pressure and recruitment maneuvers are used. This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

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INTRODUCTION

Brain lung crosstalk is a complex interaction from the brain to the lung but also from the lung to the brain. The occurrence of severe pulmonary injuries after experiencing a brain injury, such as severe traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) or stroke, has been described[1-5]. These pulmonary injuries include ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary edema (NPE). They are key points for the management of brain-injured patients because respiratory failure and mechanical ventilation seem to be a risk factor for increased mortality, poor neurological outcome and longer intensive care unit (ICU) or hospital length of stay (LOS)[4-9]. The pathophysiology of brain-lung interaction is complex and several hypotheses have been proposed with a particular interest for the recently described "double hit" model[1].

This review aims to describe the epidemiology and pathophysiology of lung injuries in brain-injured patients, but also the impact of different modalities of mechanical ventilation on the brain in the context of acute brain injury.

LUNG INJURIES AFTER BRAIN INJURIES

Major pulmonary disorders may occur after brain injuries as VAP, ARDS or NPE. In this review, the direct consequences of chest trauma, such as rib fractures, lung contusions or hemo/pneumothorax will not be discussed in the present review. Zygun *et al*[6], in an observational cohort study, reported non-neurologic organ dysfunctions in 209 patients with severe TBI. Eighty-nine percent of patients had at least one non-neurologic dysfunction (organ system component score $\geqslant$ 1), and 81% of patients developed respiratory dysfunction [arterial partial pressure of oxygen/inspired fraction of oxygen ratio (PaO_2/FiO_2) = 226-300]. Thirty-five percent of patients developed at least one organ failure (organ system component score $\geqslant$ 3), and the most common non-neurologic organ system failure was severe respiratory failure ($PaO_2/FiO_2 \leqslant 150$), occurring in 23% of patients. Other multicenter studies have also reported high incidence of extracerebral organ dysfunctions after TBI[10] or SAH[11]. These extracerebral organ failures, especially respiratory failure and ICU-acquired sepsis, seem to be more frequent in patients with brain injuries than in patients with non-neurologic conditions[12].

Lung injuries are frequent and can lead to significant consequences for patients with brain injuries by directly altering outcomes. Respiratory failure and mechanical ventilation appear to be risk factors for increased mortality and poor neurological outcomes in patients with brain injuries[6-9] and are associated with longer ICU and hospital LOS[4,5]. Pelosi *et al*[13], in a recent prospective observational and multicenter study, described outcomes among mechanically ventilated patients with various types of brain injuries (362 patients with ischemic or hemorrhagic stroke and 190 patients with brain trauma) and compared them to non-neurologic patients. Respiratory failure was the most frequent extracerebral organ dysfunction in neurologic patients. Patients with neurologic disease who were mechanically ventilated had longer ICU and ventilator-days, more tracheostomy requirement, more VAP and higher mortality rates than non-neurologic patients.

VAP

Pneumonia and VAP are frequently encountered in neurologic patients due to decrease in the level of consciousness and massive aspiration or even microaspirations[14]. Risk factors for developing VAP in brain-injured patients have been identified: polytransfusion, age, obesity, diabetes, immunocompromized status, chronic pulmonary disease and use of barbiturates[15]. Moreover, mechanical ventilation, sedation and myorelaxant use, previous antibiotic therapy and the absence of proclive position during mechanical ventilation increase the risk of developing VAP[16]. Additionally, brain injury-induced immunosuppression promotes the development of infectious diseases[17-20].

The incidence of VAP in patients with severe TBI is 21% to 60%[15,21,22]. *Methicillin-susceptible Staphylococcus aureus* is the most common pathogen reported in VAP in patients with severe TBI. Early enteral feeding and oral care has been shown to decrease the incidence of VAP in the neuro-ICU[22,23]. Pelosi *et al*[13] reported a higher rate of VAP in patients with TBI compared to patients with ischemic or hemorrhagic stroke and non-neurologic patients.

Cinotti *et al*[24] reported a retrospective analysis of 193 patients with SAH who were mechanically ventilated. VAP occurred in 48.7% of the patients, and the main responsible pathogen was also *Methicillin-susceptible Staphylococcus aureus*. This study did not find an increase in the mortality for these patients, but a longer duration of mechanical ventilation and ICU LOS[24]. Frontera *et al*[25] analyzed data of 573 patients with SAH (with or without mechanical ventilation) and quantified the prevalence of nosocomial infectious complications. The most common complication was pneumonia with a prevalence of 20%. Pneumonia was an independent factor for mortality or severe disability at 3 mo[25].

Kasuya *et al*[26] observed a 28% rate of VAP in 111 stroke patients on mechanical ventilation. VAP prolonged the duration mechanical ventilation and ICU LOS. Chronic lung disease, National Institute of

Health Stroke Score at admission and hemorrhagic transformation were independent risk factors for VAP. The most common responsible bacteria were *Methicillin-resistant Staphylococcus aureus* and *Methicillin-susceptible Staphylococcus aureus*[26]. In patients with severe ischemic stroke, VAP increased mortality by 3-fold[27].

ARDS

ARDS occur with a high incidence rate in patients with brain injuries. The definition of ARDS used in most of the studies is the American-European consensus conference criteria[28]. A recent study reported an incidence of 35% of ARDS in a cohort of 192 patients with neurologic disorders (hemorrhagic stroke, SAH, subdural hematoma, TBI and ischemic stroke)[29]. Other studies have shown an ARDS incidence of 19% to 35% in patients with a glasgow coma scale (GCS) score < 9[12,29,30].

Patients with isolated TBI present 20%-25% of ARDS[31,32], and patients with SAH present 20%-38% of ARDS[3,7,33]. A recent retrospective study conducted from 1994 to 2008 in the United States of America reported an incidence of ARDS in admissions of patients with acute ischemic stroke of 4%[4]. Aspiration-related ARDS was diagnosed in 3.6% patients in another recent retrospective cohort study on 1495 patients with acute stroke[34].

In all cases, ARDS impacts the morbidity and mortality of patients with brain injuries[4,7,30,35,36]. Occurrence of ARDS after TBI leads to a 3-fold increase in hospital mortality[32]. ARDS is an independent risk factor for increased mortality and poor neurologic outcomes and is associated with longer ICU and hospital LOS[4,30]. Risk factors have been identified for the development of ARDS. First, the severity of the initial brain injury revealed by low Glasgow coma score (GCS 3-4) and initial cerebral computed tomography (CT) scan abnormalities (midline shift and global CT findings)[31,35,36]. Secondly, induced hypertension, administration of vasoactive drugs and a history of drug abuse have been reported as independent factors for ARDS in severe TBI[35]. Finally, general risk factors have been identified such as young age, male gender, ethnicity, history of chronic arterial hypertension, diabetes, chronic obstructive pulmonary disease, development of sepsis, cardiovascular, renal and hematological dysfunctions[4,32,37]. Recently, Mascia *et al*[30] described the ventilatory management of 82 patients with severe TBI in a prospective multicenter observational study. Twenty-two percent of the patients developed ARDS, and these patients initially had higher tidal volumes (Vt) than patients without ARDS. The proportion of ARDS increased with Vt settings in a dose-response relationship. In the days preceding ARDS, 72% of patients with ARDS had a mean Vt $\geqslant$ 10 mL/kg predicted body weight (PBW)[30]. The ventilator management of patients with severe TBI seems to be a key point in ARDS development and fits into the "double hit" model which will be detailed later in this review.

The ARDS distribution over the time is bimodal, with an early peak on day 2-3 after the onset of mechanical ventilation and a later peak on day 7-8[10], often related to pneumonia[15].

NPE

NPE has been described for more than 100 years[38]. It has been defined as a clinical entity with an acute onset of protein-rich lung edema after significant central nervous system injuries such as TBI, SAH, stroke, spinal cord injury, status epilepticus, meningitis or subdural hemorrhage and the exclusion of other plausible causes[39-42].

In a review on NPE cases reported from 1990 to 2003, the most frequent neurologic injury was SAH (42.9%) and symptom onset was < 4 h after brain injury in 71.4% of patients. The mortality rate of NPE was high, nearing 10%, but patients who survived usually recover very quickly (< 72 h for 52.4%)[41]. Rogers *et al*[40] reported a large autopsy database of patients with head injuries who died at the scene or within 96 h of injury. The diagnosis of NPE included the presence of edema, congestion and hemorrhage associated with an increase in lung weight. The incidence of NPE in isolated TBI patients who died at the scene was 32%. It reached 50% for patients who died within 96 h. An inverse correlation between cerebral perfusion pressure and the PaO_2/FiO_2 ratio was observed, even if the chest X-ray was considered normal[40]. The incidence of NPE in aneurysmal SAH varies from 2% to 25%[11,43]. The incidence seems to be higher in fatal SAH[44]. Risk factors identified are old age, delay to surgery, vertebral artery surgery and the severity of clinical and CT-scan scores (Hun-Hess and Fisher grades)[11,45]. The occurrence of NPE after SAH is associated with poor outcomes and higher mortality[46,47].

NPE can be considered as a form of ARDS with the consensus definition. So, some authors proposed the following diagnostic criteria: (1) bilateral infiltrates; (2) PaO_2/FiO_2 ratio < 200; (3) no evidence of left atrial hypertension; (4) presence of severe central nervous system injury that has caused increased intracranial pressure (ICP); and (5) absence of other common causes of ARDS (*e.g.*, aspiration, massive blood transfusion or sepsis)[48].

PATHOPHYSIOLOGY OF BRAIN-LUNG CROSSTALK

Brain to lung pathway

The pathophysiology of lung injuries after an acute brain injury is still in debate, and several theories have been proposed; recently, the "double hit" model has been described[1].

The sympathetic response to increased ICP has an important role. Some authors explained some parts

of NPE with neuro-cardiac and neuro-hemodynamic paradigms[48]. It has been well demonstrated that direct myocardial injury with Takotsubo's cardiomyopathy, can participate to NPE[49-51]. Massive sympathetic discharge following brain injuries seems to induce direct myocyte injuries with wall motion abnormalities that follow a pattern of sympathetic nerve innervation[52]. The neuro-hemodynamic theory is defined by indirect ventricular compliance impairment resulting from rapid increases in systemic and pulmonary pressures. Indeed, translocation of blood flow from the highly resistant systemic circulation to the low resistance pulmonary circulation causes a hydrostatic form of pulmonary edema[53]. Animal models have shown an increase in left atrial, systemic and pulmonary pressures associated with NPE[54-56]. Although hydrostatic pressure and cardiac impairment most likely play a role in the pathogenesis of NPE, these theories do not explain the presence of red blood cells and protein in the alveolar fluid[57].

The blast theory

Theodore and Robin first defined the "blast theory" of NPE as an impairment of vascular permeability[58]. The transient increase of intravascular pressure, caused by an acute increase in ICP, damages the capillary-alveolar membrane. So, pulmonary endothelium injuries cause a leak of protein-rich plasma[58]. This theory includes the coexistence of high hydrostatic pressure and pulmonary endothelium injury. Some degree of capillary hypertension seems necessary for the occurrence of this pulmonary edema, and a pressure-dependent increase in permeability may be a common point in NPE[59,60]. Animal models have allowed the exploration of this theory. Maron *et al*[59] reported in canine isolated perfused lung lobes, a minimum of 70 torr of venous pressure is necessary to have protein permeability and to note a linear correlation between the increase in venous pressure and the osmotic reflection coefficient for total proteins[59]. Bosso *et al*[60] explored the relationship between the degree of pulmonary hypertension and post-mortem extravascular lung water content (EVLW) in rabbits with intracranial hypertension. The pulmonary arterial pressure had to exceed 25 torr to observe an increase in extravascular lung water[60]. In contrast, Bowers *et al*[61] determined the effects of intracranial hypertension in a sheep model by measuring the flow rate and protein content of lung lymph. They noted a constant increase in lung vascular permeability but with inconstant increase in pulmonary vascular pressure[61]. Few reports are available in humans because hemodynamic monitoring at the time of the initial severe increase in ICP is rare. After this initial hemodynamic instability and massive sympathetic response, systemic and pulmonary pressures could return to normal values, whereas capillary-alveolar membrane damage persists[58,62]. Some authors observed no changes in systemic pressure, despite the occurrence of NPE underlying direct pulmonary endothelial damage following brain injury[63]. This concept has been called "pulmonary venule adrenergic hypersensitivity".

Pulmonary venule adrenergic hypersensitivity

Some human cases with continuous hemodynamic monitoring reported NPE without hemodynamic instability[63,64]. So, the NPE may result, in part, from select pulmonary venoconstriction after massive sympathetic discharge following brain injury. Pulmonary vessels have α- and β-adrenergic receptors that may be activated leading to endothelial integrity changes[65]. Animal models demonstrate an increase in pulmonary vascular permeability and edema formation that could not be explained by hemodynamic changes alone[61,66]. In anesthetized dogs with raised ICP, McClellan *et al*[66] noted a 3-fold increase in pulmonary vascular permeability (exudative edema) with a moderate increase in pulmonary arterial pressures and cardiac output. However, when they reproduced these hemodynamic changes in dogs without intracranial hypertension, they did not report any changes in the protein leak index[66]. Peterson *et al*[67] administered α-adrenergic blockers to anesthetized sheep with progressive levels of intracranial hypertension. They reported the prevention of pulmonary edema formation with minor systemic arterial pressure effects supporting a direct adrenergic action on the pulmonary vascular bed[67].

Double hit model

Systemic inflammatory response appeared to play a major role in the development of pulmonary failure after acute brain injury. This pathophysiological process completes the blast injury theory[1,68]. Intracranial inflammatory response occurs after brain injury, and pro-inflammatory cytokines [interleukin 1 (IL-1), IL-6), tumor necrosis factor (TNF), IL-8] are produced locally in cerebral injured tissue[69]. Microglia and astrocytes are the principal source of inflammatory mediators. Then, alteration of the blood brain barrier (BBB) permeability allows their discharge into the systemic circulation with a transcranial gradient. This could be responsible for extracerebral dysfunctions[70-72]. This systemic production of inflammatory mediators constitutes an inflammatory environment: the "first hit". Organ are therefore more susceptible to subsequent events, the "second hit", such as mechanical ventilation, infections or surgical procedures, that are in normal condition harmless[1] (Figure 1). López-Aguilar *et al*[73] randomized rabbits to control or brain injured group with a 120 min mechanical ventilation with the same ventilator settings followed by aggressive mechanical ventilation. In the brain-injured group, lungs had more changes in the ultrafiltration coefficient, weight and alveolar hemorrhage[73]. Hyperactivated neutrophils and leukocyte-endothelial cell interactions could probably have contributed to this pathological process[74]. Acute inflammatory response in both brain and lung after brain injury has been

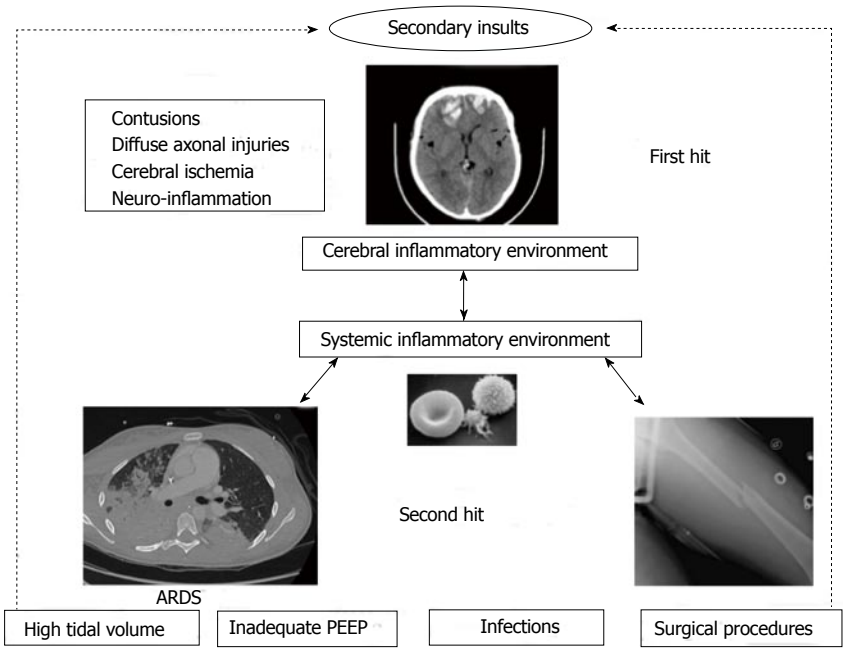

Figure 1 The double hit model in the context of brain injury. ARDS: Acute respiratory distress syndrome; PEEP: Positive end-expiratory pressure.

shown in human and animal. Experimental intracerebral hemorrhage injury is accompanied by an increase in intracellular adhesion molecule-1 and tissue factor in both brain and lung. Progressive neutrophil recruitment and morphological pulmonary damage such as disruption of alveolar structures has been observed[75]. Kalsotra *et al*[76] showed a large migration of macrophages and neutrophils in the major airways and alveolar spaces after brain injury in rats, with an increase of leukotriene B4 production within the lung[76]. Brain-dead human donors have significantly higher IL-8 levels in the broncho-alveolar lavage compared to healthy subjects or ventilated non brain-dead patients. Moreover, neutrophil infiltration in the lungs well correlates with levels of IL-8[77]. In a rat weight-drop model of TBI, ultrastructural damage in type II pneumocytes with important intracellular vacuoles and increased lipid peroxidation have been reported[78]. Recently, Heuer *et al*[79] studied pigs with acute intracranial hypertension. They reported higher scores of inflammation, edema and necrosis in the lung and other organs compared with control pigs without intracranial hypertension despite the absence of hypoperfusion and hypoxemia[79]. Previously, they compared 4 groups of pigs: control, with intracranial hypertension, with ARDS and with intracranial hypertension + ARDS. They analyzed lung CT-scans of each group. Intracranial hypertension alone increased lung density and exacerbated the increase in lung density in pigs with ARDS. Moreover, the gas-tissue ratio of the lung was decreased by intracranial hypertension in normal and injured lungs with an increase of poorly aerated and atelectatic lung areas. These lung CT-scan injuries were exacerbated by intracranial hypertension[74].

The catecholamine storm, in conjunction with the cerebral and systemic inflammatory reaction (first hit) creates an inflammatory environment leading to an increased susceptibility of the lung to further injurious events (second hit). This pathway could be the bed for lung injuries in patients with acute cerebral damage. However, this inflammatory cascade does not occur only in one way: from the brain to the lung, but also from the lung to the brain.

Hypothalamo-pituitary adrenal axis

Since several years, hypothalamo-pituitary adrenal axis [Hypothalamo-pituitary adrenal (HPA) axis] in brain injury has been explored in experimental and clinical studies and it could participate to lung dysfunction. Indeed, it has major effects on stress and systemic inflammatory response after trauma[80,81]. In the initial phase of trauma, inflammation mediators, such as IL-6, activate massively HAP axis to induce an initial hypercortisolism, main effector of compensatory anti-inflammatory response syndrome[80,82,83]. This hyper-cortisolism allow decreasing deleterious effects of inflammatory response, as its spread in organism and protect also other organs[81,84]. Moreover, endogenous glucocorticoids stimulate anti-infectious immunity[85] and HAP axis has major role in hemodynamic response and maintain of blood pressure[86,87].

After TBI, 25%-50% of patients present an acute secondary adrenal insufficiency[88-91]. These patients had worse outcomes and neurologic prognostic, lower arterial pressure, greater vasopressor use and higher mortality rate[88,89,92,93]. Moreover, trauma-induced adrenal insufficiency is correlated with systemic inflammatory response syndrome[94]. Patients with adrenal insufficiency have longer high plasma IL-6 levels than patients with normal adrenal response to

stress[89,95]. In multiple-injured patients, persistence of high IL-6 plasma level at day 7 is associated with higher mortality rate and incidence of pneumonia[96]. Persistence of systemic inflammatory response syndrome seems to be predictive of nosocomial infection in trauma patients[97,98]. The principal theory is that secondary adrenal insufficiency exposes patients to deleterious effects of uncontrolled systemic inflammation with immunodepression, nosocomial infections, especially VAP and overwhelming inflammatory response[90,98,99]. So this HAP axis dysfunction could participate to weaken the lung after TBI.

A multicenter, randomized trial reported in 150 intubated patients with severe trauma and corticosteroid insufficiency, a decrease risk of hospital-acquired pneumonia with stress-dose of hydrocortisone, particularly in the sub-group of patients with severe TBI[100]. However, this result was not confirmed with recent trial in patients with severe TBI[101]. Stroke-induced immunodepression has been described with HAP axis-related abnormalities following acute ischemic stroke[102] and is probably implicated in high incidence of pneumonia[103].

Lung to brain pathway

A complex pathway throughout autonomic, neuro-inflammatory, neuro-endocrine and immunologic systems has been described. This pathway is involved in normal physiology to contribute to maintain homeostasis, but may lead to adverse effects[104]. Two components may be involved in this lung to brain pathway: lung injuries themselves, such as ARDS, and mechanical ventilation.

Lung injuries due to inadequate ventilator settings, could result in an inflammatory response, initially located in the lung parenchyma. But this could extend to the systemic circulation and then to other organs and the brain. Multi-organ failure can occur as a result of pulmonary injuries[105]. The main cause of mortality in patients with ARDS is multiple organ failure and not hypoxemia or pulmonary dysfunction[106]. It has been well described that ARDS survivors have cognitive deterioration including memory, language and cognitive decline[107-109] and that patients with a long duration of mechanical ventilation present neurologic impairment with memory and cognitive alteration[110]. The hippocampus, which is involved in learning and memory processes, is particularly vulnerable to hypoxia[111]. However, ARDS can lead to hippocampal injuries with memory defects, regardless of the degree of hypoxia[112]. ARDS, in the same way than septic shock, can induce neuronal damages. Nguyen *et al*[113] studied 170 patients with severe sepsis or septic shock in a prospective study. They found an increase in plasmatic marker of brain damages as S-100β protein and neuron-specific enolase (NSE) in respectively 42% and 53% of these patients[114]. High S-100β protein levels were reported in patients with decreased consciousness and encephalopathy. In pig models of ARDS (lavage model), S-100β protein levels were significantly higher than in pigs with hypoxemia induced by lavage than when hypoxia was induced by reducing the inspired oxygen fraction[115]. Moreover, histopathologic changes in the hippocampus occurred only in pigs with ARDS. The authors suggested that brain damage could only be observed in ARDS independently to hypoxemia. S-100β protein and NSE might represent cerebral injuries and BBB alterations in patients with ARDS[113]. Permeability of both the blood-brain and lung barriers can be altered by pathophysiologic situations and allows communication between the brain and the lung[116].

Lung injuries may aggravate the sensitivity of the brain to acute injuries. In their previous study, Heuer *et al*[74] reported brain damage in pigs with ARDS alone and reciprocal synergistic effects between the lung and brain with worsening of brain damage in the group with ARDS + intracranial hypertension[74]. Indeed, cerebral tissue oxygenation ($PtiO_2$) and brain tissue density (reflecting cerebral edema) decreased in all animals (intracranial hypertension, ARDS and ARDS + intracranial hypertension) compared to the control group. NSE and S-100β protein levels increased significantly in all animals compared to the control group, but the most marked increase was in the group with ARDS, as for IL-1β and IL-6. So ARDS could exacerbate cerebral damage in acute cerebral hypertension. Hegeman *et al*[105] described, after injurious stress and strain in the lung, inflammation of the alveoli, recruitment of neutrophils and production of cytokines. Endothelial cells, activated by cytokines, secrete chemokines and express adhesion molecules on their surface, leading to enhanced leukocyte adhesiveness and transmigration of active immune cells across the endothelium[105]. This local inflammation can then spread into the systemic circulation. Lung inflammation could spread to the cerebral system through humoral, cellular and neural pathways[116].

Beyond pulmonary injuries, mechanical ventilation strategies, used daily in the ICU, could impair regional blood flow and brain oxygenation. Indeed, Bickenbach *et al*[117] studied $PtiO_2$ and cerebral metabolism in a porcine model of ARDS over 8 h. Pigs were randomized in 2 groups: low tidal (LT) volume (6 mL/kg) and high tidal (HT) volume (12 mL/kg)[117]. No differences between the two groups were found in terms of PaO_2, $PaCO_2$ and pH. ARDS induced a significant decrease in $PtiO_2$ in both groups, but the $PtiO_2$ increased significantly at 4 and 8 h in the LT group compared to the HT group. Lactates in microdialysis were higher in the HT group at 2, 4 and 8 h. After 2 h, the plasmatic S-100 protein level decreased in the LT group, and IL-6 increased in the HT group. Therefore, LT volume ventilation improved cerebral tissue oxygenation compared to HT volume ventilation in ARDS. HT volume ventilation could increase the inflammatory response and could impair cerebral oxygenation and metabolism. Quilez *et al*[118] studied the effect of Vt on activation in areas of

the brain in a rat model of MV with c-fos expression, a marker of neuronal activation. They randomized 3 groups of healthy-brain rats: basal (not submitted to mechanical ventilation), low Vt (8 mL/kg and positive end-expiratory pressure (PEEP) of 0 cmH_2O) and high Vt (30 mL/kg and PEEP of 0 cmH_2O). The inflammatory response (TNF-α) and c-fos expression in the retrosplenial cortex and thalamus were higher in the high Vt group than in the low Vt group[118]. So, setting of mechanical ventilation can directly affect the brain, most likely *via* inflammatory mediators. These data highlight the importance of the ventilator setting in patients undergoing mechanical ventilation and particularly in brain injured patients.

THE CONFLICT BETWEEN THE LUNG AND THE BRAIN

Mechanical ventilation allows the supply of oxygen and the removal of carbon dioxide (CO_2) with tight control of the PaO_2 and $PaCO_2$, the goal is to prevent secondary cerebral ischemia and increase neurologic outcomes.

To prevent or limit Ventilation-Induced Lung Injury (VILI) the concept of protective ventilation has been developed using with low Vt, plateau pressure < 30 cmH_2O and adequate PEEP levels[119]. VILI has been described as the results of 3 mechanisms: volotrauma, atelectrauma and biotrauma[120,121]. Volotrauma results from overdistension of the lung parenchyma with a high Vt. Atelectrauma results from the recruitment-derecruitment of collapsed alveoli due to an inadequate PEEP level. Biotrauma comes from a local inflammatory process due to overdistending tidal volumes and repetitive opening and closing lung units. However, most of the studies that have enhanced ventilation strategy in ARDS patients have excluded brain-injured patients[122-124]. The concept of "open the lung and keep it open" for ARDS with a low Vt, high PEEP and recruitment maneuvers, with permissive hypercapnia could have potential deleterious consequences on the brain, and intensivists are often fearful to use some parts of protective ventilation in patients with brain injury.

Tidal volume

The use of low Vt decreases systemic and pulmonary inflammatory responses in patients with ARDS[124-126] but also in patients with inflammatory processes such as aspiration, sepsis, pneumonia or trauma[127,128]. Mascia *et al*[30] reported that the proportion of ARDS in patients with severe TBI increased with higher initial tidal volume (Vt) settings in a dose-response relationship[30]. The ventilator management of patients with severe TBI seems to be a key point of ARDS development. As we described before high Vt could affect the brain and could be an injurious event (second hit) in the lung that is particularly sensitive due to brain injury. There is no prospective study regarding the use of low Vt in TBI patients. However, recently, Krebs *et al*[129] reported in rats with massive brain damage that a low Vt (6 mL/kg) with open lung PEEP (set according to the minimal static elastance of the respiratory system) compared to a high Vt (12 mL/kg) and low PEEP improved oxygenation reduced lung damage according to histology, genome analysis and real-time quantitative polymerase chain reaction with a decrease of IL-6[129].

The protective mechanical ventilation for ARDS includes low Vt (6 mL/kg PBW) and then low minute ventilation, with consequently permissive hypercapnia. Cerebral effects of hypercapnia are well known (vasodilation) and should be avoided in case of intracranial hypertension[130]. Objectives for the management of severe TBI are maintaining the $PaCO_2$ between 35 to 40 mmHg[131] but this goal is sometimes not possible when using protective mechanical ventilation. Individualized management with neuromonitoring could allow us, in specific difficult cases, to use higher values of $PaCO_2$ and supervise its impact on brain homeostasis. A small retrospective study in 12 patients with SAH and ARDS reported no increase in ICP with lung protective ventilation and hypercapnia (50-60 mmHg)[132]. Recently, Westermaier *et al*[133] performed a gradual increase of $PaCO_2$ to 40, 50 and 60 mmHg in patients with poor-grade SAH. Cerebral blood flow and brain tissue oxygen saturation ($StiO_2$) reacted with sustained elevation without an increase in intracranial pressure[133].

PEEP

Application of PEEP is part of the protective mechanical ventilation to recruit collapsed alveoli, improve PaO_2 and lung compliance[134]. However, the use of PEEP may alter the cerebral blood flow by CO_2-mediated and hemodynamic repercussion[135,136]. Therefore, Pelosi *et al*[13] reported in a prospective observational multicenter study that more than 80% of neurologic patients in the ICU were ventilated with a PEEP $\leqslant$ 5 cmH_2O[13]. PEEP is necessary to prevent collapse and/or recruit collapsed alveoli and thereby reduce atelectasis, especially when low Vt is used. Its application is also a key point of protective ventilation.

Some studies reported the effects of PEEP on cerebral hemodynamics. Mascia *et al*[137] randomly applied PEEP at 5 and 10 cmH_2O in 12 brain-injured patients with ARDS. Patients who were responders had decreased elastance and increased PaO_2, while patients who were non-responders had an increase of elastance and $PaCO_2$. Intracranial pressure and jugular saturation were constant in recruiters but increased in non-recruiters suggesting deleterious effects in this group[137]. Therefore, the use of PEEP in brain-injured patients seems to be safe when patients are responders to the PEEP level (*i.e.*, not creating overdistension, increase in dead space and in $PaCO_2$)[138]. When PEEP induces lung recruitment, intracranial pressure and cerebral perfusion do not change, and PaO_2 increases[1]. PEEP could be safety used and must probably be used in brain-injured patients if the optimal PEEP is searched and adapted

individually, as for patients with ARDS and a healthy brain.

Muench *et al*[139] examined the influence of PEEP levels on intracranial pressure, $PtiO_2$, cerebral blood flow and systemic hemodynamics in healthy pigs and patients with SAH[139]. High levels of PEEP did not influence cerebral parameters in pigs. In patients with SAH, changes in the regional cerebral blood flow were reported, resulting from arterial pressure changes and altered cerebral autoregulation. Normalization of systemic arterial pressure restored cerebral blood flow. Recently, Schramm *et al*[140] measured cerebral blood flow in 20 patients with ARDS. An increase in PEEP from 9 to 14 cmH_2O did not influence blood flow velocity. Caricato *et al*[141] examined the effect of respiratory system compliance on the intracranial effects of PEEP. No impact on cerebral and systemic hemodynamics were reported with 0, 5, 8 or 12 cmH_2O of PEEP[141]. The use of PEEP appears to be safe, if arterial blood pressure is maintained. Euvolemia is probably a condition that can minimize the effect of PEEP on arterial blood pressure[139,142,143].

Moreover, some authors recommend to optimize elevation of the head to enhance cerebro-venous drainage through the vertebral venous system, not subjected to intrathoracic pressure and to maintain PEEP lower than ICP to limit interference with venous outflow[1,144,145].

An accurate monitoring of macrohemodynamic, respiratory system and cerebral parameters is needed to optimize the use of PEEP in brain-injured patients.

Recruitment maneuvers

Several studies in patients with ARDS recommended recruitment maneuvers (RM) to recruit collapsed pulmonary alveoli and open the lung followed by appropriate PEEP to maintain recruitment of the lung leading to improvement of oxygenation and compliance of the respiratory system[146,147]. However, for the same reasons as PEEP, RM could decrease arterial blood pressure and increase ICP by interfering with venous blood return and causing an increase in intrathoracic pressure[137]. Bein *et al*[148] reported in 11 patients with severe cerebral lesions (traumatic and non-traumatic) and ARDS, the effects of RM, which included sustaining 60 cmH_2O for 30 s[148]. They recorded an increase in ICP, a decrease in mean arterial pressure, cerebral perfusion pressure (< 65 mmHg) and jugular oxygen saturation (< 55%) at the end of the RM. The improvement of arterial oxygenation was reported just after the RM but was not maintained after. Therefore, the authors did not recommend this maneuver. The impact on cerebral blood flow and intracranial pressure depends on the hemodynamic tolerance of RM. Re-aeration of lung units depends not only on the inflating pressure but also on the duration of sustained pressure (inflating pressure-time product)[149-151]. Constantin *et al*[146] compared 2 RM: continuous airway pressure (CPAP) with 40 cmH_2O for 40 s and extended sigh (eSigh) with PEEP maintained at 10 cmH_2O above the lower inflection point for 15 min[146]. They reported that only eSigh increased recruited volume and that eSigh was hemodynamically better tolerated than CPAP and induced a greater and more prolonged increase in arterial oxygenation. Moreover, response to RM seems to depend on the lung morphology. Patients with diffuse loss of aeration are more responsive than patients with a focal loss of aeration[152]. These parameters have to be considered before using RM. Therefore, eSigh may be better adapted to patients with severe brain injuries due to its better hemodynamic tolerance. Nemer *et al*[153] compared 2 RM: CPAP at 35 cmH_2O for 40 s and PEEP of 15 cmH_2O and pressure control above PEEP of 35 cmH_2O for 2 min in patients with SAH and ARDS[153]. CPAP recruitment leads to higher intracranial pressure (> 20 mmHg) and lower cerebral perfusion pressure (< 65 mmHg). In another study, 28 RMs were performed in 9 patients with ARDS and cerebral injury in a stepwise with 3 cmH_2O increments and decrements of PEEP. No significant differences were found for mean arterial pressure, intracranial pressure and cerebral perfusion pressure after RMs compared with baseline values[154]. Therefore the use of RM may be safe and possible with strict monitoring of systemic and cerebral parameters and use of progressive and soft maneuvers.

Wolf *et al*[155] evaluated the feasibility of the "open lung approach" with low tidal volume, a high level of PEEP and RM in 13 patients with acute brain injury and ARDS[155]. They reported a decrease of FiO_2 from 0.85 to 0.55, 24 h after the first RM with an increase of PaO_2/FiO_2 from 142 to 257. In parallel, intracranial pressure, $PaCO_2$ and $PtiO_2$ remained stable. The authors concluded that protective ventilation is safe in neurosurgical patients and improves oxygenation without side effects.

Prone position

Prone position has been used for 30 years in patients with ARDS. It has been proven to increase oxygenation with different mechanisms such as net recruitment, more homogeneous distribution of alveolar inflation and protection of VILI. Benefits in terms of outcomes and mortality have been shown in severely hypoxemic ARDS if a sufficient duration of prone position is used[156-158]. This respiratory management has been sparsely studied in patients with cerebral injuries. Some authors reported cases or series of prone position[159-161]. Reinprecht *et al*[159] analyzed the effect of this position in 16 patients with severe SAH and ARDS. They reported a significant increase in PaO_2 and $PtiO_2$ with significant, but not deleterious, increases in intracranial pressure and decreases in cerebral perfusion pressure[159]. A case report of a patient with severe traumatic chest and brain injuries showed improvement of oxygenation with a moderate, but very transient, increase in intracranial pressure after 20 h of prone position[161].

The Table 1 summarizes the effects of different parts

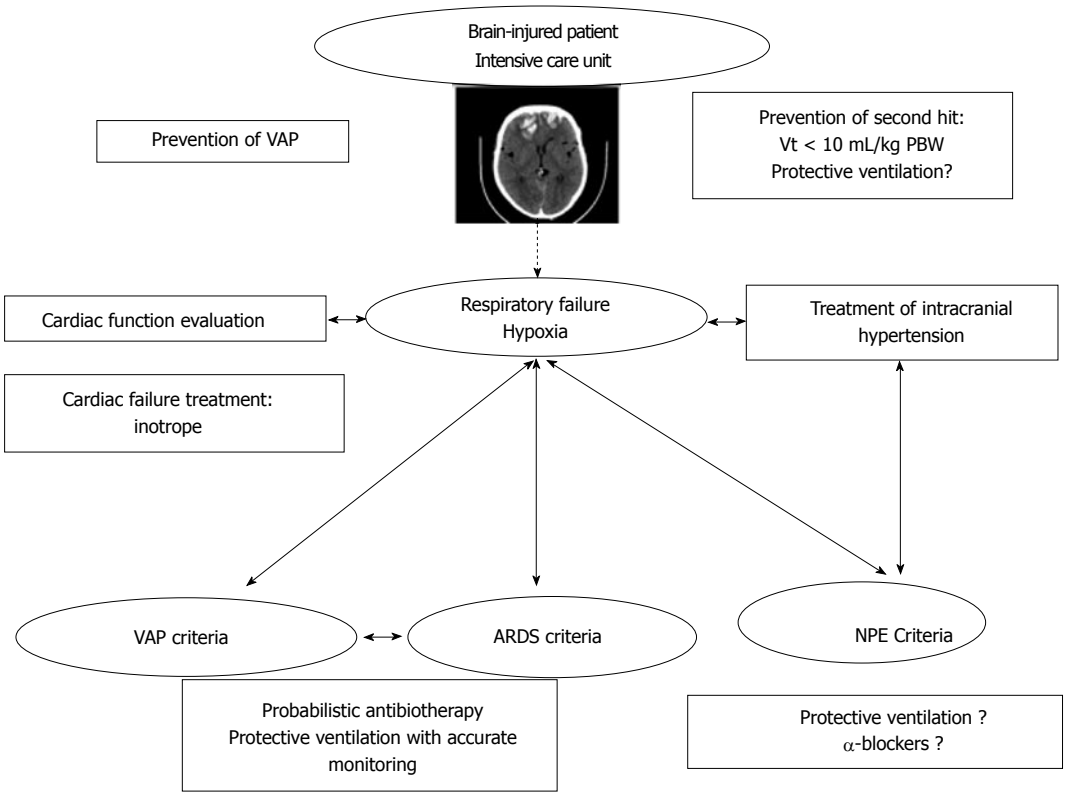

Figure 2 Algorithm approach for pulmonary dysfunction in brain-injured patient. ARDS: Acute respiratory distress syndrome; VAP: Ventilator-associated pneumonia; Vt: Tidal volume; PBW: Predictive body weight; NPE: Neurogenic pulmonary edema.

Table 1 Effects of protective ventilation on brain hemodynamic and metabolism

	CBF	ICP	CPP	$P_{ti}O_2$	SjO_2	Lactates (microdialysis)
High Vt In pigs with ARDS[117]				↓		↑
Low Vt In pigs with ARDS[117]				↑		↓
Permissive hypercapnia ($PaCO_2$: 40-60 mmHg) in patients with SAH[132,133]	↑	=	=	↑		
PEEP	= if MAP is maintained[140]	= if responder patient[137] ↑ If non-responder patient[137]	= if responder patient[137] ↓ If non-responder patient[137]			
RM		↑ If MAP decreased[148]	↓ If MAP decreased[148]		↓ If MAP decreased[148]	
Open lung approach (low Vt + high PEEP + RM) in patients with acute brain injury and ARDS[155]		=	=	=		

Responder patient to PEEP: Decrease in elastance and increased PaO_2; Non-responder patient to PEEP: Increase in elastance and $PaCO_2$. CBF: Cerebral blood flow; ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; $P_{ti}O_2$: Cerebral tissue oxygenation; SjO_2: Jugular vein oxygen saturation; Vt: Tidal volume; PEEP: Positive end-expiratory pressure; RM: Recruitment maneuvers; MAP: Mean arterial pressure; ARDS: Acute respiratory distress syndrome.

of protective ventilation on brain hemodynamic and metabolism.

Alternative methods for tight CO_2 control and refractory hypoxia such as high frequency oscillatory ventilation and extracorporeal lung support techniques (percutaneous extracorporeal lung assist and extracorporeal membrane oxygenation) have been poorly evaluated in patients with head injuries[145].

CLINICAL MANAGEMENT OF LUNG INJURIES IN BRAIN-INJURED PATIENTS

In clinical practice, there is actually no recommendation for ventilator strategy of brain-injured patients except

for PaO_2 and $PaCO_2$ targets[131].

Treatment of VAP is not specific for patients with cerebral injuries but it is important to note that prevention seems to be a key point. Treatment of VAP has to be started quickly as VAP is associated with higher mortality rate and poor neurologic outcome. It may follow the guidelines for hospital-acquired and VAP[162]. Risk factors of VAP in brain-injured patients are numerous and prophylactic measures have to focus on these, including oral care[23,103,163]. The high rate of VAP in brain-injured patients is, in part, explained by long duration of mechanical ventilation[164]. So Roquilly *et al*[165] reported in a before/after evaluation of an extubation readiness bundle, a decrease of duration of mechanical ventilation in patients with brain injury[165]. The bundle components were 1/protective ventilation (Vt: 6-8 mL/kg PBW, PEEP > 3 cmH_2O) 2/early enteral nutrition (initiation day 1 and 25 kCal/kg per day before day 3) 3/optimization of the probabilistic antibiotherapy for VAP and 4/a systematic approach of extubation (ventilator weaning and removal of tube if Glasgow Coma Scale $\geqslant$ 10 and cough). Despite a compliance with bundle elements of 21% in the intervention phase, they observed a reduction of duration of mechanical ventilation, rate of VAP and rate of unplanned extubation compared to the control observational phase. In acute stroke, the major measure is to avoid per os nutrition until swallowing is evaluated and validated[166-168]. No difference has been found between percutaneous gastrostomy or nasal feeding tube in terms of rate of pneumonia but percutaneous gastrostomy tube seems to be safer and more effective for feeding[169]. For TBI, in front of traumatic-induced adrenal insufficiency, the use of stress-dose steroids during initial management are still debated for prevention of VAP but literature doesn't allow us to provide an answer[101].

Concerning NPE, few studies have reported specific treatment in humans. Some animal studies have focused on α-blockers treatment to limit massive sympathetic discharge after brain injuries[48,170]. Two cases of human NPE were published about use of adrenergic blocker (phentolamine or chlorpromazine) and successful treatment with improvement of hemodynamic instability and oxygenation[171,172]. Further studies are needed to explore this way. But the key point of NPE management is to treat the underlying cerebral injuries to decrease ICP, mitigate the sympathetic discharge and improve oxygenation[41,48].

Concerning ARDS, protective ventilation has been largely discussed in the previous section. An accurate monitoring of macrohemodynamic, respiratory and cerebral parameters are needed to optimize the management.

When a brain-injured patient presents hypoxia, all diagnoses evoked in this review could be discussed. The Figure 2 summarizes different steps of management and prevention of respiratory failure in brain-injured patient. The response of the cardiopulmonary system varies widely among patients with brain injury (direct myocardial injury, non-cardiogenic mechanisms, *etc*.). So first of all, it is important to evaluate cardiac function to adapt our management and initiate treatment of cardiogenic failure if necessary. Moreover, normalization of ICP is an important step to decrease sympathetic discharge and its consequences. Criteria of VAP, ARDS and NPE have to be researched and for some patients in which difference between NPE and ARDS could be difficult, measurement of serum catecholamines may be helpful[48].

CONCLUSION

Brain and lung strongly interact *via* complex pathways. In cases of brain injury, therapeutic strategies should protect the brain but also the lung to avoid worsening of both brain and lung dysfunction. If correctly applied, mechanical ventilation could have beneficial effect on brain oxygenation, even if PEEP and recruitment maneuvers are used. Experimental and clinical studies are needed to explore pathophysiological processes and evaluate optimal ventilator setting in brain-injured patients with lung injuries. A strict monitoring of systemic, respiratory and cerebral parameters is probably required to optimize the management of these patients.

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REVIEW

Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function

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Abstract

Cystic fibrosis (CF) is a multisystem disorder with significantly shortened life expectancy. The major cause of mortality and morbidity is lung disease with increasing pulmonary exacerbations and decline in lung function predicting significantly poorer outcomes. The pathogenesis of lung disease in CF is characterised in part by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. This leads to accumulation of viscous mucus in the CF airway, providing an ideal environment for bacterial pathogens to grow and colonise, propagating airway inflammation in CF. The use of nebulised hypertonic saline (HTS) treatments has been shown to improve mucus clearance in CF and impact positively upon exacerbations, quality of life, and lung function. Several mechanisms of HTS likely improve outcome, resulting in clinically relevant enhancement in disease parameters related to increase in mucociliary clearance. There is increasing evidence to suggest that HTS is also beneficial through its anti-inflammatory properties and its ability to reduce bacterial activity and biofilm formation. This review will first describe the use of HTS in treatment of CF focusing on its efficacy and tolerability. The emphasis will then change to the potential benefits of aerosolized HTS for the attenuation of receptor mediated neutrophil functions, including down-regulation of oxidative burst activity, adhesion molecule expression, and the suppression of neutrophil degranulation of proteolytic enzymes.

Key words: Cystic fibrosis; Hypertonic saline; Mucociliary clearance; Neutrophils and inflammation

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Core tip: The pathogenesis of lung disease in cystic

fibrosis (CF) is characterised by decreased airway surface liquid volume and subsequent failure of normal mucociliary clearance. Therapies acting against airway mucus in CF include aerosolized hypertonic saline (HTS). It has been shown that HTS aids mucociliary clearance by restoring the liquid layer lining the airways. However, recent studies are beginning to broaden our view on the beneficial effects of HTS, which now extend to include anti-inflammatory properties. This review aims to discuss the therapeutic benefits of HTS and to identify the potential benefits of aerosolized HTS for attenuation of neutrophil function.

Reeves EP, McCarthy C, McElvaney OJ, Vijayan MSN, White MM, Dunlea DM, Pohl K, Lacey N, McElvaney NG. Inhaled hypertonic saline for cystic fibrosis: Reviewing the potential evidence for modulation of neutrophil signalling and function. *World J Crit Care Med* 2015; 4(3): 179-191 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i3/179.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i3.179

INTRODUCTION TO CYSTIC FIBROSIS AND THE ROLE OF NEUTROPHILS IN DEVELOPING AIRWAYS DISEASE

Cystic fibrosis (CF) is a complex genetic disease leading to increased risk of chronic lung disease resulting in terminal respiratory failure[1,2]. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) chloride channel. Over 1900 CFTR mutations leading to defective chloride transport have been identified to date[3] and result in misfolding of the CFTR protein. Reported mutations can be categorised into different classes depending on whether the mutation alters CFTR processing (Classes Ⅰ, Ⅱ and Ⅴ) or results in dysregulated chloride secretion (Classes Ⅲ, Ⅳ, Ⅵ) (Figure 1). The most common mutation is deletion of phenylalanine at position 508 (ΔF508) which occurs in approximately 70% of patients with CF, and 90% of CF suffers carry one copy[4]. Defects in CFTR protein function not only impact upon cAMP-dependent chloride secretion but also result in increased epithelial sodium channel (ENaC)-mediated ion absorption in the superficial airway epithelium[5,6]. CFTR absence or malfunction causes increased water re-absorption across airway epithelial cells leading to dehydration of the airway surface liquid (ASL) layer, persistent mucus hypersecretion and airflow obstruction[7]. Dehydration of the airway surface liquid layer and mucus accumulation has been implicated in exacerbated airway inflammation[8] and decline in lung function predicts significantly poorer outcomes[9]. Therapeutic interventions to improve mucus clearance is a necessary treatment in CF[10]. Hypertonic saline (HTS) at concentrations of 3% or higher is widely used to improve mucociliary clearance, as this increases the tonicity of the ASL creating an osmotic gradient drawing water into the airway hence improving ASL and facilitating removal of airway secretions (Figure 2). Furthermore, HTS improves lung function and quality of life and significantly decreases the frequency of exacerbations[11,12] and is generally well tolerated.

When considering the different immune cells present in the CF lung it has been documented that neutrophils account for approximately 60%-70% of immune cells in CF airway samples[13]. Key studies have demonstrated that infiltration of neutrophils into the airways occurs early in the course of CF lung disease and that neutrophil-released granule proteins, particularly neutrophil elastase (NE), play a crucial pathological role[14,15]. The expression of functional CFTR on the plasma membrane of neutrophils has been the topic of great debate[16-19] with studies specifying intrinsic abnormalities due to a lack of CFTR function[20,21]. Reports on reprogrammed cell activity secondary to chronic bacterial infection and inflammation have also been documented[22]. Moreover, persistent mTOR and CREB pathway activation in CF airway neutrophils[23] and augmented cell surface nutrient transporter expression are consistent with metabolic adaptation[24].

Regardless of the cause of impaired neutrophil activity however, the fundamental consequence is neutrophil mediated tissue proteolysis. Excessive neutrophil recruitment to the lung, results in prolific NE degrading protease activity and inflammation that can eventually become chronic and lead to tissue destruction. The recognition that aerosolized HTS may moderate neutrophil cytotoxicity and may function to restrain an exuberant inflammatory response in CF, provides a possible strategy for mitigating inappropriate neutrophil activity. This review will initially describe the use of HTS in treatment of CF and then extend the focus of HTS beyond mucociliary, to the potential benefits of aerosolized hyperosmolar therapy for the modulation of neutrophil activity within the confines of the CF airways. Our review of the literature was carried out using the MEDLINE database (from 1976 to the year 2014), Google Scholar and The Cochrane Library databases using several appropriate generic terms.

CLINICAL EFFICACY OF NEBULISED HTS IN CF

The use of HTS treatments has been shown to improve mucus clearance in CF and impact upon exacerbations, quality of life and improve lung function[12]. Early studies demonstrated an acute dose-response relationship between inhaled saline concentration and mucociliary clearance[25], with short-term HTS administration improving mucociliary clearance and lung function with acceptable tolerability[26]. In 2006, the National Hypertonic Saline in Cystic Fibrosis Study Group provided the first evidence for the long-term efficacy of HTS in individuals with CF. The study randomised

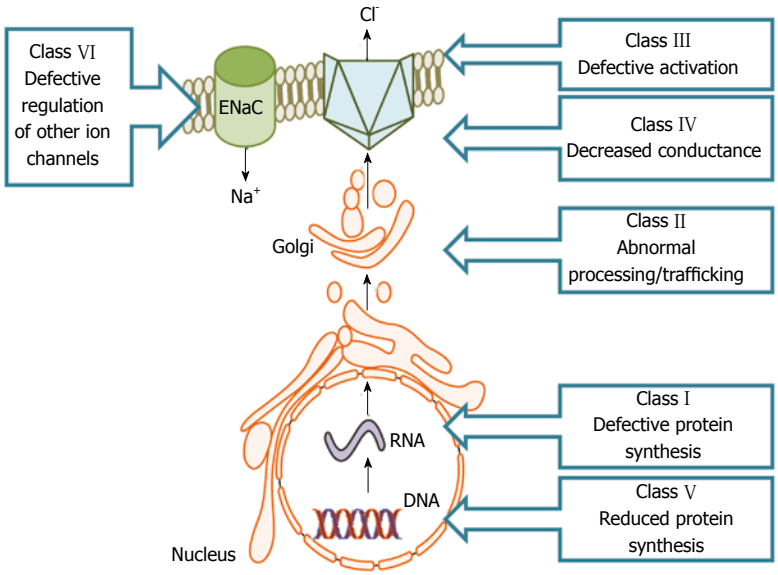

Figure 1 Classification of cystic fibrosis transmembrane conductance regulator mutations. CFTR mutations are classified into six groups according to their effect on CFTR function. Class I mutations affect biosynthesis, while class II mutations affect protein processing. Milder mutations such as class II to Class V impair CFTR channel function. CFTR: Cystic fibrosis transmembrane conductance regulator.

164 patients with CF to receive HTS (7%) or isotonic (0.9%) saline for 48 wk. Using forced vital capacity and forced expiratory volume in 1 s (FEV1) to assess the rate of change of lung function, no significant difference was observed between the two groups, but there was a statistically significant difference in the absolute change in lung function. More importantly, this study demonstrated an impressive reduction in the frequency of exacerbations in the HTS group, with fewer days missed from work or school. Furthermore, significant improvements in quality of life were observed, particularly with regard to mental health on quality of life questionnaires after long-term HTS therapy[12].

A further study by Donaldson *et al*[26] showed that repeated use of 7% HTS generated both acute and sustained improvements in mucociliary clearance while improving FEV1 following four-times-daily treatment for 14 d, when compared to HTS given in conjunction with the ENaC inhibitor amiloride, however this study lacked a 0.9% saline control group, and as a result the effect of HTS could only be compared to patient baselines. Robinson *et al*[27], in a study employing radioaerosol technique, examined the acute effect of a single administration by aerosolization of 7% HTS, amiloride, or a combination of HTS and amiloride, or a 0.9% saline control. Results demonstrated that treatment with HTS alone significantly increased mucociliary clearance compared to treatment with HTS/amiloride combined, and both of these therapies were in turn significantly more effective than isotonic saline or amiloride alone.

The efficacy of HTS in improving mucociliary clearance may also be related to the volume administered as studies of 4 mL or 5 mL aerosolized HTS[12,26] recorded smaller improvements in lung function compared to a 10 mL volume[11,28]. In 2011, Dmello *et al*[29] used a multivariate logistic regression analysis to assess 340 CF exacerbations, 99 of them involving treatment with HTS. The results confirmed the beneficial effect of HTS with regard to reduction of pulmonary exacerbation frequency, even in those with "severe" CF lung disease, categorised as those with an FEV1 below 40%. A further study, on the use of HTS during hospitalization for adult exacerbations of CF showed that nebulized treatment accelerated the recovery of FEV1 to baseline[30]. However, there is conflicting evidence on the effectiveness of HTS upon lung function and FEV1 and a Cochrane review summarising all clinical trials of HTS in CF demonstrated a significant but minimal increase in FEV1 with a mean change of 4.15% after 4 wk, however at 48 wk this was not significant and was reduced to 2.31%[31].

While spirometry, primarily FEV1, represents the measure of lung function used in the majority of HTS studies to date, the use of lung clearance index (LCI), a measure of ventilation inhomogeneity derived from the multiple breath washout test, is increasingly being employed for the early detection of CF respiratory disease[32]. LCI has been shown to be a better predictor of later lung function abnormalities than FEV1[33] and also correlates well with structural changes[34,35]. LCI has been shown to detect treatment responses to HTS in children with CF aged 6-18 years who have normal baseline spirometry[36]. It should be noted that while these studies when analysed together formed the basis for HTS use in the majority of CF centres in Europe and North America, the data for the most part only apply to adults, with a relative lack of evidence for use in children. Studies of HTS use in the CF child population have shown satisfactory safety and tolerability profiles[37-39], but it is still unclear as to whether or not HTS treatment confers a clinical benefit upon this group. This may be in part due to the fact that younger individuals typically have less-advanced lung disease, nonetheless it is still well tolerated even in very young children aged between 12 and 30 mo[38]. Although there is good evidence to suggest that HTS is of benefit regarding the enhancement of mucociliary clearance in adults, one study of HTS in CF children aged between 7-14 years published by Laube *et al*[40] demonstrated only negligible acute clearance effects, however, it should

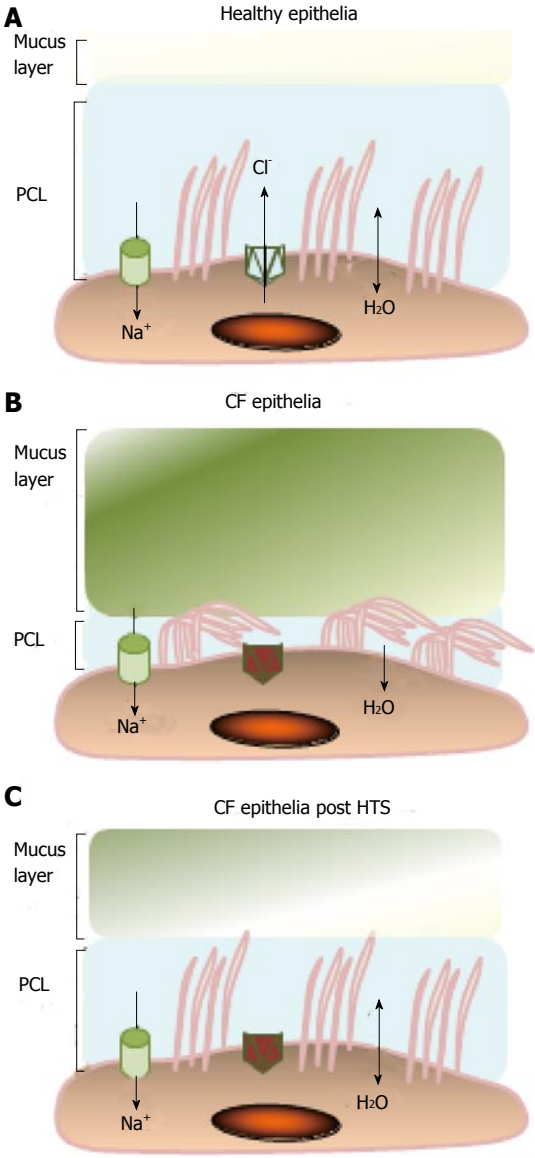

Figure 2 Effects of hypertonic saline on the airway surface liquid in cystic fibrosis. A: In healthy airway epithelia, CFTR plays a vital role in regulating hydration of the airway surface liquid (ASL) constructed of the periciliary layer (PCL) and the mucus layer; B: Due to defective CFTR in individuals with CF, Cl^- secretion is impaired and Na^+ absorption through ENaC is increased resulting in dehydration of the ASL and accumulation of thick mucus causing reduced PCL height; C: Treatment with hypertonic saline assists osmosis of water into the ASL and thus rehydrates the mucus and partially restores the PCL allowing for easier clearance of mucus. CFTR: Cystic fibrosis transmembrane conductance regulator.

be noted, that this was a single-dose study. A recent trial, from the North Carolina group at Chapel Hill, of HTS in CF children with normal lung function has shown some interesting results. This trial compares 6% HTS to 0.12% saline, with both arms of the study receiving 4 mL three times daily for four weeks. While mucociliary clearance was largely unaltered at 2 h after the initial dose, a significant acceleration of mucociliary clearance lasting greater than 12 h following the final dose was observed[41]. This sustained effect suggests that single-dose studies may not be ideal predictors of mucociliary clearance in these individuals. A further study, by Amin *et al*[36] using LCI to evaluate ventilation heterogeneity in individuals aged between 6 and 18 years with CF with normal spirometry, demonstrated a significant improvement in ventilation after four weeks of HTS treatment. Moreover, recent evidence has demonstrated that HTS is also beneficial through its ability to reduce *Pseudomonas aeruginosa* activity[42] and also to disrupt biofilm formation[43].

TOLERABILITY OF HTS IN CYSTIC FIBROSIS

Although an acute dose-response relationship between inhaled saline concentration and mucociliary clearance exists, data showing better or worse clinical efficacy with concentrations other than 7% are lacking. In this regard most clinical trials show that both 3% and 7% HTS are more effective than placebo[31], however one clinical trial in a paediatric population demonstrated a superior effect with 3% HTS. In this study, the 3% group had significantly higher FEV1 on day 14 and day 28 compared to the group receiving 7%[44], however this study was not extended beyond 28 d, so it is unclear whether there is a truly superior dose, and the majority of trials have employed 7% HTS. Moreover, the percentage of HTS administered not only has implications for clinical efficacy, but also for patient adherence, since as doses increase (from 3% to 7%), so do nebulisation times, taste and tolerability, all important factors for compliance[45]. A 1997 study by Robinson *et al*[25] showing increasing levels of sputum clearance with increasing concentrations of saline also noted that factors such as cough and oropharyngeal irritation increased in tandem with sputum clearance, and were highly disconcerting at concentrations approaching 12%, setting the ceiling of tolerability for the study. Tolerability is often a key determinant of the dose selected for an individual patient, with pre-treatment with bronchodilators aimed at facilitating a higher concentration. Roughly 5% of CF patients undergoing treatment with HTS will experience bronchospasm severe enough to restrict use[8]. A commonly-used starting point for HTS is 7%, with bronchodilator pre-treatment, and with the willingness to down-titrate should patient comfort be sufficiently compromised. Administration of 7% HTS in conjunction with 0.1% hyaluronic acid *via* the aerosolised route has been shown to significantly improve tolerability and pleasantness when compared with 7% HTS alone[46].

EFFECT OF HTS ON LEVELS OF AIRWAY INFLAMMATORY MEDIATORS INVOLVED IN NEUTROPHIL RECRUITMENT AND ACTIVATION

Circulating neutrophils are initially found in a resting state, and become primed upon exposure to chemo-

tactic stimuli comprising pathogenic molecules such as *N*-formyl peptides, cytokines including tumour necrosis factor-α (TNF-α) and chemokines including interleukin (IL)-8[47]. The release of cytokines and chemokines including IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF) by CF epithelial cells functions to signal to circulating immune cells resulting in increased numbers of neutrophils and macrophages localized to the airways[48,49]. IL-8 binds to the chemokine (C-X-C motif) receptor 1 (CXCR1) and CXCR2 on the plasma membrane of neutrophils resulting in cell adhesion[50] and migration[51]. In turn, synthesis and release of TNF-α and IL-1β by recruited macrophages, and NE induced secretion of IL-8 and IL-6 by upper airway epithelial cells, perpetuate the cycle of inflammation[52,53]. In addition, NE activity in BAL fluid is associated with early airways disease in children with CF[54] and both NE and TNF-α up-regulate leukotriene B_4 (LTB_4) production by macrophages[55,56], the latter a potent lipid inflammatory mediator. It has also been documented that CF lung epithelial cells release IL-8 in the absence of pathogens suggesting a persistent pro-inflammatory state (13, 14). Moreover, upon bacterial challenge studies have shown that the level of IL-8 released in response to infection is significantly increased in CF airway epithelial cells compared to CFTR sufficient cells and this has in part been explained by the plasma membrane surface expression of asialoganglioside 1 and toll-like receptor 4[57,58].

Observations of increased cell migration and neutrophil-dominated chronic airway inflammation at an early age in children with CF[59], supports the need for potential therapies that may target airway inflammatory mediators of neutrophil priming and migration. In this regard the ability of HTS to act as an anti-inflammatory, or alternatively pro-inflammatory agent, was studied by Chan *et al*[60]. IB3-1 bronchial epithelial cells containing the DF508/W1282X CF mutation were exposed to increasing concentrations of HTS *ex vivo* and secreted IL-8 levels were quantified. Results revealed that CFTR mutated bronchial epithelial cells produced an exaggerated level of both basal and NaCl-induced IL-8 production, indicating that HTS was acting as a pro-inflammatory stimuli[60]. However, the highest concentration of HTS employed in this study was 125 mmol/L, which is in contrast to the therapeutic concentration of HTS used *in vivo* (513 mmol/L; 3%). Nevertheless, this effect of HTS was echoed by studies that demonstrated that hyperosmolar solutions stimulated cytokine production by bronchial epithelial cells *via* p38 mitogen-activated protein kinases activation[61] and in CF bronchial gland cells *via* the NF-κB pathway[62]. Similarly, a study carried out by Shapiro *et al*[63] demonstrated that human peripheral blood mononuclear cells exposed to increasing concentrations of NaCl in combination with bacterial lipopolysaccharide or IL-1 exhibited increased protein expression of IL-8, IL-1β and TNF-α.

HTS continues to be used as a therapy available for the treatment of patients with CF[64] and in contrast to the HTS-induced increased expression of IL-8 in *in vitro* studies, a number of *in vivo* studies have measured IL-8 levels following HTS treatment. These included a long term controlled trial of inhaled HTS in patients with CF, compared to inhaled isotonic saline, with no significant difference in sputum IL-8 levels found between the groups[12]. Two further studies also investigated IL-8 levels in CF sputum post HTS (3% and 7%) nebulisation, with results showing no significant alteration in IL-8 levels[65,66]. Moreover, an investigation designed to assess the effect of 7% HTS on airway inflammation in CF, with outcome measurements including altered IL-8, myeloperoxidase (MPO) and NE levels, revealed no increase in free IL-8 and the study did not support the capacity of HTS to promote inflammation in CF[67]. Furthermore, in human pulmonary microvascular endothelial cells the ability of increasing concentrations of HTS (ranging from 140 mmol/L to 170 mmol/L NaCl) to significantly reduce TNF-α-induced IL-8 release was established[68]. However, the concentration of HTS utilised was far below that used therapeutically. More recently, the functionality of HTS in reducing levels of IL-8 bound to glycosaminoglycans (GAGs) within the CF airways was observed. Within the CF airways, the dehydrated thick mucus contains raised levels of anionic GAGs formed on the surface of bronchial epithelial cell[69], the most abundant including heparan sulphate (HS) and chondroitin sulphate (CS)[70,71]. Of major importance, increased quantities of GAGs have been found in airway samples from individuals with CF[72]. The immobilization of IL-8 by GAGs plays a major role in the establishment of gradients of the chemokine that contribute to the recruitment of neutrophils during inflammatory exacerbations[73]. The use of an IL-8 decoy (PA401) with enhanced GAG binding ability[74], or the removal of HS and CS lead to a significant reduction in the detection of this chemokine[75]. Moreover, disruption of this interaction with increasing ionic concentrations (7% HTS) displaces IL-8 from GAGs, subjecting the former to clearance by proteolytic activity by NE[76] (Figure 3). Although only a small number of patients were recruited to this latter study, and the effect of HTS on other immunomodulatory mediators in the CF airways was not evaluated, results are in line with the ability of aerosolized HTS in an animal model of acute lung injury to reduce levels of the murine analogue of IL-8, cytokine-induced neutrophil chemoattractant-1, by 44%[77].

ABILITY OF HTS TO IMPACT UPON NEUTROPHIL ADHESION AND MIGRATION

Pro-inflammatory stimuli, either individually or in combination, can stimulate the neutrophil to change morphology and migrate to the airways, the latter being

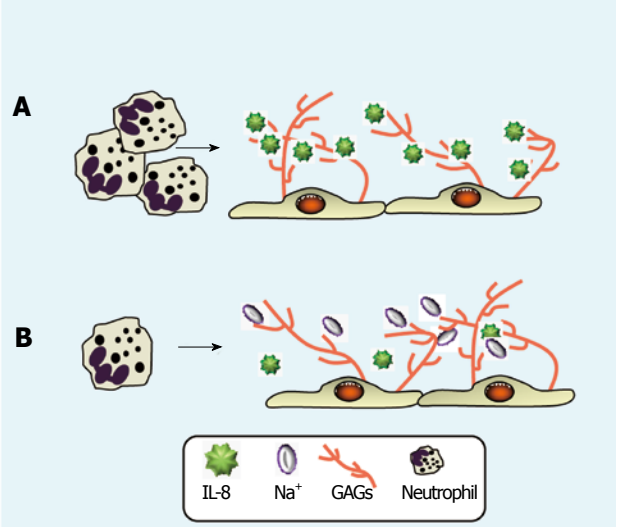

Figure 3 Hypertonic saline reduces levels of interleukin-8 in cystic fibrosis airway samples thereby reducing neutrophil migration. A: The chemokine IL-8 is a key mediator of inflammation in patients with CF and increases neutrophil migration to the airways. GAGs possess the ability to influence the chemokine profile of the CF lung by binding IL-8 and protecting it from proteolytic degradation; B: HTS functions to disrupt IL-8: GAG complexes, rendering the chemokine susceptible to proteolytic degradation. Clinical application of HTS may serve to decrease the inflammatory burden in the CF lung *in vivo*. CF: Cystic fibrosis; GAGs: Glycosaminoglycans; HTS: Hypertonic saline; IL-8: Interleukin-8.

a multistep process. Initially, after a chemotatic signal is received, the neutrophil reversibly binds to the vascular endothelium through the interactions between P-selectin and E-selectin found on the epithelium, with L-selectin expressed on the neutrophil surface. Rolling of neutrophils involves interaction between these selectins and glycoproteins such as P-selectin glycoprotein ligand (PSGL1) which is expressed by the endothelium and leukocytes. This mediated rolling of the cell allows new bonds to form before breaking of older bonds and shedding of L-selectin[78]. This slow rolling then allows for tighter bonds to form between β2 integrins expressed on the neutrophil surface including CD11b/CD18 and the corresponding ligands, intercellular adhesion molecule-1 (ICAM-1) and ICAM-2. Once neutrophils have adhered to the endothelial wall, tight junctions between endothelial cells become loose and allow transmigration. Neutrophils then follow a gradient of immobilised chemoattractants and travel to the airways along collagen and elastin fibres[78] and movement through the extracellular matrix is facilitated by release of proteolytic enzymes including metalloproteases and NE[79,80].

The capacity of HTS to reduce neutrophil migration as a result of lowering levels of the potent neutrophil chemoattractant IL-8 has been investigated. In this regard, the consequence of disruption of interactions between IL-8 and GAGs within the CF lung was addressed by assessing the chemotactic potency of sputum *ex vivo* following nebulized HTS treatment, with results demonstrating a reduction in the neutrophil chemotactic index[76]. Although IL-8 is a major chemotactic factor in CF, it is not the only chemoattractant found in the CF airways. Thus this latter study should be extended to evaluate the effect of HTS on additional chemoattractants including levels of formyl peptides, C5a[81], and the more recently described chemotactic peptide, proline-glycine-proline[82]. Nevertheless, in agreement with these latter findings, Aitken *et al*[65] showed that the percentage of neutrophils in liquefied sputum samples significantly decreased post HTS (3%) nebulization. Moreover, recent data indicates that HTS can inhibit platelet activating factor (PAF) stimulated cell adhesion. In this regard, exposure of neutrophils to PAF characteristically leads to increased CD11b/CD18 surface expression, and adhesion of PAF activated neutrophils was significantly inhibited by pretreatment with HTS, indicating that HTS may influence functional changes in neutrophils[68]. This concept is further supported by a study demonstrating that HTS considerably reduced neutrophil chemotaxis in response to zymosan-activated serum[83]. Moreover, HTS treatment decreased the number of neutrophils migrating to the airways in a rat model[84], and has been shown to reduce neutrophil adhesion and rolling in a murine model[85]. Although this latter study did not evaluate the neutrophil plasma membrane surface expression of either L-selection or CD11b, diminished levels of both adhesion molecules in response to HTS had previously been documented[86,87]. Moreover, while the use of animal models provides in-depth information on the efficacy of HTS usage, they are not representative of human disease and in particular the use of murine models in the study of CF is limited, as CF mice fail to develop spontaneous lung disease or chronic bacterial infection[88].

IMPACT OF HTS ON NEUTROPHIL CELLULAR PROCESSES INCLUDING NADPH OXIDASE ACTIVITY AND DEGRANULATION

The process of neutrophil mediated bacterial clearance can be divided into two main procedures, those that are oxygen independent, and those that are oxygen dependent. These two cell processes are tightly regulated, and upon dysregulation, can result in release of reactive oxygen species and proteolytic enzymes to the surrounding lung tissues, as occurs in CF. Reactive oxygen species are produced by reduction of consumed oxygen. This reaction is catalysed by the NADPH oxidase, an enzyme complex that consists of two membrane proteins, $p22^{phox}$ and $gp91^{phox}$, that constitute the heterodimeric flavoprotein cytochrome b_{558}, and four cytosolic components $p67^{phox}$, $p47^{phox}$, $p40^{phox}$ and $p21^{rac}$ (Figure 4). In the resting neutrophil the majority of membrane-associated flavoprotein cytochrome b558 is localised to secondary granules

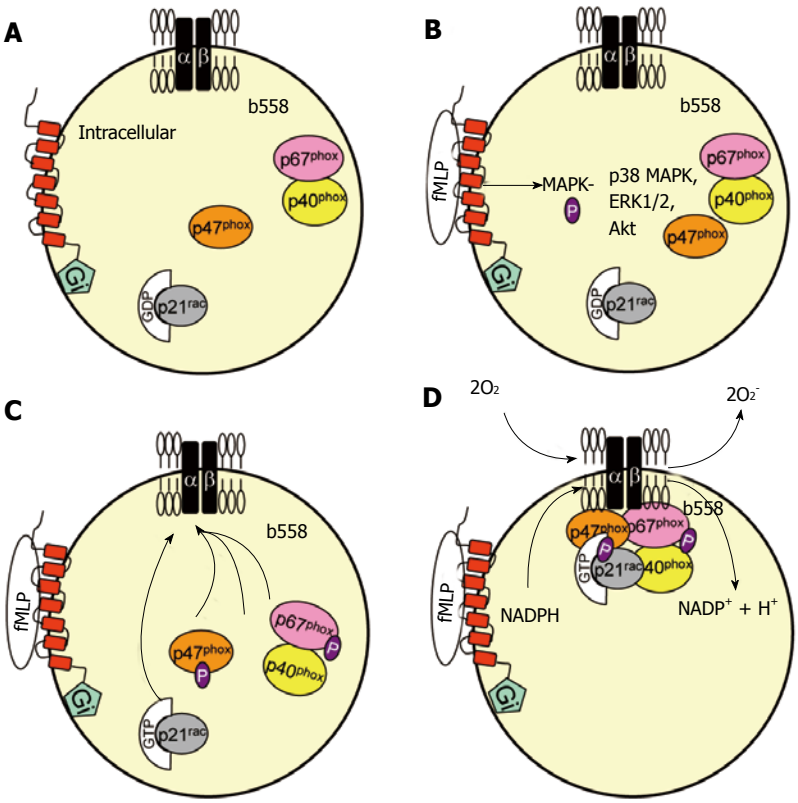

Figure 4 Schematic illustration of the NADPH oxidase of resting and formyl peptides activated cells. The neutrophil NADPH oxidase generates superoxide (O_2^-) and secondary oxygen-derived toxic products in response to bacteria or a variety of soluble stimuli (fMLP). A: The enzyme is dormant in resting neutrophils. The active site of this enzyme is located in an integral membrane cytochrome, b_{558}, which consists of the two subunits gp91^{phox} and p21^{phox} (subunits); B: Stimulation of the neutrophil by fMLP induces activation and phosphorylation (P) of a number of kinases including Akt; C: P21^{rac} is converted into the active GTP-bound form and the phosphorylation of the cytosolic components (p67^{phox}, p47^{phox} and p40^{phox}) occurs; D: These subunits then translocate to the membrane where they interact with cytochrome b_{558} to initiate reactive oxygen species production. fMLP: Formyl peptides.

and the plasma membrane, whereas components p67^{phox}, p47^{phox} and p40^{phox} are localised within the cytosol together with GDP-bound p21^{rac}. Upon priming of the neutrophil with proinflammatory stimuli including fMLP or TNF-, partial assembly of the NADPH oxidase occurs involving phosphorylation of p67^{phox} and p47^{phox} followed by translocation to the flavocytochrome. The NADPH oxidase complex becomes fully assembled upon recruitment of GTP-bound p21^{rac}. Upon assembly, the active oxidase reduces NADPH and electrons are transferred *via* the flavocytochrome across the membrane to oxygen creating superoxide (O_2^-), which dismutates to hydrogen peroxide (H_2O_2). H_2O_2 generated during the oxidative burst has limited bactericidal properties and the best-defined function of H_2O_2 in the antimicrobial activities of neutrophils comes from the function of H_2O_2 as a substrate for MPO in the presence of halides [chloride (Cl^-)], resulting in the formation of hypochlorous acid (HOCl). HOCl is the most bactericidal oxidant known to be produced by neutrophils and as Dakin's solution, was extensively used in medicine in the treatment of topical wounds until antibiotics became available. Conversely, neutrophil-derived reactive oxygen species have been implicated in activation of NF-κB, release of pro-inflammatory mediators, inhibition of apoptosis and recurring DNA damage[89].

The second mechanism contributing to bacterial killing is mediated by enzymes stored in granules (Figure 5). Essential serine proteases stored in primary granules include NE, cathepsin G and proteinase 3. Each azurophilic granule contains 5.33 mmol/L NE, corresponding to approximately 67000 molecules per granule. NE, protease 3 and cathepsin G, are found in similar amounts and distribution in neutrophils[90], however much of the research has focused on NE as it is the main mediator of proteolysis (Figure 6). As NE up-regulates expression of *other proteases* it has been suggested that neutralization of NE activity is central to reducing the overall protease burden within the airways[91]. In addition, NE plays a central role in activation of matrix metalloproteinases (MMPs) which are synthesized in an inactive zymogen precursor form[92]. For example, MMP-9 which exists as a pro-form, exhibits a molecular mass of 92 kDa which is cleaved by NE into an active molecule that is 72-kDa in size[93]. In turn, increased levels of active MMP-9 can lead to the increased production of chemotactic peptides[94] and extensive airway remodelling and inflammation[95,96]. Thus, of the serine proteases, NE is the most harmful in the lung[97] and it has been proposed as a target for therapeutic intervention in CF[98,99]. Unopposed NE proteolytic action can degrade

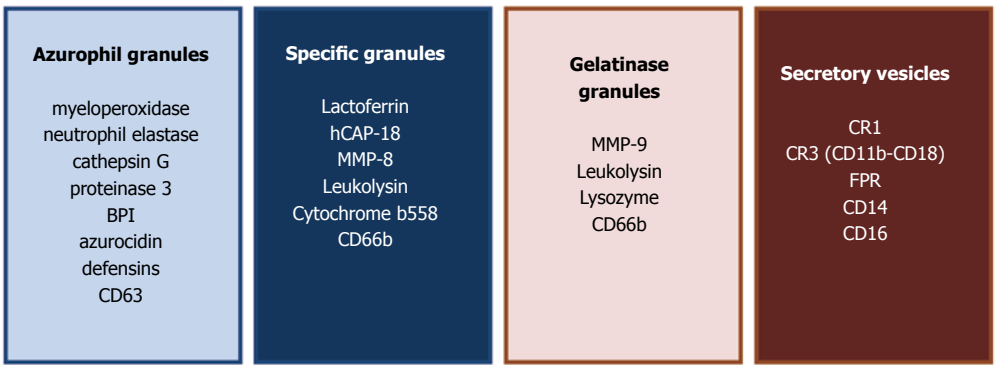

Figure 5 Components of neutrophil granules. The second mechanism of bacterial killing is mediated by enzymes stored in granules. Essential serine proteases stored in primary granules include NE, cathepsin G and proteinase 3. Other bactericidal proteins of primary granules include defensins, azurocidin and bactericidal permeability-increasing (BPI) protein, which mutually function to destabilise bacterial membranes. Additional antibacterial proteins stored in secondary or specific granules include lactoferrin, the 18-kDa human cathelicidin antimicrobial protein (hCAP18) and lysozyme. Lactoferrin, an iron binding protein displays antimicrobial properties by limiting iron availability and exhibits direct antmicrobial and antifungal properties independent of iron-binding. LL-37, the CX-terminal peptide of hCAP-18, disrupts the integrity of bacterial membranes and can neutralise bacterial endotoxins. The gelatinase or tertiary granules contain mainly gelatinase (MMP-9) whose main function is to degrade type V collagen in the extracellular matrix to aid neutrophil migration. In addition to these three granule types, neutrophils also contain secretory vesicles that contain a reservoir of essential receptors and integrins. All are degranulated to the outside of the cell or into the phagocytic vacuole.

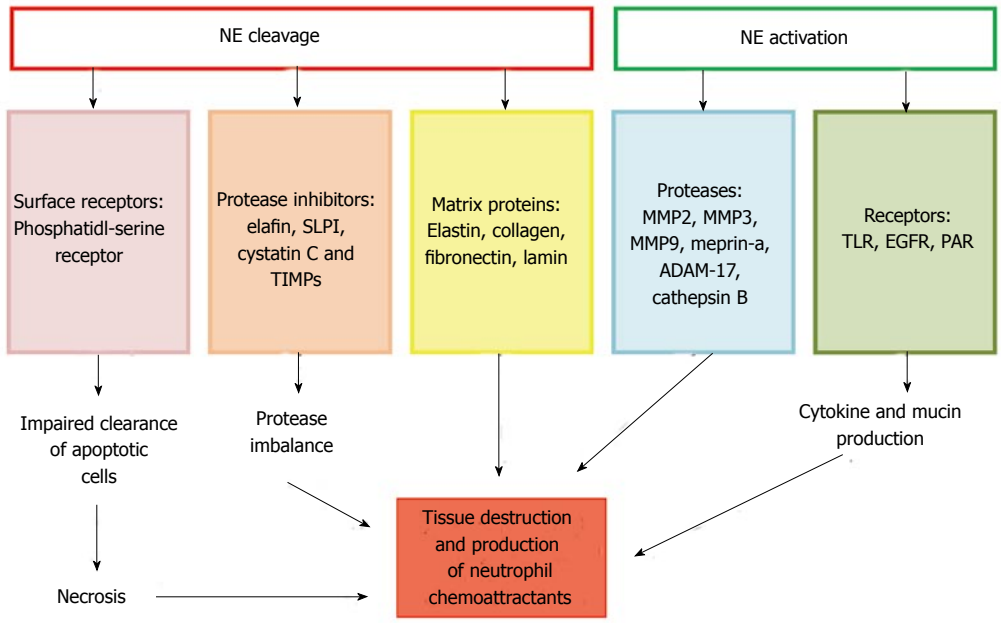

Figure 6 Potential effects of active neutrophil elastase in cystic fibrosis. Excessive NE activity can lead to proteolysis causing protease-antiprotease imbalance by cleaving protease inhibitors. Cleavage of matrix proteins and surface receptors leads to tissue damage and prolonged immune response, respectively. NE can further activate pro-inflammatory molecules (MMPs and ADAM-17) and receptors. These cumulative effects exacerbate tissue destruction and hyper-inflammation. NE: Neutrophil elastase; CF: Cystic fibrosis; MMPs: Matrix metalloproteinases.

molecules important in control of inflammation including receptors[100], particularly those required for clearance of apoptotic neutrophils[101] or bacterial phagocytosis[102,103]. NE can also inactivate and degrade antiproteases including elafin[104], alpha-1 antitrypsin and secretory leukocyte inhibitor[105]. As a consequence of the proteases/antiprotease imbalance, lung tissue is irreversibly damaged, dramatically reducing lung function and ultimately causing respiratory failure[106]. In short, HTS therapies that may modulate exuberant oxidase and degranulation activity may be used as powerful anti-inflammatories within the setting of CF airways disease.

A number of *in vitro* investigations have documented that sodium chloride slows neutrophil activity[107] and a study evaluating the effect of HTS on the mechanisms of activation of the NADPH oxidase revealed that stimulated translocation of $p67^{phox}$ to the neutrophil membrane in response to PAF was prevented. Moreover, in *in vitro* cell-free oxidase assays, the membrane content of $p67^{phox}$ post PAF activation was increased in support of oxidase activity, whereas control unstimulated and HTS-PAF activated membranes contained equivalent $p67^{phox}$ protein content[108]. Although these results

support the potential of HTS to modulate oxidase activity, the concentration of HTS utilised was 180 mmol/L, which is below therapeutic HTS and therefore higher concentrations of HTS should be investigated to determine the effect on $p67^{phox}$ membrane translocation. Nevertheless, the inhibitory effect of HTS on a second stimuli involving fMLP-induced NADPH oxidase was also confirmed. The described inhibition occurred in a dose-dependent manner with results indicating that transient increases in osmolality caused prolonged suppression of neutrophil O_2^- production to the outside of the cell, as measured by cytochrome c reduction[83]. The mechanism of inhibition was explored and shown to involve blockade of mitogen activated protein kinase (MAPK) ERK 1/2 and p38 signalling[83]. Moreover, H_2O_2 production to the outside of the cell post fMLP activation was equally reduced by two concentrations of HTS ($[Na^+]$ = 180 mmol/L and 200 mmol/L)[109]. In contrast however, and of major importance, intracellular formation of reactive oxygen species upon bacterial phagocytosis was potentiated with increasing osmolar strength[110]. Despite osmotic down-regulation of p38 and ERK-1, this later study demonstrated enhanced intracellular O_2^- generation in response to bacterial challenge suggesting that HTS may attenuate tissue injury by compromising neutrophil cytotoxic capacity, and additionally appears to enhance the response to bacteria. This may be a further beneficial role of HTS when aerosolized clinically in CF[110].

With respect to the ability of HTS to modulate the degranulation process, Junger *et al*[83] demonstrated that neutrophils exposed to > 50 mmol/L HTS alone released increased levels of MPO and NE, however, when cells were exposed simultaneously to inflammatory levels of fMLP and increasing concentrations of HTS, as would be expected in the CF airways, the fMLP-stimulated primary granule release of MPO[20] and NE was inhibited in a dose dependent manner. Moreover, HTS induced changes in the actin cytoskeleton have been reported[111] and linked to the hypertonic inhibition of neutrophil degranulation. HTS instigated a twofold increase in F-actin formation and abrogated the mobilization of all granule types suggesting cytoskeletal remodelling as a key component in the neutrophil-suppressive anti-inflammatory effects of HTS[112]. As neutrophils in individuals with CF demonstrate enhanced secretion of NE and MPO, the potential of aerosolized HTS to prevent primary granule release would have tremendous clinical implications. Furthermore, despite the fact that there is abundant extracellular neutrophil released hCAP-18/LL-37 in the lungs of individuals with CF, the lung fluid from patients exhibits poor antimicrobial activity. A recent study has demonstrated that the antimicrobial activity of endogenous hCAP-18/LL-37 in CF BAL fluid is rendered inactive by binding GAGs but is liberated following nebulized HTS[113]. The effect of HTS on levels of additional antimicrobial peptides and proteins within the CF airways was not evaluated but this study does suggest that a strategy whereby nebulized HTS augments antimicrobial activity may provide optimization of the innate antimicrobial activity in the setting of CF.

CONCLUSION

HTS treatment is associated with an improvement in lung function and marked benefits with respect to exacerbations[26,114,115]. Significant inflammation in the airways manifests from a very young age in CF most likely due to a combination of intrinsic innate immune dysregulation and infection. The obvious most effective treatment remains correction of CFTR dysfunction at a very early age, thereby curtailing development of airway inflammation. However, in the absence of CFTR ion channel modulators for each individual's genotype it will remain important to modulate or suppress the inflammatory reactions of the disease. Although in children with CF, the use of inhaled HTS did not reduce the rate of pulmonary exacerbations[116], the described studies in the present review demonstrate dramatic *in vitro* effects of HTS on neutrophil function, limiting cellular processes that govern airway inflammation including cell adhesion, reactive oxygen species production and protease release. These reports support the concept that HTS may have beneficial anti-inflammatory effects other than simply increasing mucociliary clearance and thus further investigations of the potential mechanisms of this currently available therapy in CF is crucially required.

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REVIEW

Postoperative fluid management

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Abstract

Postoperative care units are run by an anesthesiologist or a surgeon, or a team formed of both. Management of postoperative fluid therapy should be done considering both patients' status and intraoperative events. Types of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. The main goal of fluid resuscitation is to provide adequate tissue perfusion without harming the patient. The endothelial glycocalyx dysfunction and fluid shift to extracellular compartment should be considered wisely. Fluid management must be done based on patient's body fluid status. Patients who are responsive to fluids can benefit from fluid resuscitation, whereas patients who are not fluid responsive are more likely to suffer complications of over-hydration. Therefore, common use of central venous pressure measurement, which is proved to be inefficient to predict fluid responsiveness, should be avoided. Goal directed strategy is the most rational approach to assess the patient and maintain optimum fluid balance. However, accessible and applicable monitoring tools for determining patient's actual fluid need should be further studied and universalized. The debate around colloids and crystalloids should also be considered with goal directed therapies. Advantages and disadvantages of each solution must be evaluated with the patient's specific condition.

Key words: Body fluids; Body fluid compartments; Fluid therapy; Intensive care; Postoperative care

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Core tip: Types of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. Assessment of the patient's responsiveness to fluid resuscitation should determine the need of extra volume. Due to lack of evidence that supports central venous pressure (CVP) as an indicator of body fluid needs, we should not make our fluid resuscitation decisions based on CVP levels. On the other hand dynamic measures can be used to determine patient's fluid status. Among all fluid management strategies, goal directed strategy is the most rational approach to maintain optimum fluid balance.

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POSTOPERATIVE FLUID MANAGEMENT

Fluid management is an important part of overall surgical therapy. Proper administration of fluids is critical, especially in patients who undergo major surgeries such as emergency laparotomies, bowel resections and hepatectomy procedures. Body fluid composition may change in minutes or hours, resulting in impaired wound healing and homeostasis. Briefly, choice of strategy in intraoperative and postoperative fluid management may be significant.

We will examine different postoperative fluid management strategies in this review. Postoperative management of patients, who undergo surgery, is carried out by intensive care specialists, anesthesiologists and general surgeons in postoperative care units, in all over the world[1]. On the other hand, intraoperative management is a quite different expertise, which is totally put into practice by anesthesiologists only, and is not covered in this article. Although postoperative care units are mostly managed by a team of both anesthesiologists and surgeons or only by anesthesiologists in Europe and Japan, surgeons' presence and co-leadership is of great importance in postoperative care. Harmonious with this view, surgeons play the largest role in North America[1,2].

Types of the fluids, amount of the fluid given and timing of the administration are the main topics that determine the fluid management strategy. Several debates have been continued about each of these topics. In early times of modern medicine, administering large amounts of fluids was favored, instead of facing the risk of hypovolemia[3]. In 1961, Shires *et al*[4] defined the "third space" fluid deficit as nonfunctional fluid which can be accounted as fluid loss and they suggested use of large quantities of fluids to substitute this functional loss. After this strategy becomes popular, reports of adverse effects of high volume states induced by excessive saline use began to arise. Today, exact amount of fluid to maintain ideal homeostasis is still controversial. Similarly, there are varying types of intravenous fluids and all vary in their biological and chemical properties which results in varying distribution forms and varying effects on homeostasis, vascular integrity, and other hemodynamic variables. Apparently, fluid management is admitted to be an art of medicine and based on personal judgments. Although this approach may not be totally wrong, plenty of evidence acquired by large volume studies should be considered wisely.

Postoperative fluid management plays a key role in providing adequate tissue perfusion, stable hemodynamics and reducing morbidities related with hemodynamics. Understanding body fluid physiology and possible outcomes of different fluid management strategies is crucial for all surgeons.

BODY FLUID COMPARTMENTS

Total body water is approximately 60% of total body weight. One third of this water is extracellular and it can be divided to as intravascular (20%) and extravascular (80%). The remaining two-third of body water is intracellular, which also exists in intravascular and extravascular compartments. From another perspective, intravascular fluid contains of both intracellular (40%) and extracellular (60%) compounds and plasma is the intravascular-extracellular compound of total body water (approximately 4% of body weight; in example, about 2.8 L in a 70 kg individual).

The endothelium is the separating wall between intravascular and extravascular compartments, thus it is the cell wall that separates the intracellular and extracellular compartments. There are various control mechanisms on these separating walls that regulate volumes of each compartment. Cell membrane is completely permeable to water, whereas it is selectively permeable to ions and organic molecules. It has also the Na^+/K^+-adenosine triphosphatase enzyme that actively expels Na^+ ions and maintains the Na^+ gradient between compartments. There are also endocrine mechanisms that control the cellular intake of certain molecules, such as glucose.

On the other hand, the earliest theory on vascular barrier by Ernest Starling declared that the hydrostatic pressure gradient in blood vessels creates a flow and the oncotic pressure of interstitial tissue allows only reasonable amount of fluid to cross through endothelium[5]. Later studies showed the intravascular osmotic pressure is significantly higher than interstitial osmotic pressure, however this doesn't result in interstitial edema[6]. As a result, this unexplained situation led researchers to look for another actor in this fluid distribution balance. The endothelial glycocalyx is a carbohydrate-rich coating over endothelial surface which is supported by proteoglycans and glycoproteins. It is a dynamic formation, consisting of membrane-bound and soluble molecules[7]. Existence of this glycocalyx layer forms a distinct space in the interior neighborhood of the endothelium, and there develops a notable oncotic pressure in this particular protein-free space. This definition brings out the "double-layer concept" for the vascular barrier[6,8,9]. This concept is quite capable of clarifying oncotic pressure balance between two compartments.

WHAT HAPPENS TO THE FLUID BALANCE IN SURGERY?

Homeostasis defines the tendency of the organism to maintain stability and balance. In this manner, body

fluid balance is controlled by previously described compartment mechanisms. On the other hand, any physical intervention may cause imbalance of the body fluids. During relatively long lasting major surgeries, which are performed with general anesthesia, whole intake is controlled by the anesthesiologist and fluid loss happens in numerous different ways such as bleeding, drainage of ascites, urination, insensible water loss and "third space losses". Intraoperative management of acute losses is not covered in this article. However, long term effects of these intraoperative events, such as possible over-hydrating by the anesthesiologist, dehydration, and bleeding should be considered in the postoperative care unit.

The third space is a term for spaces in which body fluids lose their function to affect fluid balance between intravascular and extravascular compartments. In other words, it can be called as non-functional extracellular volume. Bowel lumen, peritoneal and pleural cavities are thought to be the major examples of the third space. Studies that tried to explain the third space loss measured the extracellular volume (ECV) and functional ECV (fECV). fECV is defined as fluid accumulations within the interstitial space combined with plasma. Shires showed that, there is up to 28% loss in extracellular volume after two hours of operative time, during elective surgeries of thirteen adult patients[4]. Subsequent studies in 1960s support this finding and existence of the third space[10-12]. However, numerous trials with improved methodology proved that fECV levels do not decrease in or after surgery[13-16]. This correction of data couldn't be recognized well enough, but still, favored common belief is in the presence and importance of the third space. Current evidence supports that fECV is not negatively affected by surgery, however over-hydration with saline and surgical trauma cause endothelial dysfunction and interstitial edema due to fluid shift to ECV[13]. In conclusion, "the third space" term should only refer to anatomical cavities like bowel lumen, peritoneum and pleura, and should only be considered in certain cases. Moreover, possible endothelial glycocalyx dysfunction and fluid shift to ECV should be our guiding facts for determining the right strategy in postoperative fluid management.

MONITORING BODY FLUID STATUS

Mostly, the main goal of fluid resuscitation is to provide adequate tissue perfusion without harming the patient. It can be also said that fluid resuscitation is generally the first step in patients with inadequate tissue perfusion. However, it should be kept in mind that infusion of large volumes of fluids to patients who don't have enough preload reserves may result in unbalanced fluid shift to interstitial tissue, having no useful effect on tissue perfusion. Intravenous fluid administration will have no effect on tissue perfusion, unless it increases the stroke volume. Studies show that nearly half of the unstable patients are not hemodynamically responsive to fluid resuscitation[17,18]. This means that, fluid resuscitation may not always be the right way to provide adequate tissue perfusion, especially in unstable patients. Thereby, assessment of the patient's responsiveness to fluid resuscitation should determine the need of extra volume.

Thus, we need to determine the actual body fluid status of the patient and build a strategy accordingly. For this purpose, static measures of intravascular volume are being used for decades and central venous pressure (CVP) has been the most favorite tool[19,20]. CVP is widely believed to indicate general intravascular volume status of the patient. Moreover, many intensivists think that, CVP is directly correlated with right ventricle stroke volume and indirectly correlated with left ventricle stroke volume. However, a systematic review of 24 studies showed no relation between CVP and left ventricle stroke volume[21]. Due to lack of evidence that supports CVP as an indicator of body fluid needs, we should not make our fluid resuscitation decisions based on CVP levels. Similarly, pulmonary capillary wedge pressure is another static measure of intravascular volume and is incapable of predicting fluid responsiveness, in contrast to the common assumption[22]. Besides, the two even less favored static measures are left ventricular end-diastolic area and inferior vena caval diameter.

On the other hand, recent studies claim that monitoring of the interactions of heart and lung in mechanically ventilated patients, so called dynamic measures, can be used to determine patient's fluid status. According to Marik *et al*[18], non-invasive techniques such as the pulse pressure variation, the stroke volume variation, and systolic pressure variation can significantly predict fluid responsiveness in mechanically ventilated patients. These techniques are based on physiological facts. The patients, whose pulse pressures or stroke volumes are more dependent on intra-thoracic pressure variations provided by the ventilator, tend to be more responsive to fluid resuscitation.

The physiological principles underlying the pulse pressure variation (PPV) and the stroke volume variation (SVV) are based on the effects of increased pleural pressure. As the mechanical ventilator increases the pleural pressure, the increased resistance in the pulmonary system causes a decrease in the right ventricle preload and an increase in the right ventricle afterload. Meanwhile, the left ventricle preload and afterload are affected exactly the opposite way of right ventricle is: Left ventricle preload increases and afterload decreases at the end of inspiration. The pulse pressure and the left ventricle stroke volume are at their highest values at this moment. Afterwards, prolongation of blood transit time through pulmonary system results in a decrease in the left ventricle preload and reduction in the left ventricle stroke volume (and the pulse pressure) during expiratory period[23,24]. Echocardiographic evaluations of aortic flow velocity and stroke volume and vena caval diameter variation

are two other dynamic parameters based on similar physiological reactions.

Another technique for predicting fluid responsiveness is called the passive leg raising (PLR). While previously mentioned techniques are used for mechanically ventilated patients especially who has no spontaneous breathing, PLR can be used on any patient. Raising the legs to provide a better cardiac preload has been used for a long time in emergency patients. Recently PLR gained interest as a predictor for fluid responsiveness. Monnet pointed out that lifting the legs passively in a lying patient induces a significant blood flow towards the heart[25]. Therefore, Marik *et al*[17] called this physiologic condition as "autotransfusion". In a study on mechanically ventilated patients, PLR-induced changes have been found to be strongly similar with the effects of 300 mL colloid infusion. As a result, PLR simulates the state after fluid administration. In other words, if the patient has enough preload reserve, PLR will increase left ventricle preload and stroke volume correspondingly. It is also been reported that, these effects are reversible, and when legs are returned to their horizontal positions, this preload increasing effect disappears[25]. Another important point is that PLR reaches its maximal effect in 1 min and its effects disappear gradually in time[26]. Accordingly, when PLR is used to predict fluid responsiveness changes in arterial pulse pressure[27], descending aorta blood flow[28], pulse contour-derived stroke volume, or pulsed Doppler-derived velocity-time integral[29] should be monitored closely at the first minute[25].

Briefly, fluid management must be done based on the patient's body fluid status. Patients who are responsive to fluids can benefit from fluid resuscitation, whereas patients who are not fluid responsive are more likely to suffer complications of over-hydration.

Therefore, common use of CVP, which is proved to be inefficient to predict fluid responsiveness, should be avoided and attempts should be made to extend the use of techniques like PLR, pulse pressure variation and the stroke volume variation. Practical tools should be manufactured and made available for common use.

TYPES OF INTRAVENOUS FLUIDS: CRYSTALLOIDS AND COLLOIDS

Intravenous fluids are classified into two main types: Crystalloids and colloids. Each group has its very own characteristics and moreover, each particular solution has its unique properties.

Crystalloids

Crystalloids consist of glucose or sodium chloride (saline) solutions. Osmolarity of the solution determines if the solution is hypotonic, isotonic or hypertonic. Isotonic solutions have the closest osmolarity to plasma and the other solution types are named comparing to plasma osmolarity. Saline solution containing 0.9 g of NaCl in each liter of water is defined as isotonic saline, and it is the most popular intravenous fluid worldwide. Some widely used saline solutions also contain one or more of these components: potassium, calcium, bicarbonate, lactate, and glucose. Isotonic glucose solution contains 50 g glucose in each liter of water and it is defined as isotonic glucose. Glucose in these solutions is metabolized right after administration and solvent is mixed into total body water. On the other hand, saline solution's high NaCl concentration serves to keep its solvent water in the extracellular compartment. However, any crystalloid solution can freely pass through double barrier of endothelium. This condition causes up to four-fifth of the infused crystalloid to distribute directly into the interstitial compartment[13,30]. Accordingly, crystalloid infusion in high amounts is related with serious complications, such as pulmonary edema[31], and hyperchloremic acidosis[32]. Despite that, colloid solutions are generally imprisoned in intravascular compartment, unless double-barrier of endothelium is impaired. Major advantage of crystalloids to colloids is containing only ions or small sized molecules which can easily be metabolized in reasonable amounts.

Colloids

Colloids can be blood products, such as human albumin solution and fresh frozen plasma, or they can also be synthetic large molecules which are not able to distribute across vascular barrier such as gelatins, dextrans, and hydroxyethyl starches.

Colloids are, like crystalloids, widely used in fluid resuscitation[33]. Although colloids are thought to be more useful than crystalloids for increasing intravascular volume and providing osmotic pressure, they are both shown to be similarly effective on mortality[34,35]. Colloid solutions are prepared by dissolving colloid molecules in isotonic saline solutions, or more rarely in other crystalloids.

Endogenous albumin is primarily responsible for intravascular osmotic pressure in healthy subjects. Thus, albumin, as an intravenous colloid solution, makes perfect sense to maintain intravascular colloid pressure. However, like all blood products, it has significant disadvantages, like allergic reactions and (theoretically) infection risks, although it is generally considered safe. Molecular weight of albumin is around 69000 Dalton. Gelatins, dextrans and hydroxyethyl starches (HES) are other common colloid substances. Gelatins are products of biochemical processes executed on bovine collagen. Although there are some concerns about its relation with Creutzfeld-Jacob disease and bovine spongiform encephalitis, there is no solid evidence proving these concerns[36,37]. Dextrans are polysaccharides that can vary in size. Most common types of dextrans are dextran 70 and dextran 40, which are named after their average molecular weights: 70000 and 40000 Dalton, respectively. Lastly, HES is a nonionic starch derivative, which is synthetized from amylopectin. HESs

also vary in molecular weight, and can be classified as low (70000-130000 Dalton), medium, and high (450000-480000 Dalton) molecular weights. They are also classified by their molar substitution degree, which defines the proportion of glucose molecules that are replaced by hydroxyethyls. HESs are the most commonly used colloids in Europe. Commonly used examples of these colloids are Voluven® (Fresenius Kabi, Bad Homburg, Germany) which is a 130000 Dalton tetrastarch, dissolved in saline with substitution degree of 0.4 and HAES-steril® (Fresenius Kabi, Bad Homburg, Germany) which is a 200000 Dalton pentastarch, dissolved in saline with substitution degree of 0.5.

Each type of colloid solution has its unique features. Effect on plasma volume and plasma viscosity, adverse reactions, and side effects on the system are the main concerns while choosing colloid solutions. Every colloid substance has a concentration decrease rate (half-life) in plasma by being metabolized, or by a loss through endothelial barrier and glomerular filtration. Half-life of a colloid determines the amount and the duration of plasma volume expansion. Higher molecular weight colloids tend to stay longer in the intravascular compartment. Besides, some studies point that the dextrans and the HESs provide significantly better expansion of plasma volume than the gelatins[38-40]. Whereas, some studies indicate that only albumin has significant advantage over other colloids and saline; and none of the other colloids is superior to others regarding plasma volume expansion[41-43].

All colloids provide a level of expansion in plasma volume and this leads to hemodilution. Hemodilution causes a decrease in plasma viscosity. However, it is known that some colloids cause a total increase in viscosity due to red cell aggregation. High molecular weight dextrans and HESs cause a significant increase in viscosity, while low molecular weight dextrans HESs and albumin solutions decrease both red cell aggregation and plasma viscosity[44-47]. Colloids have various effects on hemostasis, such as impaired platelet function, decreased factor VIIIc and von Willebrand Factor levels, in addition to previously described hemodilution and altered red cell aggregation[44,48,49]. Particularly, dextrans are known with their significant antithrombotic effects[49-51].

Accumulation of colloid substances in the body is possible. Dextrans and gelatins can be metabolized in humans. On the other hand, HESs may also accumulate. Metabolism and filtration of HES is relatively slow and storage in reticulo-endothelial system is not well recognized yet.

All colloids are large molecules and can trigger anaphylaxis of anaphylactoid events. Colloids also have minor anti-inflammatory effects.

Although it has been argued for a long time, there are still no definite rules on "crystalloid *vs* colloids" issue. There are studies that show crystalloid infusion is related with interstitial edema and worse anastomotic healing[31,52,53]. On the other side, it is still arguable that colloid solutions are able to prevent consequences of these negative effects[54,55]. In a study on pancreaticoduodenectomy patients, who are resuscitated with lactated Ringer's solution (isotonic crystalloid solution; including lactate, potassium and calcium in addition to sodium chloride), the significantly increased interstitial edema in jejunum was shown[56]. However, colloid use has been reported to have an increasing effect on mortality, in some fairly criticized studies, especially on critically ill patients[57,58]. On the other hand, CRISTAL trial, which is a multicenter randomized study on critically ill patients, failed to demonstrate this effect on mortality. In contrast, fewer death rates were found within 90 d in colloids group[54].

Moreover, although colloids are proved to be capable of maintaining efficient plasma volume, they do not appear to have positive effects on renal function. Contrarily, reports had shown significant harmful effects of dextran 40 use on kidney function in the second half of 20th century[59-61]. Some of the subsequent studies on HESs also revealed negative effects of these solutions on kidneys[62,63]. Schortgen *et al*[64] also reported that the use of hyperoncotic colloids and human albumin is significantly associated with renal dysfunction. However, in a multicenter study on over 3000 intensive care patients, no significant relation was detected between HES use and renal dysfunction[65]. Similarly, in a review of studies with different HES products, no adverse effects on kidneys were reported[66]. In a randomized clinical multicenter trial, 6997 critically ill patients were randomized into two groups. One group was assigned to receive 4% of albumin and the other group was assigned to receive saline for intravenous resuscitation during 28 d. There was no significant difference between two groups, regarding to mortality, days spent in intensive care unit, days of mechanical ventilation, or days of renal replacement therapy[67]. In addition to all of these results, it should be taken into consideration that none of the colloid solutions is proved to be directly toxic to the kidneys[68].

Considering all pros and cons of each solution family, it is still not possible to make a strict evidence based statement about how to use colloids and crystalloids[57,69]. It should be kept in mind that, crystalloids have less negative effects on hemostasis, immune system and kidneys; whereas colloids may provide a better plasma volume expansion with less interstitial edema in elective surgery patients[69].

FLUID RESUSCITATION STRATEGIES

Although there has been various different strategies defined in literature in decades, none has been adopted alone by most of the clinicians as the superior strategy. We think that many clinicians tend to keep their accustomed strategy, despite the evidences in the literature. There are studies that compare outcomes

of different strategies of fluid management. Lately, "crystalloids *vs* colloids" debates are fading, while recent studies mostly focus on the amount of fluid given perioperatively.

Traditional approach to determine the fluid amounts is more likely to generate formulas based on parameters such as patients' body weights and duration of surgeries. However, there is anevidence that each patient has his/her own body fluid status depending on the type of surgery, comorbid conditions, fluid already administered before, and various other factors. In addition, each patient should be considered as unique and his/her unique status should be monitored closely in the correct ways. As stated before, the main goal of fluid management is to maintain adequate tissue perfusion, with minimized risks of complications of over-hydration, such as pulmonary edema, cerebral edema, and intestinal edema. Both inadequate and excessive fluid administration may increase the stress on the circulatory system, and can affect tissue healing after surgery. From this perspective, without decent monitoring of patient's current status, any strategy may fail.

Debates about fluid management strategies are gathered around liberal strategy, restricted (conservative) strategy and goal-directed strategy so far. Liberal and restricted strategies are defined by different authors with variable volume ranges. For example, in one study, restricted fluid volume is defined as 1000 mL plus loss through drains[70], while in another study, patients in restricted fluid volume group were subjected to over 2000 mL fluid on the day of surgery[71]. These variances make it difficult to consider these studies as a whole. Still, majority of authors studying this subject point out that restrictive strategy has positive effects on gastrointestinal function, wound healing and pulmonary function[44,70,72-74]. Brandstrup *et al*[70] stated that, excessive hydration with crystalloids is related with increased major complications, such as leakage, peritonitis, sepsis, pulmonary edema and bleeding in patients who underwent elective colorectal surgery. Also, intestinal edema is known to be related with increased bacterial translocation and multiple organ dysfunction syndrome rates[75,76]. It can be concluded that, staying closer to the dehydration level is more reasonable, because it is safer and more efficient than administering large volumes to avoid dehydration. On the other hand, the liberal strategy is superior to the restricted strategy for reducing postoperative nausea, headache, dizziness and vomiting[77,78].

However, the goal directed strategy (GDS) is totally based on patient's current data, obtained from monitoring methods (See section: Monitoring body fluid status). Rivers and colleagues, one of the pioneers of this strategy, monitored CVP, mean arterial pressure, serum lactate, and mixed venous oxygen saturation in order to manage therapy in sepsis patients[79]. Later studies were focused on monitoring hemodynamics, and the effects of administered fluids on patients. Now, GDS can be defined as an individualized fluid therapy, based on patient's fluid responsiveness; in other words, "fluid need". The extra volume, which won't be able to affect the left ventricle stroke volume is regarded as unnecessary; and as a matter of fact, hazardous. It makes perfect sense to totally evaluate patient's needs and replace what is needed. Still, efficiency of GDS is limited with the power of our monitoring tools, which is determined by accessibility, applicability of the tools and the quality of information we acquire from them.

PPV and SVV are defined to monitor the fluid need of the patient dynamically as it is stated above[18]. Esophageal Doppler monitoring of cardiac volumes and aortic flow are also one of the helpful tools in GDS. In a systematic review of esophageal Doppler guided GDS studies; reduced hospital stay, fewer ICU admissions, and less inotropes usage were detected in GDS group[80]. In a single center, blinded, prospective controlled trial, 128 patients who underwent colorectal resection were randomized into two groups. Each group was managed with esophageal Doppler or CVP guided fluid therapy during surgery. Intraoperative Doppler guided fluid management was associated with decrease in the duration of hospital stay[81]. A randomized controlled study on 108 elective colorectal surgery patients also showed shorter hospital stay and decreased morbidity in GDS group[82]. GDS is also advantageous in patients who undergo major surgery[79]. A systematic review and meta-analysis studies by Hamilton on major surgery patients state that preemptive hemodynamic monitoring reduces mortality and morbidity[83]. Similarly, Poeze *et al*[84] showed that efforts to achieve an optimized hemodynamic condition resulted in a decreased mortality rate, in their meta-analysis study in 2005. Another meta-analysis also shows that GDS reduces both major and minor gastrointestinal complications after surgery[85].

In contrast with these studies, in a multicenter study, which included 762 high risk patients in 56 intensive care units, no significant effects of GDS were found. In this study, patients were randomly assigned to cardiac-index group, mixed venous oxygen-saturation group and standard therapy group. Predetermined hemodynamic targets were reached significantly better in the control group. There were no significant differences among the three groups, regarding mortality at six months. Even the subgroup analysis of patients, whose predetermined hemodynamic targets have been reached successfully, showed similar mortality rates among the three groups. Moreover, the number of dysfunctional organs and the duration of stay in the intensive care unit were similar in all groups[86].

Despite these evidences, low accessibility and applicability of esophageal Doppler are the major disadvantages of this method. This leads researchers to search for a more accessible and applicable method for common use in postoperative care unit, such as non-

invasive pulse oximetry and invasive arterial pressure measurement. Thus, predictive value of pulse pressure variation, systolic pressure variation and stroke volume variation tests for fluid responsiveness are defined[17]. All of these tests are applicable in an average postoperative care unit. However, the true value of these tests should be evaluated by larger studies. After that, optimization of patient monitoring devices should be done accordingly. Moreover, even PLR alone can provide important information about fluid responsiveness and lead the intensivists for GDS.

Since there is still insufficient number of randomized controlled trials with standardized criteria, the fluid management debates are going on. A consensus on criteria for each fluid management strategy should be made. We think that the related studies from all around the world with defined criteria are going to reveal the true value of each strategy.

Each surgeon should keep in mind that the patient is totally managed by the anesthesiologist during the surgery, so depending on the anesthesiologist's preference on fluid strategy, patient's fluid status after surgery may vary widely. Besides, intraoperative bleeding and other causes of surgical fluid loss should also be considered. During or after the surgery, the blood loss in patients with low hemoglobin levels is generally managed with erythrocyte suspensions. However, in patients with reasonable hemoglobin levels, appropriate fluid strategy should be chosen to avoid complications of transfusion. We think that determining the actual fluid status and the needs of a postoperative patient, by using monitoring tools and examining the report of the anesthesiologist, is of great importance.

CONCLUSION

Postoperative care units can be managed by an anesthesiologist, a surgeon or a team composed of both. Management of postoperative fluid therapy should be done considering both patients' unique status and intraoperative events. Thus, surgeons must be aware of pros and cons of current fluid management strategies and their effects on surgical outcome. Although there has been a significant progress on fluid status monitoring and fluid management strategies, most clinicians still prefer their traditional approaches for postoperative fluid management. This tendency towards empirical fluid management can be replaced by evidence based strategies, only if significant benefits of new strategies are proved with multicenter randomized controlled trials which use standardized criteria. GDS is the most rational approach to assess the patient and maintain optimum fluid balance. However, accessible and applicable monitoring tools for determining patient's actual fluid need should be further studied and universalized. The debate around colloids and crystalloids should also be considered with goal directed therapies. Advantages and disadvantages of each solution must be evaluated with the patient's specific condition.

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REVIEW

Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums

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Abstract

Thrombocytopenia is often noted in critically ill patients. While there are many reasons for thrombocytopenia, the use of heparin and its derivatives is increasingly noted to be associated with thrombocytopenia. Heparin induced thrombocytopenia syndrome (HITS) is a distinct entity that is characterised by the occurrence of thrombocytopenia in conjunction with thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin. HITS is an immunologic disorder mediated by antibodies to heparin-platelet factor 4 (PF4) complex. HITS is an uncommon cause of thrombocytopenia. Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%. It is a complex problem which may cause diagnostic dilemmas and management conundrum. The diagnosis of HITS centers around detection of antibodies against PF4-heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Several anticoagulants are used in management of HITS. In this review we discuss the incidence, pathogenesis, diagnosis and management of HITS.

Key words: Heparin; Thrombocytopenia; Critically ill; Diagnosis; Management

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Core tip: Thrombocytopenia is common in critically ill patients. While there are several causes of thrombocytopenia, heparin induced thrombocytopenia syndrome (HITS) is an uncommon cause often difficult to diagnose and manage. This article summarises the current diagnostic techniques and management options with a focus on critically ill patients with HITS.

Gupta S, Tiruvoipati R, Green C, Botha J, Tran H. Heparin induced thrombocytopenia in critically ill: Diagnostic dilemmas and management conundrums. *World J Crit Care Med* 2015; 4(3): 202-212 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i3/202.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i3.202

INTRODUCTION

It has been over 90 years since the discovery of heparin[1], and by the 1930s heparin was being used clinically as an anticoagulant[2]. Embolic events during heparin therapy were first described in 1957 and were followed by subsequent reports; however thrombocytopenia as a result of heparin therapy was not described until 1969[3-6]. The central features of heparin induced thrombocytopenia (HIT) syndrome (HITS) - thrombocytopenia, thrombosis and its immune pathogenesis - weren't recognized until the early 1970s[7].

Heparin and its derivatives are used frequently in the critically ill, either as thromboprophylaxis or for anticoagulation in patients with thromboembolic diseases. Thrombocytopenia occurs in 15%-58% of ICU patients[8,9]. Critically ill patients might suffer from a variety of acquired thrombotic risk factors related both to a host of chronic conditions such as obesity, hypertension, and diabetes mellitus, as well as acutely acquired conditions such as the postoperative state, sepsis, trauma, malignancy, other clonal disorders, *etc*.[10]. Hence, diagnosis of HIT syndrome is one of exclusion in the critically ill.

As HIT syndrome is a highly prothrombotic state, affected patients require ongoing anticoagulation with alternative anticoagulation such as the use of antithrombin anticoagulants or anti factor Xa agents[11,12].

As none of these agents have effective antidotes, management of bleeding associated with these agents is fraught with uncertainty.

HITS has been classified into two subtypes: HITS type 1: Benign non-immune condition occurring in 30%-40% patients exposed to heparin. platelets counts rarely fall below 100000/mcl. Heparin can be safely continued in this scenario and this condition is not discussed any further in the review; HITS type 2: Life threatening condition caused by antibodies against complexes of platelet factor 4 (PF4) and heparin, though occasionally other antigens may be implicated. Further discussion will relate to "type 2 HITS" only.

In this review, we focus on diagnostic dilemmas and management challenges associated with this complex problem.

PATHOGENESIS

Heparin mediated thrombocytopenia is an immunologic disorder mediated by antibodies to heparin-PF4 complex[13-16]. The Fab fragments from the IgG subclass of antibodies to PF4 bind platelet associated PF4. The F_c fragments of these antibodies bind to Fc_{γ}IIa receptors on the same or adjacent platelets, resulting in cross linking causing platelet activation. This results in generation of platelet microparticles that have procoagulant activity. This prothrombotic phenomenon is the principal difference between thrombocytopenia induced by heparin and other drugs such as quinine[17]. This marked release of the platelet microparticles is associated with massive thrombin generation, which explains the increased risk of thrombosis associated with HITS[18]. Significantly fewer platelet microparticles are generated in the presence of very high amounts of Heparin or in its absence, suggesting a stoichiometric relationship between HIT-IgG antibodies and heparin[17]. In addition to the increased thrombin generation in HITS, HITS antibodies also bind to endothelium-bound heparin resulting in release of tissue factor (TF) contributing to the overall prothrombotic state[19]. Recently, Monocytes have been found to bind hPF4 onto their surface and form antigenic complexes leading to monocyte activation and ultimately culminating in expression of TF. Both monocyte and endothelial activation may explain recurrence of thrombosis in many patients treated with direct thrombin inhibitors as none of them target these cells[20]. This may also explain the fact that HITS predisposes to both arterial and venous thrombosis even though it is primarily a platelet activation disorder. HIT-IgG antibodies also inhibit the generation of activated protein C by thrombin/thrombomodulin in the presence of PF4, augmenting the thrombotic state[21].

It seems that there might be a crucial period of exposure to heparin in patients who develop HITS. Patients, who suffer from conditions associated with high amounts of PF4 release prior to exposure to heparin, tend to be at a higher risk of developing HITS. For example, amongst elective hip replacement patients who receive preoperative low-molecular weight heparin (LMWH) are at a lower risk of HITS as compared to patients who receive post-operative thromboprophylaxis. This phenomenon of "point immunization" is probably explained by the fact that stoichiometrically optimal concentrations of heparin-PF4 are most likely to occur when PF4 is released prior to exposure to heparin[22]. Free nucleic acids in plasma can induce similar conformational changes in PF-4 as are induced by heparin, mainly because of the highly anionic Phosphate entities on the nucleic acid molecules. This finding may further explain the propensity for certain subgroups of patients (such as those with major

tissue damage) to develop pathological antibodies to heparin-PF4 complexes[23].

Two key determinants of antigenicity of a heparin preparation are chain length (approximately 1000 Da) and minimal amount of sulfation per saccharide unit. This explains lower risk of HITS with LMWH preparations as compared to unfractionated heparin (UFH)[24].

Occasionally, HITS can be caused by antibodies to other antigens such as neutrophil activating peptide-2 or interleukin 8.

EPIDEMIOLOGY

Reported incidence of HITS in patients exposed to heparin varies from 0.2% to up to 5%[25]. HITS is rare in ICU populations, with estimates varying from 0.39%-0.48%[26]. The incidence of HITS varies widely depending on the preparation of heparin, sex of the patients, and clinical population. The risk of HITS is higher amongst women [Odds ratio (OR) = 2.37]; among surgical patients as compared with medical patients (OR = 3.25); and patients on UFH *vs* patients receiving LMWH (OR = 5.29)[27]. Amongst surgical patients, although post-cardiac surgery patients tend to have a higher risk of developing HIT-IgG than post-orthopaedic surgical group (20% *vs* 3.2%), patients are much more likely to develop HITS after Orthopaedic surgery (OR = 21.1)[28]. Patients with major trauma are more likely to be Heparin-PF4 antibody positive and develop HITS as compared to patients with minor trauma[29]. HITS is very rare in obstetric or pediatric patients.

CLINICAL FEATURES

Heparin induced thrombocytopenia is characterized by thrombocytopenia and thrombotic manifestations after exposure to unfractionated heparin or low molecular weight heparin.

Thrombocytopenia

Onset of thrombocytopenia is usually between 5-10 d after the exposure, but it is faster (within a few hours to a day) if the patient has been exposed to heparin within 100 d of current exposure[30].

Platelet count usually drops to 50% or less of the baseline platelet count. Drop in platelet counts 30%-50% of baseline occurs in 10% of the cases[25].

Platelet counts usually do not fall below 20000/mcl. Lower platelet counts may be observed if HITS causes disseminated intravascular coagulation (DIC).

Bleeding is very rare as a complication of thrombocytopenia.

Recovery typically takes 4-14 d after cessation of heparin.

Pattern of thrombocytopenia occurring after the inciting event (such as cardiothoracic surgery) is important as well. A continuous decline after cardiopulmonary bypass is less likely to be due to HITS. A fall in platelet count of at least 40% between 5-10 d post cardiopulmonary bypass is likely to be due to HITS[31].

Thrombotic manifestations

Thrombotic manifestations develop in 20%-50% of the patients. HITS that is not associated with thrombotic phenomena is known as "isolated HITS".

Thrombosis can affect both arterial and venous beds. However, Venous thromboembolic complications are twice as likely as compared to arterial thrombotic phenomena. About 10%-20% patients suffer DIC.

Risk of thrombosis is higher for days to weeks after heparin is discontinued, even after normalization of the platelet counts[11].

Risk of thrombosis is higher in patients with higher level of antibodies to PF4-heparin complexes[32].

Other clinical manifestations that should raise the suspicion of HITS in appropriate clinical scenario: (1) acute anaphylactoid/anaphylactic reactions after heparin administration: Heparin induced anaphylactoid and anaphylactic reactions are two distinct patho-physiological entities. Heparin induced anaphylactoid reactions are due to activation of platelets and leukocytes in patients harbouring anti heparin-PF4 antibodies, typically administered a heparin bolus after prior exposure to heparin. Heparin induced anaphylactic reaction is due to a contaminant (oversulphated chondroitin sulphate or OSCS) activating the contact system resulting in the clinical manifestations. However, patients exposed to OSCS contaminated heparin are more likely to develop pathological HITS antibodies[33]; (2) heparin induced skin lesions: These painful or pruritic necrotic lesions develop at the site of injection, beginning on day 5 or later after exposure to heparin or LMWH. Non-necrotic lesions at the injection sites are almost always due to delayed hypersensitivity to heparin rather than a manifestation of HITS, especially after exposure to LMWH rather than Unfractionated heparin[34]; (3) heparin induced skin necrosis and venous gangrene: especially in the presence of coumarin, attributed to both macro and micro vascular thrombosis with preserved arterial flow. Inhibition of activated protein C by heparin PF4 antibodies could be a strong contributory factor[21]; and (4) transient global amnesia[35].

These manifestations curiously, tend to occur in the absence of thrombocytopenia[25].

DIAGNOSIS

The diagnosis of HITS centers around detection of antibodies against PF4-Heparin complexes. Immunoassays performed by most pathology laboratories detect the presence of antibodies, but do not reveal whether the antibodies are pathological. Platelet activation assays demonstrate the presence of clinically relevant antibodies, but only a minority of laboratories conduct them. Before elaborating further on the diagnostic assays, it is vital to consider the following

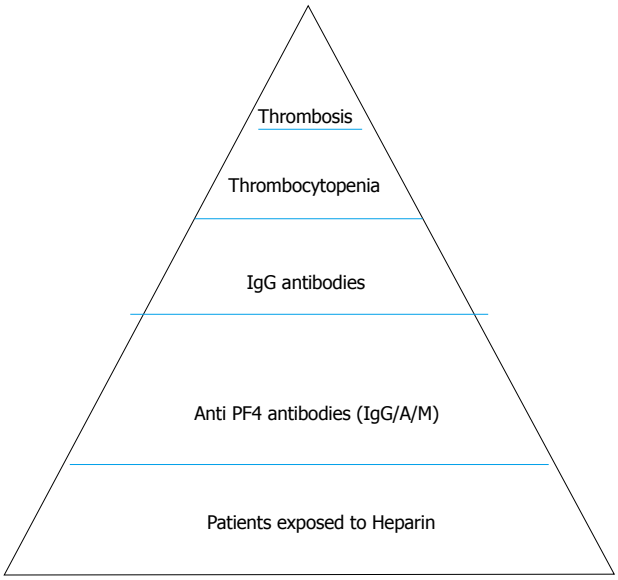

Figure 1 Iceberg model for heparin induced thrombocytopenia syndrome heparin induced thrombocytopenia syndrome as proposed by Warkentin *et al*[37]. The size of various iceberg sections and the portion seen, can vary in proportion to the other sections depending on the population of patients, preparation of heparin used, *etc*.

facts: (1) heparin-PF4 antibodies can exist naturally in people unexposed to heparin in the past[36]; (2) only IgG subclass of antibodies are pathological. Hence assays which are not IgG specific are likely to yield a higher false positive result; (3) out of the patients who are anti heparin/PF4IgG positive, only a minority will be positive by the "Gold Standard" platelet activation assays; (4) not all patients with platelet activating antibodies develop the clinical syndrome of HITS; and (5) fraction of the patients with heparin/PF4 antibody depends on the patient population and the type of heparin preparation used.

The above phenomena observed have been conceptualized as an "iceberg model" by Warkentin *et al*[37], and highlight the fact that HITS is a clinicopathological syndrome rather than just a laboratory diagnosis (Figure 1).

The diagnosis of HITS centers around the pretest probability of HITS being the cause of the drop in platelet count and/or the thrombotic phenomenon observed. In light of this the "4-T's" scoring system was introduced (Table 1)[38]. Low pretest probability score ruled out HITS in all but one of the 119 patients studied.

Patients with intermediate or high pre-test probability of HITS should be investigated further with enzyme linked immunosorbent assay (ELISA) based methods[12].

These assays use heparin-PF4 or polyvinyl sulfate-PF4 immobilised onto microtiter plates as antigens. Antibodies in the patient's plasma bind to these antigens and is detected using goat anti human IgG/A/M bound to alkaline phosphatase. Substrate, subsequently added, changes colour in presence of the enzyme. The intensity of the colour change is measured as optical density (OD) and is directly proportional to the concentration of the antibodies[39]. Even though these tests are very sensitive (negative predictive values of close to 100%), they tend to yield a high number of false positive results for HITS, depending on the manufacturer of the assay kit and the clinical population. Higher rates of false positive ELISAs are noted in patients post cardiac surgery and those with antiphospholipid antibody (APLA) syndrome. Anti PF4 antibodies rather than anti PF4/heparin antibodies are responsible for false positive ELISA in sera with APLA syndrome[40].

Following measures may be taken to increase the specificity of ELISA based assays (Table 2): (1) using IgG specific assays: As IgG antibodies are pathogenic, using specific assays targeting IgG antibodies rather than non-specific assays improves the specificity of the test without sacrificing the sensitivity of the assay; (2) using higher OD cut offs: As higher titers of antibodies are associated with a greater probability of HITS, using higher cutoff values (for example 1.0 instead of 0.4) might increase the specificity of the assay. However, this comes at cost of sacrificing sensitivity of the assay; and (3) confirmatory step using high concentration of heparin: As heparin and anti heparin-PF4 antibodies have a stoichiometric relationship, re-performing the ELISA test with higher concentrations of heparin may confirm the presence of anti heparin-PF4 antibodies. However, this approach requires the test to be performed twice, increasing the cost and the turn around time. It can also be falsely negative if the titre of the antibodies is very high.

Diagnosis of HITS should be confirmed with functional platelet assays in patients with intermediate pretest probability and positive ELISA or in patients with high pretest probability with negative ELISA (Figure 2).

Selection of platelet donors can be potentially critical for these assays as certain polymorphisms on the $Fc_{\gamma}RIIa$ receptors affects the response of platelets to the activating monoclonal antibodies[41].

Serotonin release assay (SRA) is the gold standard test for diagnosis of HITS. It utilizes washed donor platelets incubated with ^{14}C-labelled serotonin. It is considered positive when more than 20% serotonin is released at therapeutic heparin concentrations (0.1-0.3 IU/mL), but not at supra-therapeutic heparin levels (10-100 IU/mL)[42]. In Australia, out of 675 SRAs requested to the only centre performing this assay between 2010-2012, around 19% were positive for HITS. Interestingly, amongst cases in which 4T score was available, almost 96% had intermediate or high probability 4T score[43].

Whole blood impedance aggregometry (WBIA) is emerging as a useful alternative to SRA with faster turnaround time (around 15 min), does not use washed platelets and no radioactive waste products. The laboratories running this assay still need access to high reactive platelet donors as using less responsive platelet donors might result in false negative WBIA. The agreement of WBIA with SRA improves if a higher cut

Table 1 4T score as studied by Lo *et al*[38]

Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)			
	2	1	0
Thrombocytopenia	> 50% fall or platelet nadir ≥ 20 × 10^9/L	30%-50% fall or platelet count 10-19 × 10^9/L	Fall < 30% or platelet nadir < 10 × 10^9/L
Timing of fall in platelet count	Clear onset between day 5-10[1]; or less than 1 d (if history of heparin exposure within 30 d)	Consistent with d 5-10 fall, but not clear (*e.g.*, missing platelet counts) or onset of thrombocytopenia after d10 or fall ≤ 1 d (prior heparin exposure 30-100 d ago)	Platelet count fall < 4 d without recent heparin exposure
Thrombosis or other sequelae (*e.g.*, Skin lesions)	New thrombosis; skin necrosis; acute systemic reaction post unfractionated heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause of thrombocytopenia	None apparent	Possible other cause is evident	Definite
4T score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low			

[1]5-10 d after exposure to heparin or low molecular weight heparin.

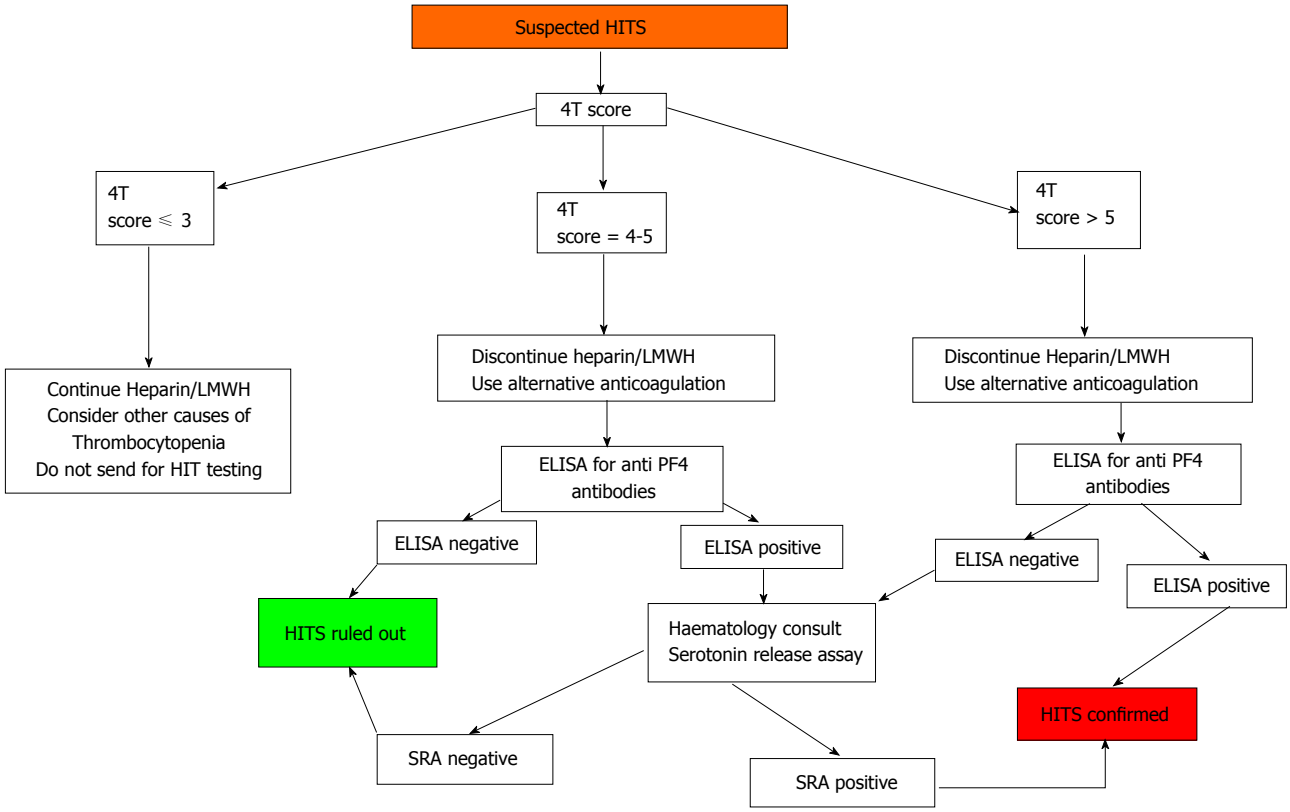

Figure 2 Diagnostic algorithm for Heparin induced thrombocytopenia syndrome. Note that Confirmatory assays for HITS should be considered on the basis of pre test probability rather than ELISA alone. HITS: Heparin induced thrombocytopenia syndrome; SRA : Serotonin release assay. ELISA : Enzyme linked immunosorbent assay.

off of 50% instead of 20%, and if a high dose heparin confirmatory step is used[44].

TREATMENT

Once a presumptive diagnosis of HITS is made on the basis of pretest probability and anti PF4 antibody assays, therapeutic dosing of alternative anticoagulant is needed along with cessation of the offending agent. Patients are hypercoagulable for days to even weeks despite normalization of platelet counts[11]. Hence, patients may need to be transitioned to oral anticoagulants once platelet counts have normalized.

Ideal anticoagulant for treatment of HITS should have following characteristics: (1) should have no risk of generating HITS antibodies; (2) should have robust evidence supporting its use in HITS; (3) should be able to provide predictable anticoagulation and be able to be monitored by an widely available assay; (4) should have short half life; (5) should be easily reversible by an antidote which is readily available; (6) should have a low risk of bleeding and other adverse effects; (7) metabolism and elimination should be reliable and independent of renal or hepatic dysfunction; (8)

Table 2 Characteristics of various assays for heparin induced thrombocytopenia syndrome

	4T score ≤ 3[73-76]	ELISA[77]	IgG specific ELISA[77]	OD cut off ≥ 1.0[78]	Heparin confirmation step for IgG specific ELISA[79]	Serotonin release assay[80]	Whole blood impedence Aggregometry[44]
Sensitivity	-	100%	100%	80%	94%	100%	90.3%-93.6%
Specificity	-	81%	89%	85%	90%-93%	95%-97%	89%-96%
PPV	-	28%	40%	42%	45%	NA	84.4%-94.8%
NPV	100%	100%	100%	84%	99.50%	NA	-

PPV: Positve predictive value; NPV: Negative predictive value; NA: Not applicable as serotonin release assay is the gold standard assay for diagnosis of heparin induced thrombocytopenia syndrome.

Table 3 Characteristics of alternative anticoagulants

Drug	Route of elimination	Plasma half life	Monitoring	Interaction of antibodies with HITS antibodies	Antidote
Lepirudin	Renal	60 min, up to 200 h in anuric patients[81,82]	aPTT (1.5-2 times baseline) ACT on CPB ECT (Not affected by presence of VKAs or UFH)	None	None ?Haemofiltration[47]
Desirudin	Renal	2-3 h	None	None	None
Danaparoid	Renal	24 h	Anti-Xa activity (0.5-0.8 U/mL)	Possible, but very rare	None
Argatroban	Hepatic	40-50 min	aPTT (1.5-3 times baseline) ACT on CPB	None	None
Bivalirudin	Enzymatic 80% (Thrombin), renal 20%	25 min	aPTT (1.5-2.5 times baseline) ACT on CPB	None	None ?Haemofiltration[52]
Fondaparinux	Renal	17-20 h	None, Anti Xa levels with renal impairment	Case reports only[45,61,62]	None

aPTT: Activated partial thromboplastin time; ACT: Activated clotting time; ECT: Ecarin clotting time; CPB: Cardiopulmonary bypass; HITS: Heparin induced thrombocytopenia syndrome; UFH: Unfractionated heparin.

should be safe to use in special subgroup of patients such as those who are pregnant or need to go on to cardiopulmonary bypass; and (9) should be easily available in both oral and intravenous preparations for easy transition between short and longer term anticoagulation.

Unfortunately, such an anticoagulant doesn't exist. Most of the problems from anticoagulation in HITS arise because of the lack of familiarity with non-heparin anticoagulants.

Following are the different categories of anticoagulants which can be used for HITS, based on the clinical scenario (Tables 3 and 4): (1) direct thrombin Inhibitors: Univalent direct thrombin inhibitors (argatroban; dabigatran), bivalent direct thrombin inhibitors [recombinant hirudins (lepirudin, desirudin); synthetic hirudin (bivalirudin)]; and (2) factor Xa antagonists: danaparoid, fondaparinux, rivaroxaban, apixaban.

DIRECT THROMBIN INHIBITORS

Lepirudin

A recombinant hirudin derived from yeast cells, Lepirudin was the first drug approved by United States Food and Drug Administration, for the treatment of HITS in 1998. Even though it reduced new thromboembolic manifestations, it increased the risk of major bleeding in a combined analysis of 3 prospective trials with historical controls[45].

Retreatment with lepirudin can increase the risk of anaphylaxis almost half the patients will develop antibodies to lepirudin on initial use. The risk of antibody formation can be reduced by avoiding the bolus and reducing the duration of infusion as much as possible[46].

Although no antidote is available, use of activated Factor VII to control bleeding and haemofiltration has been described[47,48].

Argatroban

Argatroban is a synthetic L-arginine derivative, which is tolerated well by patients with moderate renal dysfunction[49].

Even though the half life is short and use in mild to moderate renal dysfunction is safe, rebound hypercoagulability after cessation of infusion, and spurious prolongation of Prothrombin time when given with warfarin are significant issues, especially when transitioning to longer term oral anticoagulation.

A severity of illness based dosing regime for continuous renal replacement therapy in critically ill is available but not validated[50].

Bivalirudin

Bivalirudin is a hirudin based synthetic direct thrombin

Table 4 Dosage and availability of anticoagulation agents for heparin induced thrombocytopenia syndrome

Drug	Bolus	Dosage	Dosage in renal impairment	Dosage in hepatic impairment	Availability in Australia
Lepirudin	Only if life or limb threatening thrombosis. 0.4 mg/kg *iv*	0.1-0.15 mg/kg per hour	Cr. Cl. 45-60: 50% of original infusion rate. Cr. Cl. 30-44: 30% of original infusion rate. Cr. Cl. 15-29: 15% of original infusion rate according to body weight. Avoid if Cr. Cl. Lower or use 0.005 mg/kg per hour if on haemofiltration	No change	Discontinued
Desirudin	None	15-30 mg *sc bd*. Limited data	Not recommended given paucity of data	No change	Not available
Danaparoid	IV according to body weight. < 60 kg: 1500 U; 60-75 kg: 2250 U; 75-90 kg: 3000 U; > 90 kg: 3750 U	400 U/h IV × 4 h followed by 300 U/h IV × 4 h followed by 200 U/h *iv*	Reduce dose by 30% and monitor antiXa activity	No change	Available
Bivalirudin	None	0.15-0.2 mg/kg per minute	Cr. Cl 10-29: 0.06 mg/kg per minute; Cr. Cl < 10: 0.015 mg/kg per minute *iv*	No change	Available
Fondaparinux	None	< 50 kg: 5 mg *sc*; 50-100 kg: 7.5 mg *sc*; > 100 kg: 10 mg *sc*	Cr. Cl 30-50: monitor closely. Cr. Cl < 30: Contraindicated	No change	Available
Argatroban	None	2 mcg/kg per minute *iv*	No change	0.5 mcg/kg per minute	Not available

Cr. Cl.: Creatinine clearance in mL/min; *sc*: Subcutaneous; *iv*: Intravenous.

inhibitor, which binds to free as well as bound thrombin reversibly. It has the shortest half-life amongst the direct thrombin inhibitors and has higher reversibility as up to 80% is eliminated by enzymatic proteolysis[51]. Due to better pharmacokinetic profile, this is the agent used most widely in patients needing cardiopulmonary bypass. hemodialysis, haemofiltration or plasmapheresis may be used to reverse its effect, even though the data available for efficacy of these therapies is limited[52].

Desirudin

Desirudin is a recombinant hirudin and is a bivalent, irreversible direct thrombin inhibitor. There is very limited data about use of Desirudin for HITS. An open label randomized pilot trial comparing Desirudin with Argatroban for HITS (PREVENT-HIT) was closed because of poor accrual[53,54].

FACTOR XA INHIBITORS

Fondaparinux

Fondaparinux is a sulfated pentasaccharide derivative of heparin which binds to antithrombin, inhibiting factor X[55]. Even though the frequency of heparin - PF4 antibody is similar to Low molecular weight heparins, Fondaparinux induced antibodies are seldom pathogenic[56,57].

The risk of bleeding while treating HITS is around 5%. Even though some cases of HITS caused by Fondaparinux have been described in literature, benefits such as ease of administration, predictable pharmacokinetics in patients with normal renal function and lack of effect on aPTT makes it an attractive option in patients in whom benefits outweigh low risk of exacerbation of HITS[45,58-62].

Danaparoid

Danaparoid, a mixture of low molecular sulphated glycosaminoglycans, Heparan, dermatan and chondroitin sulphate is a factor Xa inhibitor. The requirement for monitoring anti Xa levels in most of the critically ill patients developing HITS and risk of cross reaction with heparin-PF4 antibody (< 10% patients) are the factors which need to be considered before using Danaparoid for HITS[63].

TRANSITION TO ORAL VITAMIN K ANTAGONISTS

For isolated HITS, alternative anticoagulation with or without transition to oral vitamin K antagonists is recommended for up to 4-6 wk. For HITS associated with thrombosis, switching to warfarin followed by continuation of warfarin therapy for 3 mo is recommended.

Transition to warfarin should only be made once platelet count is > 150000/mcl. Warfarin needs to be overlapped with alternative anticoagulation for at least 5 d and until the INR is in the therapeutic range.

Fondaparinux or Danaparoid may be required for transition of Argatroban to oral vitamin K antagonists due to effect of Argatroban on INR.

SPECIAL PATIENT POPULATIONS

Pregnancy

HITS is extremely rare during pregnancy and all the data regarding diagnosis and management is anecdotal. Thrombocytopenia occurs in 7%-8% pregnancies. Most common reason for thrombocytopenia is gestational (haemodilution, increased platelet aggregation due to

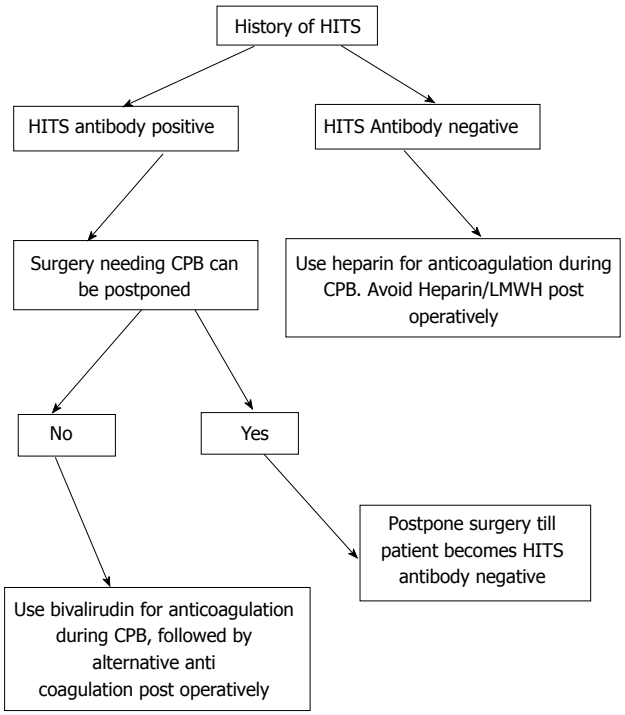

Figure 3 Suggested approach for patients with heparin induced thrombocytopenia syndrome needing cardiopulmonary bypass. HITS: Heparin induced thrombocytopenia syndrome; CPB: Cardiopulmonary bypass.

raised thromboxane A_2, increased platelet consumption) followed by other causes such as HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, Preeclampsia/eclampsia, acute fatty liver disease of pregnancy, Idiopathic thrombocytopenic purpura, *etc*.[64].

In a review of 2777 pregnancies involving exposure to LMWH, none of the patients developed thrombocytopenia attributable to HITS[65].

Ease of administration, safety in longer term use, and transplacental transfer are special considerations in this group of patients. Despite case reports of the use of argatroban, fondaparinux and danaparoid are preferred because of their subcutaneous administration and availability of large data on longer term use during pregnancy[66-68].

Cardiopulmonary bypass

Patients with history of HITS that require cardiopulmonary bypass can be managed based on their HITS antibody status (Figure 3).

Bivalirudin is the alternative anticoagulant most well described in literature, however lepirudin and argatroban have also been described[69-72].

We recommend Bivalirudin for anticoagulation while on cardiopulmonary bypass, as it has been compared directly with heparin in an open label randomized control trial with heparin and protamine reversal. As Bivalirudin is metabolized by thrombin in the blood, care must be taken to avoid any stasis in the venous circuit, surgical field, and the vein grafts. Citrate phosphate dextrose acetate is used for anticoagulation in the cell saver.

CONCLUSION

The diagnosis of HITs in critically ill patients requires early recognition for successful management. Exclusion of other causes for thrombocytopenia and or thrombosis with special consideration to the temporal relationship of onset of thrombocytopenia with exposure to UFH/LMWH is vital. Use of clinical pretest probability scores such as 4T score in conjunction with more specific assays such as anti-IgG heparin PF4 antibody may reduce over-diagnosis of the disease. Confirmatory tests such as the SRA should be considered for equivocal cases; new tests such as WBIA based assay show promise. Attention to risk of bleeding with invasive interventions, presence and degree of renal/hepatic dysfunction, and availability and cost of alternative anticoagulation agents is important. Finally, patients requiring cardiopulmonary bypass and pregnant patients present rare and challenging scenarios.

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REVIEW

Steps to consider in the approach and management of critically ill patient with spontaneous intracerebral hemorrhage

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Abstract

Spontaneous intracerebral hemorrhage is a type of stroke associated with poor outcomes. Mortality is elevated, especially in the acute phase. From a pathophysiological point of view the bleeding must traverse different stages dominated by the possibility of re-bleeding, edema, intracranial hypertension, inflammation and neurotoxicity due to blood degradation products, mainly hemoglobin and thrombin. Neurological deterioration and death are common in early hours, so it is a true neurological-neurosurgical emergency. Time is brain so that action should be taken fast and accurately. The most significant prognostic factors are level of consciousness, location, volume and ventricular extension of the bleeding. Nihilism and early withdrawal of active therapy undoubtedly influence the final result. Although there are no proven therapeutic measures, treatment should be individualized and guided preferably by pathophysiology. The multidisciplinary teamwork is essential. Results of recently completed studies have birth to promising new strategies. For correct management it's important to establish an orderly and systematic strategy based on clinical stabilization, evaluation and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies, including hemostatic therapy and intensive control of elevated blood pressure. Uncertainty continues regarding the role of surgery.

Key words: Intracerebral hemorrhage; Prognosis; Hematoma expansion; Inflammation; Hemostatic therapy; Oral anticoagulants

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Core tip: Spontaneous intracerebral hemorrhage is associated with poor outcome. Neurological deterioration and death are common in early hours, so it is a true neurological-neurosurgical emergency. Nihilism and early withdrawal of active therapy clearly influence the outcome. Action should be taken fast and accurately. Treatment should be individualized and guided preferably by pathophysiology in a multidisciplinary team work. For correct management it's important to establish an orderly and systematic strategy based on clinical stabilization, evaluation and establishment of prognosis, avoiding secondary insults and adoption of specific individualized therapies, including hemostatic therapy and intensive control of elevated blood pressure.

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INTRODUCTION

Intracerebral hemorrhage (ICH) is defined as the spontaneous extravasation of blood into the brain parenchyma with or without extension of bleeding into subarachnoid or intraventricular spaces[1-4]. ICH account for 10% to 30% of all stroke-hospital admissions[1-4], and is one of the most devastating forms of stroke. Its estimated incidence is between 12 and 15 cases per 100000 inhabitants per year. Arterial hypertension and oral anticoagulants are the major risk factors[1-4]. The clinical presentation is characterized by a rapidly deteriorating neurological status coupled with signs and symptoms of elevated intracranial pressure[1-5]. The diagnosis is established by the use of neuroimaging [computed tomography (CT) scan or magnetic resonance imaging (MRI)][1-5]. The mortality rate is averaging 50%, most of which occur during the first 5 d[1-5]. Only one-third of the survivors resume his life prior to the event[1-5]. Unfortunately, there is no proven specific treatment; however, a comprehensive and multidisciplinary approach based on pathophysiology helps to achieve favorable results[1-5]. The main objective of this manuscript is to review all aspects of spontaneous ICH, with emphasis on its pathophysiology with the intention to suggest steps to consider for the management of this lethal entity (Figure 1).

TO DELETE NIHILISM AND SELF-FULFILLING PROPHECIES

Nihilism (from the Latin nihil, "nothing") is the philosophical principle that is based on the negation of one or more of the supposed meanings of life. Nietzsche indicates that denial or disbelief in anything are the results of doubt and disorientation[6]. The nihilism has dominated the scene of spontaneous ICH for many years, perhaps due to the absence of specific therapies. One of the most important determinants of the outcome of the individual victims of ICH is the level of support provided. If this support is not adequate or suspended based on beliefs of poor prognosis, it can trigger self-fulfilling prophecies[7]. As stated by Robert Merton, self-fulfilled prophesies are based on a false conception or belief that eventually triggers a behavior or conduct false that with the time becomes true[8].

Moreover, in ICH and other brain injuries, orders of do-not-resuscitation (DNR) or withdrawal of support based on self-fulfilled prophesies or nihilism, have a definite influence on mortality[7,9,10]. Delete nihilistic attitude is indispensable in the management of spontaneous ICH.

These philosophical principles have scientific evidence that supports them. Various studies have highlighted the impact of treating this population of patients in specialized, multidisciplinary units, which increase the probability of survival and good outcome[11,12]. The reasons remain uncertain, but several factors seem to influence, such as; the absence of nihilistic attitude, decreased stay in intensive care units, a lower incidence of neurological or systemic complications and early discharge to rehabilitation units[11-13].

TO KNOWN NATURAL HISTORY AND PATHOPHYSIOLOGY OF INTRACEREBRAL HEMORRHAGE

Natural history

Thirty-day mortality of ICH victims is nearly to 50%, most of which occurs during the acute phase[1-4]. The causes of death vary according to the time course of the disease[14-16]. Nearly 80% of cases of early death are of neurological origin[14-16]. About one-fifth of these patients does not reach the hospital and dies due to the magnitude of the primary or initial damage[17]. The rest of the patients dies by withdrawal of support due to brain death secondary to localization of the bleeding (brainstem); intracranial hypertension due to initial bleeding or as a result of the expansion of the hematoma[14-16]. The remaining 20% died by cardiac causes[14-16]. After the first week, death is caused by medical complications, mainly sepsis[14-16].

One-year mortality varies according to different locations: 51% for deep (thalamic or putaminal), 57% for lobar, 42% for cerebellar and 65% for brain stem

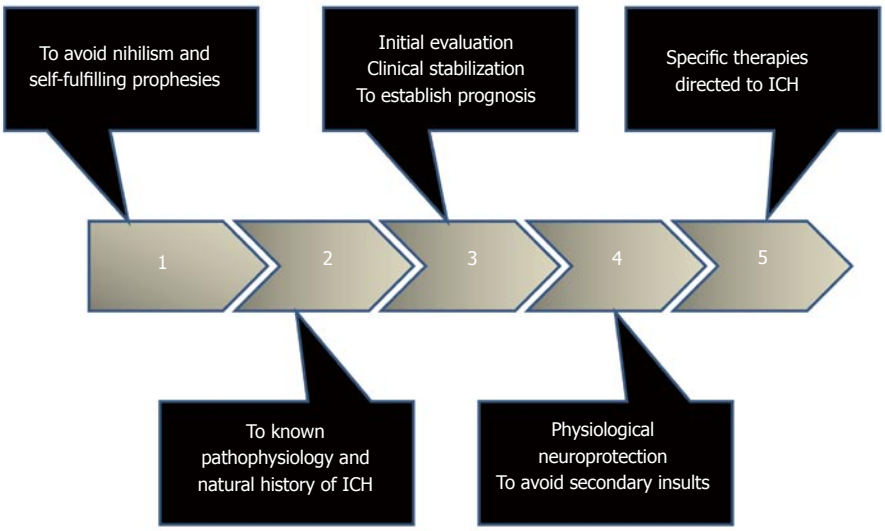

Figure 1 Steps to consider in the approach to the critically ill patient with spontaneous intracerebral hemorrhage. ICH: Intracerebral hemorrhage.

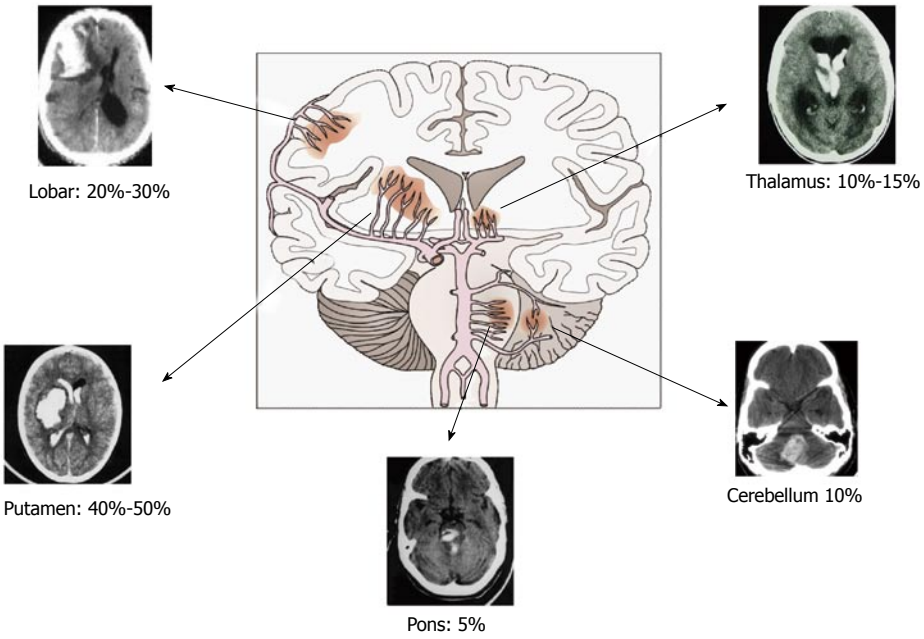

Figure 2 Typical sites of bleeding in spontaneous intracerebral hemorrhage.

hemorrhages, respectively[1].

Pathophysiology of spontaneous ICH

The events that follow bleeding within the brain parenchyma are varied, complex, simultaneous, and interrelated. For teaching purposes, we will divide them, in different phases[18].

Vascular rupture: Arterial hypertension is a common risk factor for ICH[1-5]. Nearly 80% of patients with ICH present arterial hypertension at the admission and most have a history of hypertension[1,5]. Chronic hypertension imposes constant mechanical stress to cerebral arterioles (60-100 μ in diameter), which triggers hyperplasia of smooth muscle cells[1-5,19]. Over time, muscle cells die, are replaced by collagen, weakening the arterial wall, making it prone to stasis, occlusion, and rupture[19].

The sites at higher risk for these changes are the bifurcations or branches of penetrating arteries, such as lenticulostriate, thalamus and brainstem perforating arteries, thus explaining the most common hematoma locations[1-5] (Figure 2).

The extent of bleeding is mainly determined by the size of the gap in the arteriolar wall, systemic blood pressure, and hemostatic mechanisms[19].

Sometimes, the arterioles invaded by collagen develop microscopic dilatations, known as "Charcot-Bouchard aneurysms". These changes can be found in autopsy specimens, but they are not always associated

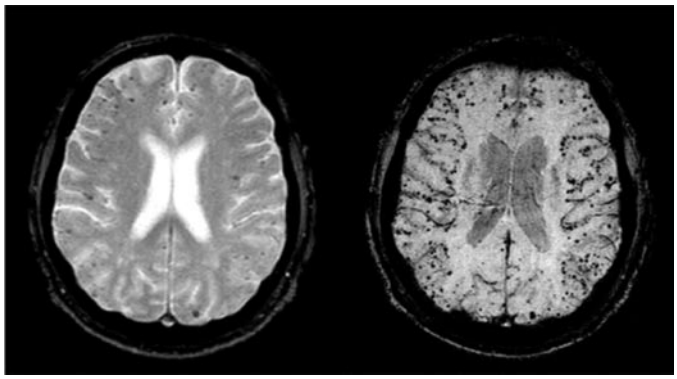

Figure 3 Micro bleeds in magnetic resonance image.

with bleeding sites; therefore, their clinical significance is controversial[1-5,19].

In non-hypertensive individuals, particularly the elderly, amyloid angiopathy is the substrate of arterial bleeding. It results from the deposition of amyloid protein in the tunica media and adventitia of capillaries, arterioles, cortical and leptomeningeal arteries causing fragility of the vessel wall. These vessels could break spontaneously or for sudden and abrupt blood pressure changes. Distinctive features of this entity are the predilection for lobar regions (especially in the posterior areas of the brain), multifocality, and recurrence[1-5,19].

Today, attention is directed towards early detection of micro hemorrhages by MRI, because these have been shown to predict higher risk of lobar ICH[19,20] (Figure 3).

Following vascular rupture, the phase of *hematoma formation* begins, which develops within 60 min of the initial bleeding[18]. The sudden bleeding into the brain causes mechanical destruction of the parenchyma and may produce mass effect with increased intracranial pressure, distortions and tissue shift with potential herniation and cerebral ischemia[1-5,19,20]. The bleeding also triggers cell death through necrosis and apoptosis[18,21]; inflammation[18,21,22]; and vasogenic edem[18,21-23].

A substantial proportion of patients has enlargement of the *hematoma* after the initial event. This expansion is often associated with deterioration of neurological status and poor clinical outcomes[1-5,24-26].

An increase in the volume of the hematoma is seen in 38% of patients during the first three hours post-stroke. In two-thirds of this population, expansion of the hemorrhage is evident in the first hour[24-26]. Hematoma growth may occur despite the absence of coagulopathy and although knowledge of the mechanisms of expansion remain inconclusive, they seem to involve continuous bleeding from the initial site or additional bleeding from damage to adjacent small vessels causing satellite hemorrhages at the periphery of the clot[19].

Various risk factors have been associated with hematoma enlargement. Alcohol abuse, irregularly shaped hematomas, low levels of fibrinogen and prothrombin, diabetes mellitus, liver disease, are frequently reporters factors. However, the most consistent is the time elapsed between symptom onset and first CT scan[18,24,27,28]. Longer is the time until the first imaging study, lower the probability of detecting this complication.

After the initial 24 h, the next phase is dominated by the development of edema around the hemorrhage. This period reaches its peak on the third day after the first bleeding, and then declines slowly[18,21,23].

The most severe form of edema is localized around the clot, mainly spread through the white matter. This edema is primarily vasogenic due to alteration of the blood-brain barrier (BBB). Physical destruction damages the BBB and for the synthesis of substances that contributes to damage, such as thrombin and extracellular matrix metalloproteinases[18,21,23].

Cerebral blood flow and metabolism during intracerebral hemorrhage

After ICH, cerebral blood flow (CBF) changes with a characteristic temporal profile[29]. Three phases have been described[29]: (1) phase I: first 48 h. Metabolism and CBF are reduced in a coupled manner. This period is known as "hibernation phase"; (2) phase II or reperfusion phase: between days 2 to 14. CBF and metabolism vary in the whole cerebral parenchyma, with areas of hypo normal and high CBF; and (3) phase III - normalization: starts in the second week after hemorrhage. CBF and metabolism return to normal values, except in the hemorrhagic site.

Multiple factors contribute to CBF alterations: mechanical compression of microvasculature, intracranial hypertension, disruption of cerebral autoregulation, vasoactive substances and inflammation[29]. Following ICH, CBF decrease, with lowest values in the perihematomal region[30,31], however in this zone, metabolic activity also decrease, indicating the absence of ischemia[32-34].

In summary, the available data allow us to confirm that the area around ICH is characterized by a slight decrease in regional cerebral blood flow but this occurs as a result of the concomitant decrease in metabolic demands. Mitochondrial dysfunction might be responsible for the metabolic depression[35].

Metabolic penumbra

Recent studies of metabolism in perihematomal zone have revealed a remarkable metabolic distress

Table 1 Intracerebral hemorrhage score

Components	Points
GCS score	
3-4	2
5-12	1
13-15	0
ICH volume (cm^3)	
⩾30	1
< 30	0
IVH	
Yes	1
No	0
Infratentorial origin of ICH	
Yes	1
No	0
Age (yr)	
⩾ 80	1
< 80	0
Total ICH score	0-6

GCS: Glasgow coma scale; IVH: Intraventricular hemorrhage; ICH: Intracerebral hemorrhage.

Table 2 Secondary insults

Systemic	Intracraneal
Arterial Hypotension	Intracranial hypertension
Hypoxia	Cerebral hematoma
Hypercapnia - Hypocapnia	Edema
Hyperthermia	Seizures
Hyperglycemia - Hypoglycemia	Vasospasm
Hyponatremia - Hypernatremia	Hydrocephalus
Anemia	Infections
SIRS	
DIC	

SIRS: Systemic inflammatory response syndrome; DIC: Disseminated intravascular coagulation.

characterized by an increase in the uptake and glucose utilization especially in the first 4 d after hemorrhage[36]. This metabolic crisis may persist for about one week, and it is not a consequence of ischemia; therefore, we should speak of metabolic penumbra rather than ischemic penumbra[36].

The other phenomena taking place around the hematoma are inflammation and neurotoxicity[18,21,22]. Bleeding activates astrocytes and microglia, which in turn stimulate the release of pro-inflammatory mediators, such as cytokines, intercellular adhesion molecules, and matrix metalloproteinases[18,21,22].

Neurotoxicity occurs through extravasation of proteins and osmotically active solutes that promoting the development of edema and stimulation of proteinases such as thrombin, fibrinogen, and tissue plasminogen activator. The coagulation cascade is activated in conjunction with lysis of red blood cells, which releases potent neurotoxic substances, such as iron, bilirubin, and hemin[18,21,22].

TO SET THE SEVERITY AND PROGNOSIS

Prognostication is essential for a correct approach. From a practical point of view, the severity of ICH can be established accurately with clinical examination and neuroimaging[1-5,37]. Glasgow coma scale (GCS) is the most commonly used tool to assess the level of consciousness. Deficits can be established with NIHS scale[1-5,37].

Non-contrasted CT scan is the imaging of choice in the acute phase (Recommendation I, Level A). It confirms the bleeding with excellent sensitivity, determines its location, size, ventricular or subarachnoid extension, degree of distortion or displacement structures and the presence of complications such as hydrocephalus or edema[2,3,37]. It also helps to establish prognosis, monitoring the evolution and the response to different therapeutic modalities.

Recent studies have indicated that CT angiography with contrast can be very useful[38-40]. Extravasation of contrast within or in adjacent areas of hematoma indicates active bleeding. It has been called "spot sign" and predicts hematoma expansion[38-40] (Figure 4).

Multiple and varied factors (clinical, biochemical, images) have been described as independent predictors of mortality, however, only GCS score and hematoma volume have shown the most predictive power[1-5,37].

Unlike other neurocritical entities, there is no universally accepted and validated scale for ICH.

Hemphill, basing on multivariable model of their population, detected five independent factors associated with 30-d mortality, developing a risk stratification scale, which e called ICH score[41] (Table 1). In this scale, mortality increased as the punctuation increased. No patient with an Score of 0 died, whereas all patients with 5 points died[41]. This scale has been validated externally[42,43]. Since the original description of ICH score, several scales have been developed, each with their strengths and weaknesses[44-46].

It is important to note here that any prediction model lacks validity in centers with nihilism, self-fulfilling prophesies, withdrawal support or DNR politics[9,10].

INITIAL STABILIZATION, ORGANIC HOMEOSTASIS (PHYSIOLOGICAL NEUROPROTECTION), TO AVOID SECONDARY INSULTS

The main objective should be directed to ensure the ABC (patent airway, adequate breathing, oxygenation, and circulation), achieve clinical stability and then, transfer to imaging study. The neurosurgeon should be actively involved in decision-making[1-5,37] (Figure 5). It is very important to develop a strategy to prevent, detect and correct secondary insults[2-5,37,47,48] (Table 2).

This strategy has a significant impact on the outcome[2,3,7,47,48].

The basis of therapeutic of any neurological injury

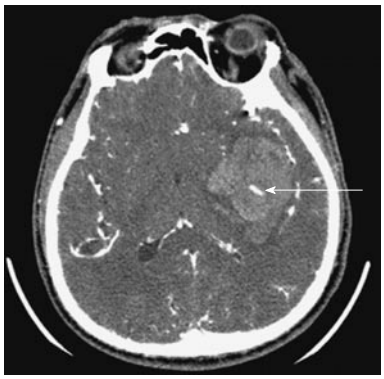

Figure 4 Spot sign.

is to achieve organic homeostasis, which we call "physiological neuroprotection"[47,48]. From a practical point of view and easy to remember is to maintain healthy 6 principal clinical variables (6 N rule), such as euvolemia, paO_2 and $paCO_2$ levels, temperature, glycemia, and natremia[47,48]. Target to achieve for each variable are depicted in Figure 6.

To ensure airway patency and oxygenation (ab)

ICH patients are susceptible to develop ventilation and oxygenation alterations[1-5,37,47-51] due to compromise of defense reflexes of the upper airways such as cough and swallowing, increasing the risk of aspiration of gastric contents[1-5,47-51]. Pons or supratentorial hemorrhages with mass effect can compromise respiratory rhythm. This population is also at risk for neurogenic or cardiogenic pulmonary edema. We recommend keeping low threshold for intubation and as a general rule all patients in coma should be intubated[1-5,37,47-51]. Therapeutic targets will be directed to maintain SaO_2 greater than 92% while maintaining normal levels of CO_2, since hypercapnia causes cerebral vasodilatation and ICP increased, whereas that hypocapnia causes vasoconstriction triggering cerebral ischemia[1-5,37,47-51].

To optimize circulation (c)

During resuscitation is essential to avoid systemic hypotension, ensuring blood pressure levels that allow adequate cerebral perfusion pressure (CPP)[1-5,37,47-51]. For this reason, it is necessary to normalize blood volume. The first therapeutic step is infusion of fluids, preferably isotonic saline[1-5,37,47-51], avoiding hypotonic fluids (0.45% saline, 5% dextrose, Ringer's lactate) that exacerbate brain swelling. Hypertonic saline solutions are an option especially for individuals with signs of herniation, intracranial hypertension or severe hyponatremia. If fluids are not sufficient to ensure adequate blood pressure, vasopressors (noradrenaline) or inotropes (dopamine) should be started[1-5,37,47-51].

To avoid hyperthermia

Hyperthermia is highly prevalent in neurointensive care[52]. Initially, elevated temperature is attributable to acute phase response[52,53], during which inflammatory mechanisms are triggered, and sympathetic activity is increased[52,53]. However, directly or indirectly damage of hypothalamus and thermoregulatory centers cannot be excluded[52,53]. The brain is more warmer than the rest of the body[52,53]. Hyperthermia exerts its deleterious effects through various mechanisms: it increases levels of excitatory amino acids, cytokines, and reactive oxygen species, inhibits proteolytic enzymes, damages BBB, increases intracranial pressure and triggers apoptotic mechanisms[53].

Clinical studies have shown a close association between hyperthermia on admission or during the first 24 h and outcome. Moreover, hyperthermia has demonstrated its independent predictive power of poor outcome[53-55]. Hyperthermia can be controlled with the use of external cooling methods (ice, thermal blankets), internal (intravascular cooling devices) or pharmacological (acetaminophen, aspirin)[56,57]. Until now, there is no a study that prospectively evaluated the impact of fever control on the outcome nor that is the most suitable method to control fever[56,57], and due to ethical concerns is very unlikely to be performed ever.

Sodium homeostasis

Disorders of sodium and water metabolism are common in neurocritical ill patients[58]. Imbalances in the metabolism of sodium produce changes in osmolarity and in water distribution, which in turn, trigger changes in the volume cerebral[58].

In neurocritical care patients, hyponatremia (serum $Na^+ < 135$ mEq/L) occurs in 15% to 20% of patients, increasing the likelihood of unfavorable outcomes[58]. The elderly population is very susceptible to this disorder. The causes are varied, highlighting the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt-wasting syndrome (CSWS)[58,59].

The treatment of hyponatremia, depend on the presence or absence of symptoms and the underlying cause[58-60]. In the presence of SIADH, fluid restriction is indicated while in the presence of CSWS volume expansion is necessary. In symptomatic cases, hyponatremia should be corrected with hypertonic saline solutions at a slow rate, preferably not more than 10 mmol/liter per day to avoid severe complications such as pontine myelinolysis. Sometimes, fludrocortisone can be used as an adjunct at 0.1-0.4 mg/d[58-61].

Hypernatremia (serum $Na^+ > 145$ mEq/L) is less frequent[58]. Its incidence is about 10%, and it is considered a marker of severity of injury with negative predictive power[58,61]. The most common causes are iatrogenic due to excessive sodium intake or water loss secondary to mannitol infusion[58,61]. Diabetes insipidus is another disorder to take in mind[58,61]. The cornerstone of treatment are reposition and retention of water[58,61]. The replacement should be performed with hypotonic solutions like 5% dextrose or ringer lactate because isotonic saline can exacerbate losses. To avoid loss of water desmopressin at 0.4 mg IV or 100-200 μg *via* nasal route should be utilized. Such doses may

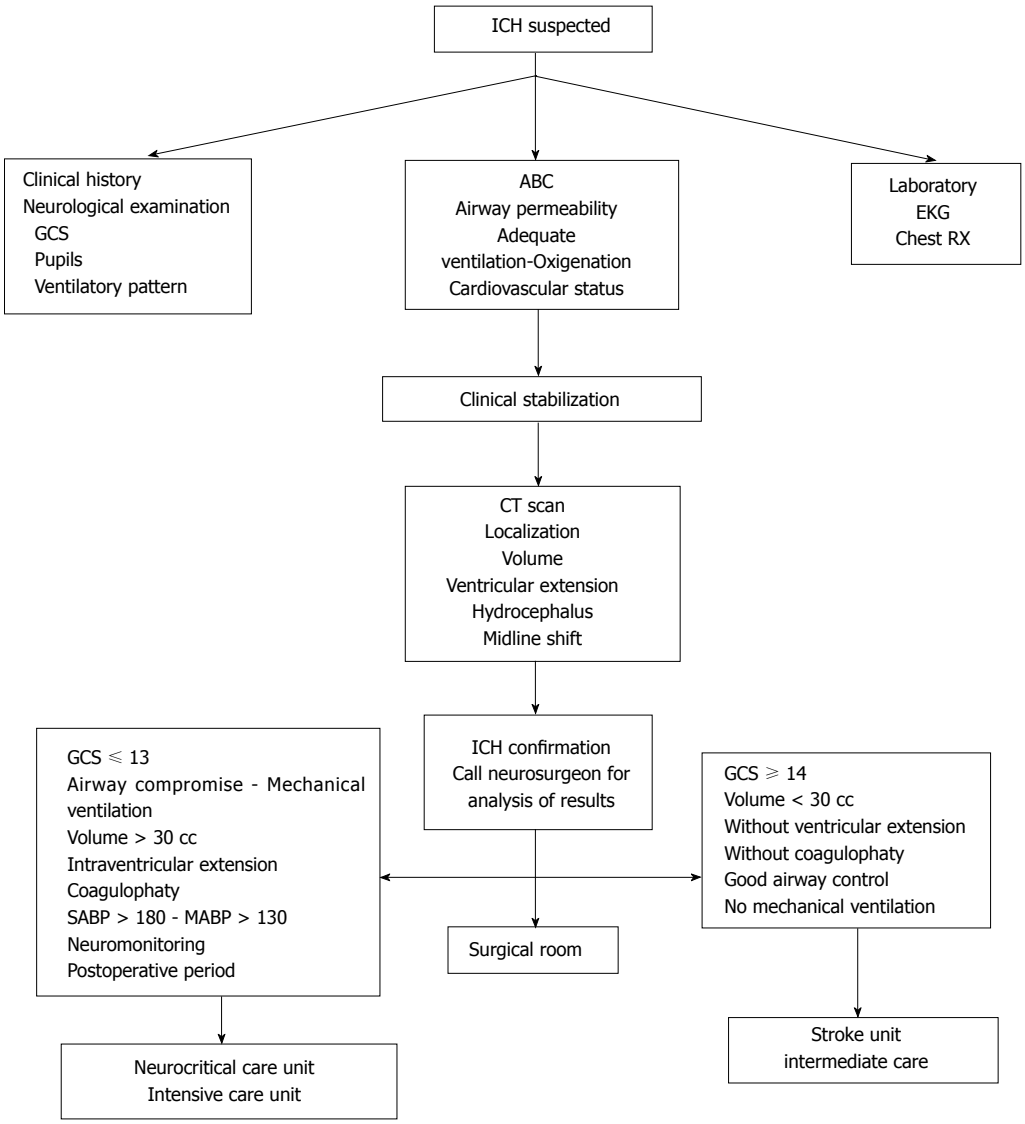

Figure 5 Initial approach of the patients with suspected intracerebral hemorrhage. GCS: Glasgow Coma Scale; ABC: Airway, breathing, circulation; EKG: Electrocardiogram; CT: Computed tomography; ICH: Intracerebral hemorrhage; SABP: Systolic arterial blood pressure; MABP: Mean arterial blood pressure.

be repeated if necessary. Sharp corrections should be avoided[58,61].

Glycemic control

Blood glucose levels should be kept within a narrow range, avoiding extreme variations since the brain is very vulnerable to such situations[62,63]. Hypoglycemia should not be allowed in any way and must be corrected immediately[62,63]. The brain does not tolerate episodes of hypoglycemia as their compensatory mechanisms are exhausted quickly and easily[62,63].

During injury, the brain increases susceptibility to acute derangements of blood glucose[62,63]. After injury, the brain increased glucose demand.

Hyperglycemia is common during the acute phase of ICH[62,64]. Its incidence averages 40% and is independently associated with worse outcome[61,62,64].

Its etiology is variable, not being clear whether it is a marker of severity or only one component of the metabolic response to injury[62-64]. Hyperglycemia contributes to brain damage through various mechanisms that provoke edema and cerebral ischemia[63]. IV regular insulin is the drug of choice to correct high blood glucose levels but still not yet well determined when starting therapy[62-65]. Intensive insulin therapy (glucose levels between 80-110 mg/dL) is contraindicated because at these levels starts cellular metabolic distress[66,67]. The current trend is to maintain the lower limit of about 150 mg/dL and not higher than 200 mg/dL[2,3,37,62,65].

Gastrointestinal care nutrition

The gastrointestinal tract is of vital importance in patients with brain injury[68]. Multiple hormones and neuropeptides are released by the brain and intestine in response to injury, establishing an interaction finely regulated by enteric nerve plexus and the autonomic nervous system[68]. In ICH patients, a number of factors combine to break the normal physiology, including hypothalamic damage, intracranial

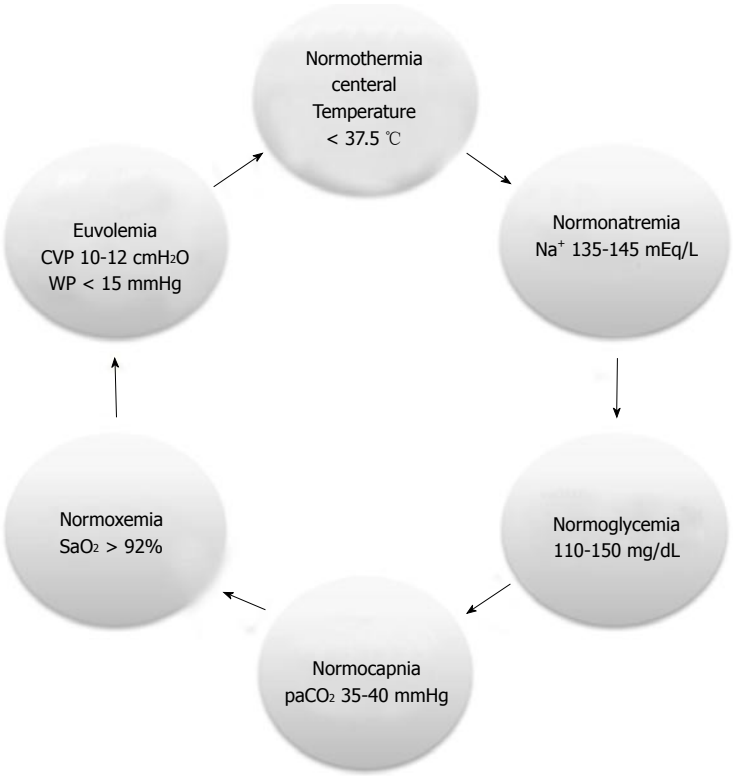

Figure 6 Physiological neuroprotection 6 N rules. CVP: Central venous pressure; WP: Wedge pressure; SaO_2: Oxygen arterial saturation; Na^+: Serum sodium levels; $paCO_2$: Carbon dioxide arterial levels.

hypertension, prolonged fasting, mechanical ventilation, drugs (vasopressors, anticonvulsants, opioids, antibiotics, corticosteroids), inflammation (cytokines), hypoalbuminemia, electrolyte imbalances[68,69]. The most important complications are gastrointestinal bleeding, diarrhea, gastroparesis and ileus, which favor bacterial translocation and malnutrition, sepsis and multiorgan dysfunction[68,69].

The incidence of clinically significant gastrointestinal bleeding (erosive gastritis or stress ulcer) ranges from 0.6% to 6%[69]. The main substrate for gastric mucosal damage is the presence of inadequate splanchnic perfusion[69]. Risk factors are mechanical ventilation (> 48 h), coagulopathy, severe traumatic brain and spinal cord injury[69]. Some principles are relevant for management, to avoid arterial hypotension and some drugs (steroids, noradrenaline); early nutrition and protection with proton pump inhibitors or local agents[69]. H_2 receptors blockers are not recommended because they are associated with encephalopathy, interaction with anticonvulsants and modify the local pH favoring bacterial colonization and pneumonia[69].

Constipation is common after neuroinjury with a negative impact upon outcome[68]. Incidence rates are between 30% to 60%[68]. Predisposing factors are immobility, fasting, electrolyte disturbances, and drugs (opioids, sedatives, dopamine). Its prevention is based on adequate fluid and electrolyte balance, rich-fiber diet and laxatives[68].

Diarrhea is a complication with a prevalence of 8% to 21%[68]. Fever, hypothermia, hypoalbuminemia, sepsis, multiple organ dysfunction, broad spectrum antibiotics, enteral nutrition, and clostridium difficile (CD) colonization are predisposing factors[68].

Brain injury, determines a hypermetabolic state, with exaggerated protein catabolism[68,70]. During injury, the brain increases its metabolic requirements[62,70]. Nutrition should become one of the key goals of therapy. Malnourished patients are more prone to developing infectious complications, bedsores, gastrointestinal bleeding, all associated with poor outcomes[68]. Enteral feeding must be supplied early with low calories (25-30 kcal/kg per day), 40% of which in the form of lipids and 15%-20% as protein (1.5-2 g/kg per day) accompanied by a regimen of glycemic control and the contribution of fiber, vitamins, oligoelements and pharmaconutrients (glutamine, arginine)[70].

SPECIFIC THERAPIES DIRECTED TO ICH

Seizures control

The incidence of seizures after ICH varied between 4.6% and 8.2%[71]. Acute seizures should be treated following classical algorithms since they are associated with increased cerebral metabolism, ICP and midline shift contributing to secondary injury[71-76]. Lobar location and small hematomas are independent predictors of early seizures[72]. Although antiepileptic drugs (AEDs) may reduce the incidence of seizures in cortical and subcortical hemorrhages[72], their prophylactic use is not recommended because it is unclear their efficacy and impact over final outcome[73,74]. Phenytoin use was associated with more fever burden and worse outcomes after ICH[74]. Electroencephalographic seizures without clinical manifestations occur in around 30% of patients after ICH[75]. Nonconvulsive seizures are associated with early hematoma growth and a trend toward poor outcome[76]. Continuous EEG monitoring should be

considered in all patients with a decreased level of consciousness without clear reason to justify[2]. Current Guidelines recommended anti-epileptic treatment for up to one month, after which therapy should be discontinued in the absence of seizures[2,37].

Hydrocephalus and ventricular extension of bleeding

There are two mechanisms involved in the genesis of acute hydrocephalus: extrinsic compression of ventricular system by proximity (thalamic, cerebellar hematomas); displacing midline structures (putaminal hematomas); or obstruction of CSF circulation by clots[1,2,4,37,77]. Hydrocephalus causes impairment of consciousness, intracranial hypertension and cerebral ischemia, being an independent predictor of mortality and poor outcome[77].

The extent of bleeding to the ventricular space complicates about 40% of spontaneous ICHs[2,4,37,77-80].

Intraventricular blood is a poor prognostic factor[2,4,37,77-80]. Its volume determines the predictive power, being lethal when exceeding 20 cc, due to hydrocephalus, intracranial hypertension and ischemia of the cerebral cortex[2,4,37,77-80]. External ventricular drainage is a therapeutic option but insufficient and ineffective when used as a single measure[2,4,37,77-81].

Patency of the ventriculostomy is difficult to maintain due to frequent plugging clots. Thrombolytic drugs were tested with different protocols and doses[2,4,37,78-82]. Studies with small numbers of patients showed a trend to reduce need for definitive ventricle peritoneal shunts, and decrease mortality rates with acceptable functional outcomes; however, there is an increased risk of infectious or hemorrhagic complications[2,4,37,78-82].

CLEAR-IVH study evaluated the strategy of external ventricular drainage more rtPA instillation[82]. Resolution rates of clots were significantly higher with shorter permanence time of ventriculostomy in rtPA group[82]. By contrast, symptomatic bleeding rate was higher in the group rtPA. Mortality rates not changed significantly[82]. The study had several methodological limitations, for example; selection criteria for study inclusion, did not include location of bleeding or extension of intraventricular hemorrhage; management of known factors that influence rates of bleeding such as blood pressure levels or coagulation state not were considerate and the study was not designed to assess long-term functional outcome[82], a situation that is being evaluated in CLEAR Ⅲ study[83].

Endoscopically removal of the clot and controlled lumbar drainage are promising therapeutic alternatives that need large-scale validation[79-81]. Preliminary results indicate that lumbar drainage after radiological permeation of third and four ventricles was associated with a reduction in the need for permanent ventricular shunting[78,80].

Intracranial hypertension

Although ICH causes structural changes in brain parenchyma and intracranial hemodynamics than potentially increase ICP, is unclear its prevalence, temporal profile and the impact that intracranial hypertension have on the outcome.

Intracranial hypertension is more common immediately after bleeding[84]. Elevated ICP only have an impact on the outcome only in comatose patients[85]. There was not relationship between ICP values at any time and outcome at 6 mo[86].

An observational study of ICP recordings in patients with IVH and ICH of less than 30 mL found that the percentage of readings above 30 mmHg was an independent predictor of mortality ($P < 0.001$) and disability at 30 d ($P = 0.01$)[87]. Kamel and Hemphill analyzed ICH patients with ICP monitoring. Seventy percent of them presented at least one episode of ICP above 20 mmHg while, in 63%, ICP exceeded 25 mmHg. Intracranial hypertension was less frequent in older and infratentorial hemorrhages and was not related to poor outcome[88].

Recently, a prospective, randomized controlled study assessed the impact of ICP monitoring in the management of supratentorial ICH. The risk of herniation was lower in ICP group (10.9% *vs* 20.5%, $P = 0.04$). At 6 mo, mortality and disability were lower in ICP group (6.5% *vs* 9.1%, $P < 0.05$)[89].

Current recommendations are based on low level of evidence (Class Ⅱb C). However, they suggest ICP monitoring in comatose patients with signs of herniation, hydrocephalus or widespread ventricular hemorrhage[2,3,37].

Specific treatment of intracranial hypertension

The treatment of intracranial hypertension has been extrapolated from severe head trauma[2,3,37]. Briefly, after evacuating hemorrhage when were indicated, we follow a staggered, step by step, phased, sequential pathway[1-4,37,90]. CT scans are performed periodically[1-4,37,90].

We begin with general measures (sedation, analgesia, prevention and correction of secondary insults) positioning the head in a neutral position at 30 degrees of horizontal[1-4,37,90]. If ICP remains high, we continue with CSF drainage at not more than 20 mL per hour. If we don't have ventricular drainage or if it resulted ineffective, we start osmotherapy with hypertonic saline or mannitol until the limit of sodium or serum osmolality of 155 mEq/L or 320 mosm/kg respectively[1-4,37,90]. After this measures, if ICP remains increased, we hyperventilate slightly, maintaining $paCO_2$ levels between 30 and 35 mmHg. At this point, we indicate monitoring of cerebral oxygenation. We do not utilize neuromuscular paralysis unless strictly necessary for ICP normalization. Mean arterial pressure would be titled to a CPP target between 55-70 mmHg[1-4,37,90].

The non-response to initial therapy, define a state of "refractory intracranial hypertension". Prior to the adoption of "second level" measures (barbiturates at high doses, hypothermia, decompressive craniectomy) we performed indomethacin test[90].

Optimal levels of arterial blood pressure

Elevated arterial blood pressure (ABP) levels are common in the acute phase of ICH[2,3,37,91]. Etiology is multifactorial[2,3,37,91]. There are arguments for and against their control. Those who are in favor of lowering the pressure levels are based on that hypertension is associated with poor outcomes[92] and may cause expansion of the hematoma[28,93]. INTERACT study, randomized patients to intensive BP control (target SBP 140 mmHg) *vs* traditional management (SBP 180 mmHg) within 6 h of ICH onset, showed a trend towards reduction in hematoma growth in the intensive treatment group, without increase the rate of neurological deterioration or other adverse events[94].

ATACH I study demonstrated safety of nicardipine for acute reduction of BP in acute ICH[95], while ADAPT trial showed that control arterial hypertension to a target of SBP of lower than 150 mmHg within 24 h of onset did not produce clinically or CBF changes in perihematomal region[96].

INTERACT Ⅱ trial[97], randomized patients with spontaneous ICH and elevated SBP (≥ 150 and ≤ 220 mmHg) to a strategy of intensive control (SBP < 140 mmHg) *vs* guideline-recommendations (SBP < 180 mmHg) within 6 h of symptoms onset, showed a borderline decrease in poor outcome at 90 d (OR = 0.87, 95%CI: 0.75-1.01; $P = 0.06$)[97].

ATACH Ⅱ trial[98] is an ongoing multi-center, randomized phase Ⅲ trial to determine the efficacy of early, intensive, BP control initiated within 4.5 h of symptom onset[98]. The expansion of window from 3 to 4.5 h was based on ATACH-I that suggests a reduction of hematoma expansion, death and disability in patients treated within 4.5 h after symptom onset[98].

SCORE-IT is an ancillary study of ATACH Ⅱ that tests the hypothesis that patients with a Spot Sign will receive clinical benefit from intensive ABP reduction[99].

With regard to pharmacological management, its preferably use agents that do not cause cerebral vasodilation and sudden hypotension, so labetalol (loading dose of 10-20 mg in 1-2 min, repeated every 1-20 min until the desired level of blood pressure were reached or until a maximum dose of 200 mg) or nicardipine (5-15 mg/h) are good options[2,3,37].

Venous thromboembolism prevention in ICH

Venous thromboembolism (VTE) is one of the most feared complications of ICH. The incidence varies between 2%-17%, with a mortality rate of 5%[2-4, 37,100,101].

Risk factors for VTE are: older age, female gender, obesity, prolonged bed-rest, legs paralysis, lobar hematoma, great volume, NIHSS score ≥ 12, withdrawal of antithrombotic treatment, and pro-hemostatic agents such as prothrombin complex or recombinant activated factor Ⅶ[102]. For optimal selection of strategy for VTE prevention is crucial for maintaining the balance between risk of hematoma enlargement and VTE. Strategies to prevent VTE in ICH patients are pharmacological and nonpharmacological[103]. Non-pharmacological agents are graduated compression stockings (CS), intermittent pneumatic compression (IPC) plantar venous pump, vena cava filters and early mobilization[103].

VICTORIA study compared the combination of IPC with CS *vs* CS alone. The combination of the two strategies was significantly superior in reducing the risk of VTE[104].

CLOTS Ⅱ study[105], showed that CS positioned to the root of the thighs are superior to the CS positioned below the knees. In CLOTS Ⅲ, IPC was associated with a significant reduction in the risk of VTE[106].

The main indication for vena cava filters is represented by the absolute contraindication to anticoagulant therapy[107], so, it is reasonable to reserve filters for patients with very high risk of VTE[107]. The role of early mobilization for prevention of VTE is controversial and unclear[108].

Systematic reviews and meta-analysis in terms of efficacy and safety of pharmacological prophylaxis for prevention of VTE balanced with the risk of hematoma expansion showed that unfractionated heparin or low molecular weight heparins significantly reduces the risk of pulmonary embolism, whereas not reduced the risk of DVT or death from all causes[109,110]. No increase in the risk of hematoma expansion was observed[110]. Based on actual recommendations[2,3,37,110] a possible flow chart for VTE prevention in ICH is depicted in Figure 7.

URGENT REVERSAL THERAPY IN ANTITHROMBOTIC, ANTICOAGULANTS-RELATED INTRACEREBRAL HEMORRHAGE

The urgent reversal therapy represents the cornerstone of management of antithrombotic-related ICH. It aims is to restore adequate hemostasis by neutralizing the anticoagulant or antiplatelet activity with specific antidotes, avoiding hematoma growth and devastating consequences of drugs induced coagulopathy[102].

Specific antidotes are available only for few anticoagulants, such as vitamin K antagonists (VKAs), unfractionated heparin (UFH) and idrabiotaparinux, not marketed yet.

Protamine sulfate is the recognized specific antidote for unfractionated heparin[111]. The goal of protamine for the reversal of unfractionated heparin is the normalization of activated partial thromboplastin time (aPTT). Protamine has a partial effect on LMWH reversal. Therefore higher dose may be necessary[112].

Despite intravenous administration of vitamin K1 (VK1) represents the most used for VKAs reverse (recommendation IA), it is not the only strategy because it's slow onset of action and because need between 12-16 h to complete its action[111-113]. VK1 should be always administered together with prothrombin complex

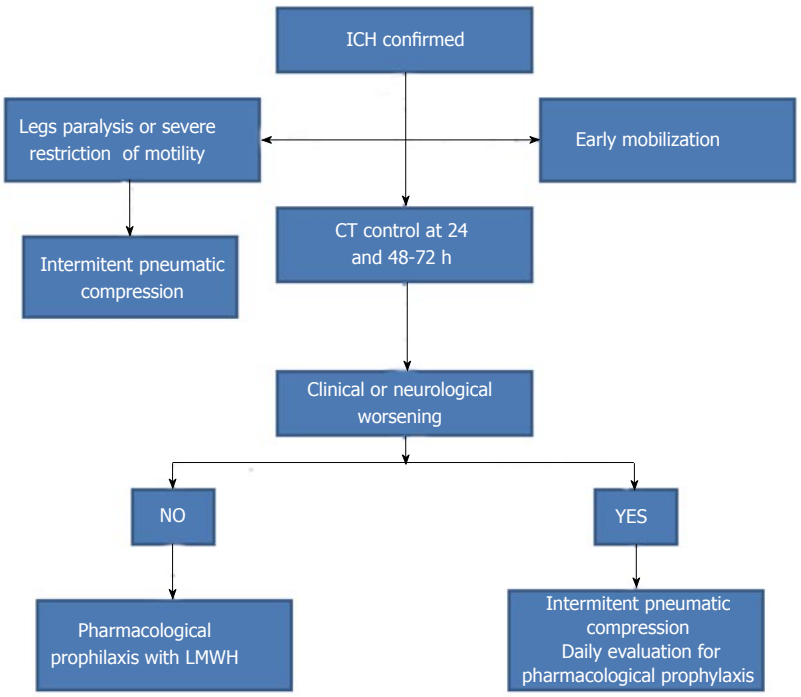

Figure 7 Algorithm suggested for venous thromboembolism prevention in intracerebral hemorrhage. ICH: Intracerebral hemorrhage; CT: Computed tomography; LMWH: Low molecular weight heparin.

concentrates (PCCs), rFVII or fresh frozen plasma (FFP) because all these agents prove VK dependent coagulation factors[102].

PCCs, rFVII and FFP have short half time, therefore, the missed dose of VK1 could determine the rebound of International Normalized Ratio (INR) values after their pharmacological action[102-111].

The goal of urgent VKAs reversal in ICH is to bring the INR values $\leqslant$ 1.4 within 2-4 h[102,114-116]. At the end of pro-hemostatic infusion, INR should be re-checked, and the adjunctive dose should be infused if its values continue to be $\geqslant$ 1.5[102,116] (Figure 8).

PCCs a derivate of plasma contain three or four non-activated vitamin K depending coagulation factors (II, VII, IX, and X). Three factors PCCs lack for Factor VII[117]. PPCs restore INR and reduce hematoma enlargement rates, but it is controversial if it's associated with mortality reduction or better functional outcome[117,118].

PCCs are considered the first choice for VKAs urgent reversal from many scientific Societies[2,37]. Limitation of PCCs derived from thromboembolic risk. Thromboembolic burden of PCCs is lower than 2%[119].

FFP is another effective strategy that leads to VKAs neutralization in 4-6 h but has it certain limitations, such as volume overload, especially in elderly or patients with limited cardiac reserve; delays in time due to thawing and blood group typing; infectious risk and TRALI (transfusion acute lung injury)[102].

Many reports have demonstrated that rFVII is effective for prompt VKAs reversal in few minutes without volume overload, but its use in this context is not recommended due to high risk of arterial and venous thromboembolic complications[119,120].

Recent trials have demonstrated that new oral anticoagulants, dabigatran, apixaban, edoxaban, rivaroxaban, reduce the risk of ICH in comparison with warfarin, however this effect is not negligible, ranging from 0.2% to 0.4% per year. Case-fatality rate of new oral anticoagulants related ICH is not significantly different compared with warfarin ranged between 50%-70%[121-123].

After urgent reversal, coagulation parameters should be performed but, again, it is unclear if adjunctive dose should be administered if coagulation parameters remain abnormal[102]. Therefore the proposed coagulation assays, such as aPTT, aPTT ratio, dTT, PT, PT ratio and anti-Xa, are suboptimal tools for predicting the response to pro-hemostatic agents, whereas methods aimed at global evaluation of hemostasis, such as thromboelastogram, platelet reactivity, and thrombin generation might be more useful[102,124].

Which is the optimal strategy for urgent reversal of antiplatelet activity in antiplatelet-related ICH remain unclear? Despite platelets transfusion or intravenous desmopressin have been proposed, literature failed to demonstrate their beneficial effect in ICH[125,126]. Desmopressin has been proposed as a nonspecific strategy in antiplatelet related bleeding. However, its role in antiplatelet-related ICH is uncertain[127].

SURGERY OR NOT SURGERY: HAMLET'S DILEMMA

Despite the time elapsed the debate continues, with an open end. The removal of the hematoma reduces

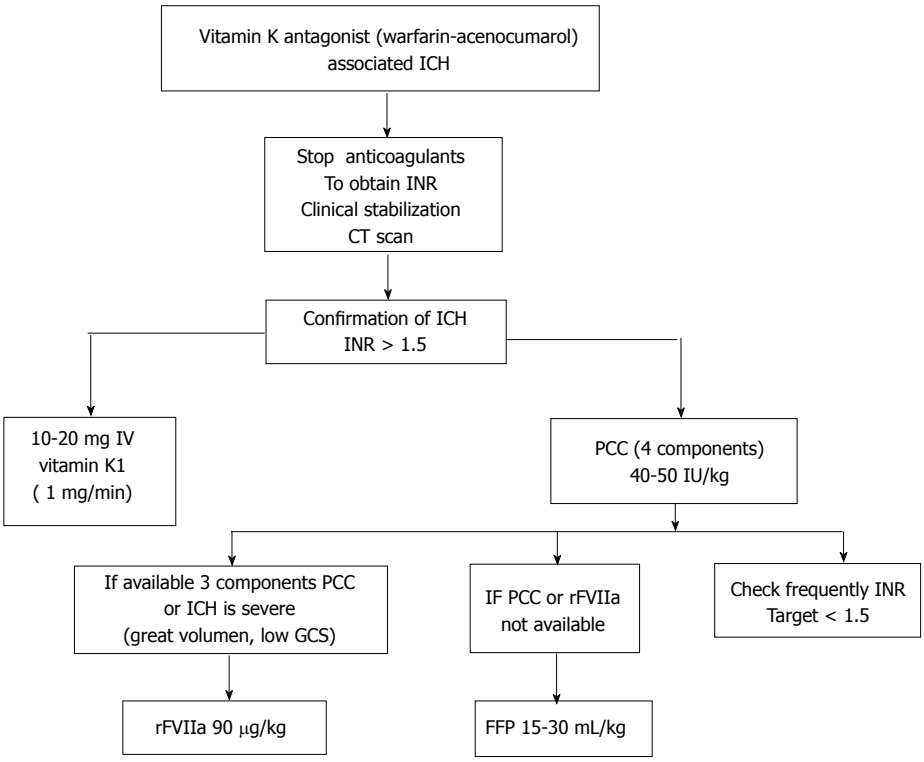

Figure 8 Algorithm to urgent reversal therapy in vitamin K antagonist related intracerebral hemorrhage. ICH: Intracerebral hemorrhage; INR: International normalization ratio; CT: Computed tomography; IV: Intravenous; PCC: Prothrombin concentrate complex; IU: International units; GCS: Glasgow coma scale; rFVIIa: Activated recombinant seven-factor; FFP: Fresh frozen plasma.

its volume, corrects distortions and displacements, reduces ICP and improves CPP. Furthermore, abort the continuation of neurotoxic and inflammatory cascades[2,4,37,128-131]. However, these theoretical advantages must be weighed against parenchyma damage required to access to the hematoma[128-131].

Most neurosurgeons agree to operate lobar or cerebellar hematomas in patients who deteriorate clinically, however, uncertainty remains regarding deep hemorrhages[128-131].

Current guidelines, recommend surgical treatment in the following situations[2,3,37]: (1) cerebellar hematomas of more than 3 cm in diameter in patients who deteriorate clinically with secondary hydrocephalus or compression of brainstem or fourth ventricle (grade C); (2) hemorrhages secondary to arteriovenous malformations, angiomas, cavernous malformations, aneurysms, *etc.* (grade C); and (3) lobar hematomas of moderate or larger volume in young patients with neurological impairment (grade B).

The STICH study, enrolled patients with supratentorial hemorrhages within the initial 72 h of symptoms onset, and then randomized them to medical *vs* surgical treatment based on the principle of uncertainty about the usefulness of surgery[129]. Mortality and functional outcomes were the same for both groups[129]. A small subgroup of patients was identified as able to evolve better. They are individuals aware (GCS between 9 and 12 points) with superficial hematomas, located at 1 cm or less in the cerebral cortex[129].

The STICH Ⅱ study[130], compare surgery (within 12 h of randomization), with conservative medical treatment in patients with spontaneous supratentorial hemorrhage, lobar, superficial (≤ 1 cm from the cortex), with a volume between 10 and 100 mL, without ventricular extension of bleeding within 48 h of onset of symptoms[130]. There were no differences between groups in terms of mortality or disability rates at 6 mo. The subgroup of patients with worse initial prognosis evidenced a favorable trend if they were operated early[130].

A recent meta-analysis found that surgery seemed effective in patients with a higher consciousness level (GCS score 9-12) operated within eight hours of symptom onset[131].

Recently, the European Stroke Organization declaims that there is no evidence to support surgical intervention on a routine basis to improve outcome after supratentorial ICH, but early surgery may be of value for patients with a GCS score 9-12[37].

There is a worldwide tendency to operate these patients with minimally invasive techniques, either by endoscopy or stereotaxic with or without the combination of a catheter into the hematoma to instill fibrinolytic in order to accelerate the resolution of hematoma[2-5,37,131-133].

MISTIE Ⅱ study randomized patients to a control group or clot aspiration with rtPA in putaminal (58%) or lobar (42%) hemorrhages above 25 mL and GCS < 14 and NIHSS > 6. Higher rates of clot removal and lower mortality were observed in the treated group[132].

MISTIE Ⅱ and other trials of minimally invasive surgery (MIS) have shown encouraging results, so a phase Ⅲ trial started in 2013[133].

Zhou's meta-analysis concluded that patients who would most benefit from minimally invasive surgery are those between 30 and 80 years with superficial supratentorial hematomas, with volumes between 25 and 40 mL, admitted within 72 h in a good level of consciousness (GCS ⩾ 9)[132].

CONCLUSION

The spontaneous ICH is a neurological-neurosurgical emergency far from diminishing its prevalence will increase in the coming years. Despite being one of the most devastating forms of stroke, a light on the horizon looms as a result of advances in knowledge and the results of recent trials. It is extremely important and essential to remove nihilism and self-fulfilling prophesies. A multidisciplinary approach is essential. Set the prognosis helps us in the process of decision-making and communication with the patient or their relatives. The therapy should be individualized and follows a deep pathophysiologic analysis. The cornerstones of therapy are correct evaluation, avoiding secondary insults through neuroprotection physiological measures, intensive control of blood pressure especially in acute and rapid reversal of antithrombotic and anticoagulant drugs. The role of surgery is still open to debate especially in deep bleeding.

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MINIREVIEWS

Myeloproliferative and thrombotic burden and treatment outcome of thrombocythemia and polycythemia patients

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Abstract

Prospective studies indicate that the risk of microvascular and major thrombosis in untreated thrombocythemia in various myeloproliferative neoplasms (MPN-T) is not age dependent and causally related to platelet-mediated thrombosis in early, intermediate and advanced stages of thrombocythemia in MPN-T. If left untreated both microvascular and major thrombosis frequently do occur in MPN-T, but can easily be cured and prevented by low dose aspirin as platelet counts are above 350 × 10^9/L. The thrombotic risk stratification in the retrospective Bergamo study has been performed in 100 essential thrombocythemia (ET) patients not treated with aspirin thereby overlooking the discovery in 1985 of aspirin responsive platelet-mediated arteriolar and arterial thrombotic tendency in MPN-T disease of ET and polycythemia vera (PV) patients. The Bergamo definition of high thrombotic risk and its persistence in the 2012 International Prognostic Score for ET is based on statistic mystification and not applicable for low and intermediate MPN-T disease burden in ET and PV patients on aspirin. With the advent of molecular screening of MPN patients, MPN-T disease associated with significant leukocytosis, thrombocytosis, constitutional symptoms and/or moderate splenomegaly are candidates for low dose peglyated interferon (Pegasys^R, 45 μg/mL once per week or every two weeks) as the first line myeloreductive treatment option in JAK2^{V617F} mutated MPN-T disease in ET and PV patients. If non-responsive to or side effects induced by IFN, hydroxyurea is the second line myelosuppressive treatment option in JAK2^{V617F} mutated ET and PV patients with increased MPN-T disease burden.

Key words: Myeloproliferative neoplasms; Essential thrombocythemia; Polycythemia vera; JAK2^{V617F} mutation; Aspirin; Interferon; Hydroxyurea

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Core tip: Spontaneous endogenous erythroid colony formation and low serum erythropoietin (EPO) levels are highly specific for JAK2^{V617F} mutated essential thrombocythemia (ET), prodromal polycythemia vera (PV), masked PV and classical PV. The quantitation

of JAK2^{V617F} mutation allele burden plays a key-role in the diagnostic work-up and staging of ET, PV and MF patients. The JAK2^{V617F} mutation allele burden in heterozygous mutated ET is low but high in combined heterozygous - homozygous or homozygous mutated PV. The combined use of JAK2^{V617F} mutation load, spleen size and pretreatment bone marrow biopsy are of major prognostic significance and therapeutic importance in ET and PV patients. Large Prospective Unmet Need studies are warranted to delineate the natural history and outcome of targeted treatment in MPN patients of various molecular etiology during long-term or life long follow-up.

Michiels JJ. Myeloproliferative and thrombotic burden and treatment outcome of thrombocythemia and polycythemia patients. *World J Crit Care Med* 2015; 4(3): 230-239 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i3/230.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i3.230

INTRODUCTION CLINICAL MANIFESTATIONS IN PV AND ET

The bleeding manifestations in 100 case histories of hemorrhagic thrombocythemia (HT) ranged from gastrointestinal chronic occult blood loss, melena and hematemesis to mucocutaneous bruises, hematomas, ecchymoses, gum bleedings and secondary bleeding[1,2]. HT was usually associated with significant leukocytosis and splenomegaly and the platelet count at time of bleeding in 100 HT cases ranged from 800 to above 4000 × 10^9/L (Figure 1, left). The manifestation in erythromelalgic thrombotic thrombocythemia (ETT) in 67 ET and 32 PV patients included erythromelalgia, acrocyanosis, digital gangrene, amaurosis fugax, transient ischemic attacks, stroke, angina pectoris and myocardial infarction, superficial thrombophlebitis and deep vein thrombosis[3]. The platelet count at time of ETT in ET and PV patients ranged from 400 to 2000 × 10^9/L in ET patients and from 350 to 1250 × 10^9/L in PV patients (Figure 1, left).

Microvascular ischemic and thrombotic complications such as erythromelalgia, atypical and typical TIAs, ocular transient ischemic events and migraine-like headache dominate the clinical picture at presentation ET and early PV. In contrast to the inefficacy of coumadin, control of platelet function with low dose aspirin and reduction of platelet counts to normal prevented the recurrence of microvascular circulation disturbances in the end-arterial microvasculature of the cerebral, coronary and peripheral circulation[3-10]. Clinicians should be aware that a starting low dose of aspirin, 50 mg daily, in symptomatic ET patients complicated by erythromelalgia induces a slow relief of pain and gradual inhibition of platelet cyclo-oxygenase (COX-1), as it takes 4 to 6 d to completely inhibit platelet COX-1 and to relief erythromelalgia by such a low dose of aspirin. Consequently, symptomatic thrombocythemia vera patients at time of presentation with microvascular circulation disturbances or major thrombosis should be immediately treated with a loading dose of aspirin 300 to 500 mg followed by a low maintenance dose of 50 to 80 mg daily. Our observational studies on a high frequency of microvascular thrombotic complications in particular indicate the existence of platelet thrombophilia in thrombocythemia for which aspirin is a safe and effective antithrombotic agent in ET and PV patients (A1 level of evidence). Low dose aspirin at platelet counts in excess of 1250 ± 250 × 10^9/L is frequently associated with the paradoxical occurrence of thrombosis and bleeding (ETT + HT, Figure 1). Bleedings spontaneously occur at platelet count in excess of 1250 ± 250 × 10^9/L due to an acquired von Willebrand Disease (AVWD, type 2A with absence of high and intermediate von Willebrand factor (VWF) multimers increasing in severity at increasing platelet counts to high levels above 1500 × 10^9/L (Figure 1, upper part)[8]. Correction of the platelet counts to normal (less than 350 × 10^9/L) is associated with no recurrences of microvascular events after discontinuation of aspirin[2,6,7] together with complete correction of the VWF-multimeric pattern and of all VWF-parameters to normal values[8].

RISK ON MICROVASCULAR AND MAJOR THROMBOSIS IN PV AND ET

The risk stratification for thrombosis by Cortelazzo *et al*[11] in 1990 in 100 ET patients not treated with aspirin overlooked the 1985 key reference of Michiels *et al*[3] on the demonstration of aspirin responsive platelet-mediated arteriolar and arterial thrombotic tendency in ET and PV patients. The characteristics of the thrombotic events in the retrospective Bergamo cohort of 100 patients were in Tables 1 and 2.

The age distribution of this cohort of ET did not reflect real life experience since the number of young ET patients was artificially manipulated to one third in the young age group to reach statistical significance. The risk for thrombotic complication was low (1.7%) in MPN-T at young age below 40 years, but was high at age of > 60 years (15%), and moderately increased (6.3%) in the age group of 40 to 60 years not on aspirin[11]. In the Dutch prospective ET and PV studies the risk of thrombosis is untreated ET and PV is not age dependent and causally related to platelet-mediated thrombosis in the various stages of ET and PV patients[1-10]. The type and number of 25 arterial and 3 venous thrombotic episodes in 20 out of 100 untreated ET patients in the 1990 Bergamo study were mainly microcirculatory events including digital ischemia, transient ischemic attacks, superficial thrombophlebitis, ususual site of DVT, no stroke, and major thrombosis only in 4, myocardial infarction in 3 and femoral DVT in 1 (Table 2)[11]. If left untreated symptomatic ET patients with microcirculatory

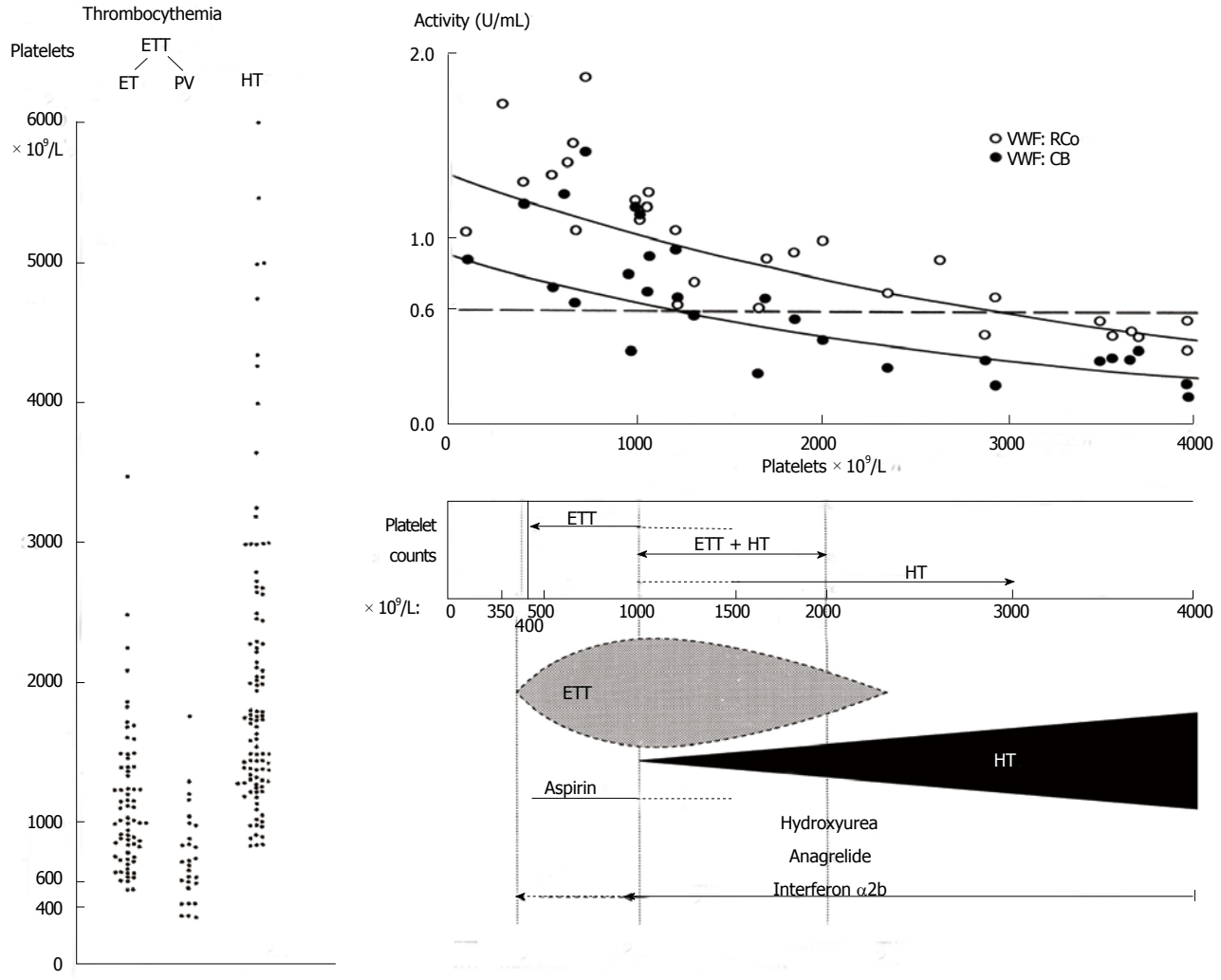

Figure 1 Platelet counts in 100 case histories of hemorrhagic thrombocythemia and 99 cases of erythromelalgic thrombotic thrombocythemia subdivided in patients with essential thrombocythemia and polycythemia vera (left)[1,2]. The relationship between platelet-mediated microvascular thrombosis in ETT at platelet counts between 350 to 1000 × 10^9/L in ETT and mucocutaneous bleedings at platelet counts between about 1000 to above 2000 x 10^9/L in HT patients (Table 3)[1-7]. The relationship of increasing platelet counts and decreasing von Willebrand factor (VWF) levels, VWF:ristocetine cofactor activity (VWF:RCo), and VWF collagen binding activity (VWF:CB) as the cause of an acquired Von Willebrand Disease (AVWD) type 2A due to proteolysis of large VWF nultimers in patients with paradoxical occurrence of ETT and HT and in patients with HT[8]. HT: Hemorrhagic thrombocythemia; ETT: Erythromelalgic thrombotic thrombocythemia; ET: Essential thrombocythemia; PV: Polycythemia vera.

disturbances are at very high risk for digital ischemia, TIAs, stroke or acute coronary ischemic syndromes. Based on the results of our prospective studies in Table 3[4,5] we concluded that the stratification in low, intermediate and high thrombotic risk in the 1990 Bergamo study[11] can only be applied to ET patients not on aspirin. This means that the stratification in aspirin responsive low, intermediate and high thrombotic risk in the retrospective Bergamo ET study is based on statistic misinterpretation and mystification leading to authorative overtreatment recommendation with hydroxyurea for ET and PV patients on low dose aspirin. The so-called high thrombotic risk ET as defined by a history or presentation of thrombosis at time of diagnosis or by reaching the age 60 years is not in line with the observed low thrombotic incidence in aspirin treated ET and PV patients[10,12-14]. The 1995 Bergamo prospective randomized clinical trial (RCT) of 114 ET patients comparing hydroxyurea *vs* placebo in high thrombotic risk ET patients is unbalanced since 69% of the placebo group and 70% of the HU-treated ET patients did not receive aspirin[15]. Two of 56 high thrombotic risk ET patients on hydroxyurea had major thrombotic events (one stroke, one myocardial infarction) and 14 of 58 high thrombotic risk ET patients in the placebo group had microcirculatory disturbances in 12, and major thrombosis in 2. However, 10 of these 14 symptomatic patients in the placebo arm manifested aspirin responsive microvascular disturbances but were not on treatment with aspirin[15]. The conclusion from this RCT is that HU *vs* low dose aspirin alone in high thrombotic risk ET patients is predicted to be equally effective for the prevention of microvascular circulation disturbances in ET (Figure 1, Table 3)[4,5]. Consequently, the high thrombotic risk in the 2012 IPSET (International Prognostic Score for ET)[14] with the indication of

Table 1 Incidence of thrombotic events related to age in 100 patients with essential thrombocythemia not on aspirin in the 1990 Bergamo study[11]

Age (yr)	No. of patients	Patient/years	Events number	Events % pt/yr
< 40	34	118	2	1.70%
40-60	37	112	7	6.30%
> 60	29	73	11	15%
Total thrombotic events in 20 of 100 ET patients				

ET: Essential thrombocythemia.

Table 2 The type and number of microvascular thrombotic events in the 1990 Bergamo study are very characteristic for untreated thrombocythemia[11]

Cortelazzo *et al*[11] 1990	No. of patients	No. of events
Total	20	32
Arterial	17	25
Digital ischemia		7
Transient ischemic attacks		15
Stroke		0
Myocardial infarction		3
Venous	3	7
Superficial Thrombophlebitis		3
Femoral DVT		1
Unusual localization DVT		3
Bleeding complications	4	

DVT: Deep vein thrombosis.

hydroxyurea (HU) simple leads to significant HU over-treatment in ET and PV patients on aspirin with a low or intermediate MPN-T disease burden[12,13].

With the advent of molecular screening of MPN-T patients, it should be realized that WHO-ET patients with less than 50% JAK2^{V617F} mutation load are usually heterozygous, and WHO-PV patients with less than 50% JAK2^{V617F} mutation load are frequently combined heterozygous homozygous positive for the JAK2^{V617F} mutation[16-18]. In the study of Vannucchi *et al*[19], the JAK2^{V617F} allele burden in 173 PV ranged from 1%-25% in 33%, from 25%-50% in 29%, from 50% to 75% in 20% and from 75% to 10% in 18%. Treatment consisted of phlebotomy in 49% and cytoreductive therapy (mainly hydroxyurea) in 51%. The JAK2^{V617F} allele mutation burden correlated with MPN disease activity in terms of stimulated erythropoiesis by higher hematocrit and erythrocytes, lower MCV, serum EPO and ferritine, and stimulated myelopiesis by higher leukocytes, serum LDH and LAP score[19]. Comparing PV patients with low (1% to 50%) *vs* high (50%-100%) JAK2^{V617F} allele burden, the relative risks for MPN disease burden increased from 1 to 4 for pruritis, from 1 to 4 for palpable splenomegaly and from 1 to 4 for spleen sizes above 15 cm length diameter on scan. In a subsequent elegant study Vannucchi *et al*[20] assessed the incidence of thrombosis related to the JAK2 allele burden in a large retrospective study of 962 MPN-T patients subdivided

Table 3 Incidence of thrombotic and bleeding complications in the prospective 1975-1996 Rotterdam study of 68 ET patients during a median follow-up of 6.7 years according to treatment strategy (Van Genderen *et al*[4,5] 1997)

Treatment strategy	Duration of follow-up person (yr)	Thrombotic events		Bleeding events	
		Events (*n*)	Events/100 person (yr)	Events (*n*)	Events/100 person (yr)
Asymptomatic 14 patients					
Watchful waiting	127	27[1]	33.3	2	1.6
Symptomatic 54 patients					
Low-dose aspirin	139	5	3.6	10[3]	7.2
Platelet reduction	113	10[2]	8.9	2	1.8
Low-dose aspirin + platelet reduction	40	0	-	4	10
Total	419	42		18	

[1]Mean platelet count 610, range 410-831 × 10^9/L at time of thrombotic event; [2]Platelet count 624 ± 255 × 10^9/L at time of thrombotic event; [3]Platelet count 1737, range 661-3460 × 10^9/L at time of bleeding event. These observations by Van Genderen *et al*[4,5] confirm the concept in Figure 1 on the relationship between platelet-mediated microvascular thrombosis in thrombocythemia at platelet counts between 350 to 1000 × 10^9/L in ETT and mucocutaneous bleedings at platelet counts of 1000 to above 2000 × 10^9/L in HT patients.

in 323 PV and 639 ET patients[20]. Aspirin responsive platelet thrombophilia or microvascular symptoms due to microvessel disorder including migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances were excluded by definition and not considered in this retrospective analysis[20]. Only major thrombotic events ischemic stroke, transient ischemic attacks, myocardial infarction, angina pectoris, deep vein thrombosis abdominal vein thrombosis, and pulmonary embolism were assessed. The incidence of major thrombotic events in 188 JAK2^{V617F} homozygous MPN patients (JAK2^{V617F} mutation above 50% in 104 PV and 14 ET) and in 587 heterozygous (JAK2^{V617F} mutation less than 50% in 219 PV and 257 ET) and 257 wild type ET patients was assessed and calculated in Table 4 and Figure 2. Anno 2014, JAK2 wild ET are predicted to carry one of the CALR positive in 80%[21]. Homozygous JAK2^{V617F} positive patients with JAK2^{V617F} mutation above 50% in ET and PV are truly homozygous. Homozygous JAK2^{V617F} mutated MPN patients with a mutation allele load above 50% were older, had higher leukocyte counts, hematocrits and larger spleen volumes indicating advanced MPN disease. One hundred seventy-six patients (18.3%) had a major thrombotic event at diagnosis with a similar frequency in PV (19.2%) and ET (17.8%)[20]. A similar incidence was found in our analysis of the literature in 1241 ET patients not on aspirin from 14 retrospective studies[22]. In the Italian study, major thrombosis (usually not on aspirin) occurred in 122 patients (12.7%), corresponding to 14.9% in PV and 11.6% in ET patients and hemorrhages

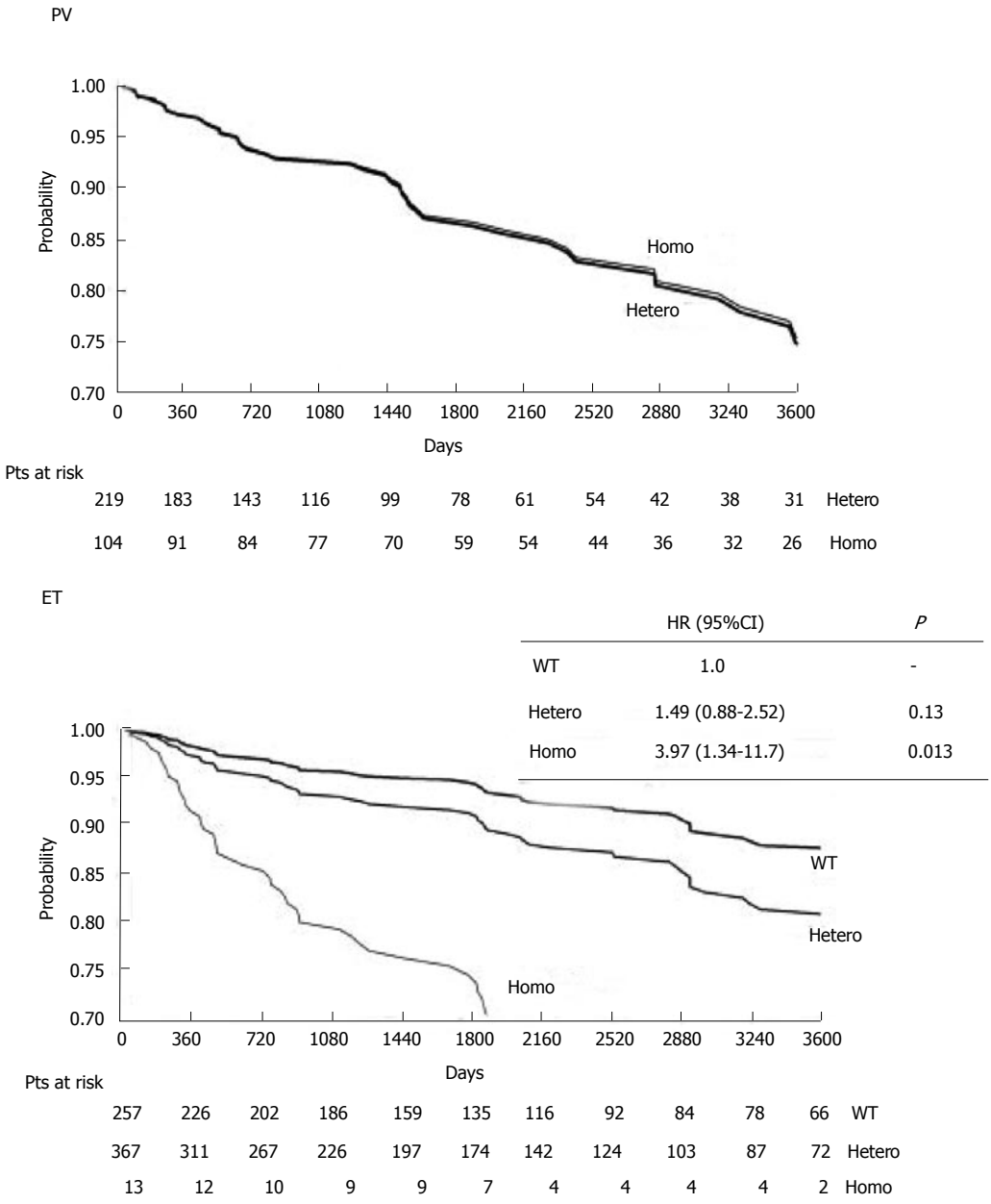

Figure 2 Retrospective study on the probability of cardiovascular thrombotic event-free survival (days up to 3600 d = 10 years) according to the JAK2^{V617F} mutational state in 323 polycythemia vera and 639 essential thrombocythemia patients (Vannucchi *et al*[20]). Only major thrombotic events were retrospectively recorded and the erythromelalgic peripheral, ocular and cerebral ischemic events were excluded from evaluation. The overall incidence of major thrombotic events in JAK2^{V617F} mutated PV patients during 10 years follow-up is about 25% in the Italian study[20]. A similar incidence of thrombotic events was found in our literature analysis of 1241 ET patients not on aspirin from 14 retrospective studies[22]. Source Vannucchi *et al*[20] Blood 2007. ET: Essential thrombocythemia; PV: Polycythemia vera.

at diagnosis manifested in 55 (5.7%) patients, 5.3% in PV and 6.0% in ET[20]. The overall incidence of major thrombotic events during 10 years follow-up usually not on aspirin was about 20% in ET heterozygous for the JAK2^{V617F} mutation and in about 10% for JAK2 wild type ET[20]. Hemorrhages during follow-up was recorded in 45 (4.7%) ET/PV patients. A similar incidence of hemorrhages was found in our analysis of the literature in 1241 ET patients from 14 retrospective studies[22]. The frequency of bleeding was higher in JAK2^{V617F} homozygous (21.4%) than in wild type or heterozygous ET patients, 3.1% and 3.8% respectively. The higher bleeding tendency in homozygous JAK2^{V617F} MPN-T patients is predicted to be related to higher erythrocyte counts at increased platelet and leukocyte counts and its pathophysiology of the underlying mechanisms is currently under our investigation[10].

CLINICAL SYMPTOMS AND DIAGNOSIS IN 497 DUTCH MPN PATIENTS

The results from the 2008 MPN Questioaires of the Dutch MPN Patient Foundation are the reflection of ECMP criteria for the diagnosis, classification and staging of MPN and treatment recommendations of ET

Table 4 Major cardiovascular and venous thrombotic events at diagnosis or during long-term follow-up in 323 polycythemia vera and 639 essential thrombocthemia patients according to the JAK2^{V617F} mutation status in the retrospective study of Vannucchi (only major thrombotic events were retrospectively recorded excluding the erythromelalgic and migraine like cerebral ischemic events[20])

Patients	PV *n* = 323		ET *n* = 625	
JAK2^{V617} mutation status	Hetero homozygous hetero wild type			
No. of patients	219	104	368	237
At diagnosis				
Major arterial events	21%	15.4%	21.7%	10.5%
Venous events	2.9%	2.9%	7.9%	4.7%
During 10 yr follow-up (not on aspirin)				
Major arterial events	10.1%	12.5%	6.3%	5.8%
Venous events	4.1%	7.7%	6.3%	2.7%
Total during life time follow-up				
Major arterial	31.1%	27.9%	28%	16.3%
Venous	10.5%	10.6%	14.2%	7.4%

In 14 homozygous ET patients total major arterial and venous events had occurred in 78.6% and 57.1% respectively. PV: Polycythemia vera; ET: Essential thrombocthemia.

and PV patients in The Netherlands between 2000 and 2008[13,23,24]. Low dose aspirin in ET and phlebotomy on top of aspirin is effective in the majority of ET and in two third of PV patients with low or mild MPN disease burden. Low dose pegylated interferon is recommended in PV with mild to moderately increased MPN disease like leukocytosis, itching and mild to moderate splenomegaly to postpone hydroxyurea. The collected Dutch MPN data were published in PUR SANG in 2010 based on 497 filled forms by MPN patients: 271 females (54%) and 212 males (43%), mean age at diagnosis 57 years (range 20 to 84 years)[23]. The diagnoses of 497 MPN patients were ET in 181 (36%), PV in 244 (50% of whom 18 as ET/PV), MF in 67 (13%), and MPN unclassifiable in 5 (1%). The detection of MPN disease 115 Dutch and Belgian hospitals was related to MPN specific complaints in 55%, coincidental (*e.g.*, routine laboratory investigation for other reasons) in 30% and after significant delay of disease specific complications 15%. Diagnosis of MPN was confirmed by bone marrow investigations in 475 (96%) of 497 MPN patients[23]. Red cell mass (RCM) measurement to diagnose PV and to distinguish ET from PV was performed in 31%. PCR test for the JAK2^{V617} mutation anno 2008 was performed in 230 (46%) MPN patients and found positive in 74% (ET *n* = 52, PV *n* = 103, MF *n* = 14) and negative in 26%. Sixty percent of ET, 91% of PV and 52% of MF patients were JAK2^{V617F} positive, thereby confirming the data in the literature. After primary diagnosis 144 (25%) MPN patients (ET *n* = 38, PV *n* = 49, MF *n* = 27) were referred for a second opinion. The second expert evaluation led to a change in diagnosis in 8% and a change in treatment in 28% (*n* = 29). The second treatment option in 29 (28%) proved to be superior to the initial treatment. A change of diagnosis during follow-up occurred in 60 MPN patients, from ET into PV in 16 (9% of PV), from PV into MF in 15 (6% of PV), and from ET into MF in 10 (6% of ET)[23].

MPN RELATED SIGNS AND SYMPTOMS IN 497 DUTCH ET, PV AND MF PATIENTS

Based on the Dutch MPN questionaire including 36 questions the top 20 complaints at time of diagnosis in 399 out of 497 (81%) MPN patients is shown in Table 5[23]. The most frequent complaint is fatigue (81%) equally high in ET, PV and MF patients. Apart from variable severity of fatigue a specific pattern of signs and symptoms could be retrieved. The signs and symptoms in ET are mainly featured by aspirin responsive tingling and prickling sensations in footsoles, hand palms, toes and fingers (erythromelalgia), and aspirin responsive cognitive concentration and visual disturbances (Table 5). PV patients presented with similar signs and symptoms but on top of that both aspirin resistent itching (PV 58% *vs* ET 30%) and fatigue were much more prominent in PV. A second most frequent complaint were various degrees of night sweats related to splenomegaly in about half of the MPN patients. About one third of MPN patients suffered from bone pain (Table 5). MF patients suffered more frequently from constitutional symptoms of prominent fatigue and night sweats related to pronounced splenomegaly. Before the MPN diagnosis was made the complaints were ascribed by doctors in 173 (35%) patients to other causes including stress, burned out or overstrained in 41 (24%), to depression or hystery in 14 (8%), migraine of unknown origin (and therefore not treated with aspirin) in 13 (8%) and to rheuma, hypertension or fibromyalgia in a few[23].

TREATMENT AND ADVERSE EVENTS IN DUTCH MPN PATIENTS 2003-2008

Treatment in 497 MPN patients was started with low dose aspirin or calcium carbasalate (Ascal) in 70% and phlebotomy in 42% (mainly PV 91%), hydroxyurea in 29%, and pegylated interferon-alpha2a in 7%, wait and see in 8% (*n* = 42 of whom 26 with MF) of MPN patients at time of diagnosis (Figure 3)[23]. The treatment changed during follow-up in 294 (60%) of MPN patients: ET in 64% (*n* = 115), PV in 59% (*n* = 143) and MF in 49% (*n* = 33). Out of 459 evaluable adverse drug reactions or side effects were recorded in one third (*N* = 168 = 35%) of MPN patients. Out of the 168 recorded side effects were related to HU in 41% (*n* = 69) and to IFN in 28% (*n* = 47) of all side effects. Most frequent side effects of HU were skin and mucocutaneous complaints including dry skin, skin lesions, skin ulcers, itching, skin carcinoma, brittle nails, aphtous ulcers and hair loss, and most frequent side effects of IFN were flue-like symptoms, fatigue

Table 5 Top 20 clinical manifestations in patients with who defined myeloproliferative neoplasm essential thrombocythemia, polycythemia vera and myelofibrosis based on the Dutch myeloproliferative neoplasm Questionaire 2009-2010[23]

Symptom	Top 20 MPN complaints	All MPN	MPN	ET	PV	MF
		n = 497	%	%	%	%
1	Fatigue, listless	399	81	80	81	85
2	Microvascular acra[37]	278	57	61	56	46
3	Cognitive disturbances[37]	262	53	52	56	45
4	Visual disturbances[37]	249	51	50	52	46
5	Night sweats	236	48	44	50	52
6	Itching	220	45	30	58	36
7	Dizziness	218	44	44	46	39
8	Bruises, bleedings	211	43	40	45	43
9	Splenomegaly constitutional symptoms	198	40	22	43	78
10	Tinnitus	188	38	38	39	37
11	Migraine headache without visual symptoms	184	37	46	35	22
12	Bone pain	172	35	33	36	34
13	Heart arrythmias	154	31	34	31	24
14	Dysarthria, dyslexia	151	31	31	31	30
15	Hypersensitive to sounds and noices	149	30	29	32	28
16	Paleness	145	29	30	26	40
17	Claudicatio intermittens	140	28	28	30	24
18	Hypersensitive to lights	136	28	25	32	16
19	Visual disturbances without headache	18	33	54	3	90
20	Headache without visual symptoms	24	43	43	4	90

Microvascular acra: Tingling, prickeling sensations, redness,swelling and/or bluish discolouration of footsoles, handpalms, toes and/or fingers[37]. Cognitive disturbances of concentration and memory and sudden attacks of unconscienceness. Visual disturbances of scintillating scotomas, light flashes, blurred vision, transient monocular blindness, rapid spreading of visual figure disturbances[37]. Attacks of migraine-like headaches followed by nausea or vomiting or loss of consciencenous or transient paresis of one extermity[37]. MPN: Myeloproliferative neoplasm; ET: Essential thrombocythemia; PV: Polycythemia vera; MF: Myelofibrosis.

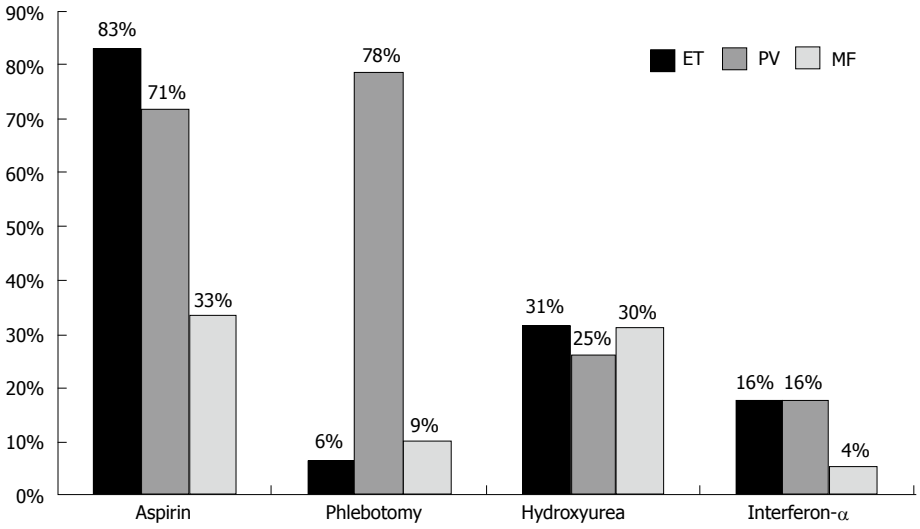

Figure 3 Mode of treatment in the Dutch 2008 survey of 363 myeloproliferative neoplasm (123 essential thrombocythemia, 190 polycythemia vera and 50 myelofibrosis) patients: 93% of polycythemia vera, 71% of essential thrombocythemia and 37% of myelofibrosis were on aspirin; 6% of essential thrombocythemia, 78% of polycythemia vera and 9% of myelofibrosis were treated with phlebotomy[23]. Because of symptomatic MNP disease burden 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET, 16% of PV and 4% of MF were on treatment with pegylated interferon (Pegasys®)[23]. ET: Essential thrombocythemia; PV: Polycythemia vera; MF: Myelofibrosis; MNP: Myeloproliferative neoplasm.

and mood disturbances[23]. Low dose aspirin or Ascal induced gastritic complaints in 11% for which treatment with metronidazol was usually indicated[23].

DISCUSSION

In the Dutch 2008 survey of 363 MPN (123 ET, 190 PV and 50 MF) patients 93% of PV, 71% of ET and 37% of MF were on aspirin mainly because of microvascular symptoms including migraine-like headache, acral paresthesia, erythromelalgia, transient neurological and visual disturbances. Phlebotomy became the first line treatment in 6% of ET, 78% of PV and 9% of MF[23]. Because of advanced or symptomatic MPN disease 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET and PV and

Table 6 Staging of JAK2^{V617F} positive prodromal polycythemia vera, erythrocythemic polycythemia vera, and five stages of PV according to WHO-ECMP criteria related to therapy anno 2014[10,13,34-37]

PV: WHO-ECMP stage	0	1	2	3	4	5	6
WHO-ECMP clinical diagnosis	Prodromal PV	Erythrocythemic PV	Early PV	Overt PV Classical PV	PV PMF Masked PV	Post-PV MF Spent PV	Leukemic PV MDS/AL
LAP-score	↑	↑	↑	↑	↑/↑↑	Variable	Variable
Red cell mass	N	↑	↑	↑	↑	Variable	N/↓
Serum EPO	N/↓	N/↓	↓	↓	↓	Variable	N/↓
Erythrocytes × 10^{12}/L	< 5.8	> 5.8	> 5.8	> 5.8	< 5.8	Variable	N/↓
Leukocytes × 10^{9}/L	< 12	< 12	< or > 12	< or- > 15	> 15	> 20	> 20
Platelets × 10^{9}/L	> 400	400	< or > 400	> 400	< or > 1000	Variable	Variable
WHO-ECMP bone marrow	Early PV	Early PV	Early PV	Trilinear PV	Trilinear PV	Myelofibrosis	Leukemic
Bone marrow cellularity (%)	50-80	50-80	60-100	80-100	80-100	Decreased	Increased
Grading reticulin fibrosis: RF	RF 0-1	RF 0-1	RF 0-1	RF 0/1,	RCF 2/3	RCF 3/4	
Grading myelofibrosis: MF[57]	MF 0	MF 0	MF 0	MF 0	MF 1/2	MF 2/3	
Splenomegaly on palpation	No/+	No	No/+	+	++/+++	/Large	Large
Spleen size, echogram cm	< 12-15	< 13	12-15	12-18	18 - > 20	> 20	> 20
Spleen size on palpation cm	0-3	NP	0-3	4-6	> 6	> 8	> 8
JAK2^{V617F} in Granulocytes %	low	low	Moderate < 50	High > 50	High > 50	High > 50	No or ++
JAK2^{V617F} in BFU-e (exon 12)	+(++)	+(++)	+(++)	++	++	++	
Therapeutic implications Anno 2014	Low risk	Low risk	Low risk	Intermediate risk PV	High risk PV-MF	Post-PV MF Spent phase PV	Leukemia
First line aspirin/Phlebotomy	Aspirin	Aspirin	Phlebotomy	Phlebotomy[1]	If IFN resistant	JAK2	Chemotherapy
Second line IFN *vs*	Phlebotomy	Phlebotomy	Aspirin	Aspirin	→	Inhibitor →	Bone marrow
HU			Low dose IFN	IFN à resistant	HU or JAK2	Bone marrow	transplantation?
Third line JAK2 inhibitor			→ responsive	→ HU	inhibitor	transplantation	Supportive

[1]↑: Increased; ↓: Decreased; N: Normal; +: Present or heterozygous; ++: Homozygous; HU: Hydroxyurea; PV: Polycythemia vera; MF: Myelofibrosis; WHO-ECMP: World Health Organization and European Cliical Molecular and Pathological; LAP: Leukocyte alkaline phosphatase; EPO: Erythropoietin.

4% of MF were on treatment with pegylated interferon (Pegasys^{R}). In the study of Vannucchi *et al*[20], a total of 214 patients were treated with phlebotomy, 58% of 219 PV and 4% of 257 ET patients. Myelosuppressive chemotherapy was administered to 497 patients (52%) including 59% of 219 PV and 48% of 257 ET patients. The 20% difference of HU use (50% of Italian MPN-T patients *vs* 30% of Dutch MPN-T patients) can readily be ascribed to significant differences in the Italian *vs* the Dutch guidelines for MPN-T disease in ET and PV patients. MPN-T patients in the Netherlands were treated according to the 2000 guidelines for ET and PV[13]. Low risk MPN-T disease in ET and PV patients at ages 18 to 80 years is defined by platelet count < 1500 × 10^{9}/L, absence of vascular risk factors like hypertension, hypercholesterolemia, diabetes atherosclrosis and absence of bleeding complications. First line treatment option in MPN-T disease in ET and PV patients followed the published Dutch guidelines since 2000[6-10]. If asymptomatic, no microvascular symptoms and no major thrombosis like minor stroke of myocardial infarction low dose aspirin 40 mg a day is given in JAK2^{V617F} mutated MPN-T. Symptomatic MPN-T patients including migraine atypical TIAs, minor TIAs, low back pain, painfull toes or fingers, and major thrombosis were treated low dose aspirin. When MPN-T is associated with leukocytosis, moderate splenomegaly or platelet count above 1000 × 10^{9}/L low dose Pegasys 45 μg/mL will become the treatment of choice in JAK2^{V617F} mutated ET and PV. At age above 70 freedom to choose hydroxyurea or low dose pegasys must prevail. Please note that these are general Dutch MPN-T treatment guidelines, which has to be discussed with the local hematologist or internist for approval[22-26].

The 2013 WHO-ECMP criteria clearly define and stage the JAK2^{V617F} defined MPN entity of prodromal PV, prefibrotic PV, early fibrotic PV, PV complicated by myelofibrosis (post-PV MF), significant myeloid metaplasia of the spleen with splenomegaly and related constitutional symptoms (Table 6)[13]. Within the JAK2^{V617F} MPN phenotypes, the JAK2^{V617F} mutated hypercellular ET is associated with clustered pleiomorphic megakaryopoiesis, increased granulopoiesis and relative decrease of erythropoiesis without a documented history of ET or PV. The integrated WHO-CMP criteria surely will have important implications in choosing proper targeted treatment options for the prevention of thrombotic and bleeding complications in prodromal PV and PV and for the management of serious complications of progressive MPN disease burden requiring myeloreductive treatment with pegylated interferon (Pegasys^{R}) and if non-responsive or side effects low dose hydroxyurea to correct increased blood cell counts in overt and advanced PV patients (Table 6)[10,13]. Venesection aiming at a hematocrit below 0.45 in males and below 0.42 in females is the first line treatment option in PV patients[24-29]. Phlebotomy aiming more strictly at a hemotocrit of less than 0.40 and a MCV of less than 70 fl in males and females on top of well controlled low dose aspirin in PV patients will significantly reduce the cumulative incidence of major thrombosis, but the microvascular syndrome of associated thrombocythemia

persist when not on aspirin[13]. According to current insights, low dose interferon is the treatment of choice in intermediate stage PV patients (Figure 1, Table 6)[13,30-33]. If not responsive to IFN or side effects induced by IFN, hydroxyurea is the second line myelosupressive treatment option in JAK2^{V617F} mutated ET and PV patients (Table 6). Hydroxyurea is not an innocent drug and should be used with caution (Table 6). The final analysis of the 1980 French PVSG study of HU as upfront therapy at time of diagnosis in 136 evaluable PV patients younger than 65 years is published in 2011[32]. The cumulative incidence (probability) of myelofibrosis (MF) at 10, 15 and 20 years was 15%, 24% and 32% in the HU arm and the cumulative incidence of AML/MDS at 10, 15 and 20 years was 7.3%, 10.7% and 16.6% for HU treated PV patients. Proper staging of PV in terms of JAK2^{V617F} mutation load, and MPN disease burden by measuring the degree of splenomegaly and severity of constitutional symptoms including itching on top of bone marrow histology and grading of fibrosis is of huge importance since it has significant implications for a non-leukemogenic or the least potential leukemogenic treatment options in low, intermediate and high risk PV patients (Figure 1, Table 6)[10,34-37]. As shown in Table 6, high risk PV and MF patients with advanced MPN-T disease in terms of high JAK2^{V617F} allele burden, progressive MPN disease with splenomegaly and constitutional symptoms are candidates for myelosuppressive (hydroxyurea) or myeloreductive (JAK2 inhibitors) treatment[10,34-37].

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MINIREVIEWS

Intensive care organisation: Should there be a separate intensive care unit for critically injured patients?

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Abstract

In the last two decennia, the mixed population general intensive care unit (ICU) with a "closed format" setting has gained in favour compared to the specialized critical care units with an "open format" setting. However, there are still questions whether surgical patients benefit from a general mixed ICU. Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requiring immediate surgical intervention and/or intensive care treatment. The role and type of the ICU has received very little attention in the literature when analyzing outcomes from critical injuries. Severely injured patients require the years of experience in complex trauma care that only a surgery/trauma ICU can provide. Should a trauma center have the capability of a separate specialized ICU for trauma patients ("closed format") next to its standard general mixed ICU?

Key words: Intensive trauma care; Trauma intensive care; Critical care; Intensive care medicine; Trauma

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Core tip: Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requires immediate surgical intervention and/or intensive care treatment. Severely injured patients require the years of experience in complex trauma care that only a surgery/ trauma intensive care unit can provide.

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INTRODUCTION

The contribution of organizational structure - in a wide variety of settings - for the delivery of critical care to patients has been the topic of study since the mid-

1980s[1-9]. The preponderance of evidence recommends that intensivist-directed patient management is related to a reduced length of intensive care unit (ICU) stay, reduced hospital length of stay, and most likely decreased mortality. In the last two decennia, the mixed population general ICU with a "closed format" setting has gained in favour compared to the specialized critical care units with an "open format" setting, especially in Europe[8-15]. Therefore, critical care physicians have taken responsibility for the treatment of critically ill patients, and more and more specialized units are embedded in the intensive care department. These units are subsequently transformed into overall general units with a mixed population of different diseases. Although there seems to be more positive results towards the general mixed ICU within a "closed format" setting in the literature[4,6-8,10,16-23], there are still questions whether surgical patients benefit from a general mixed ICU. The only evidence accessible on this field comes from the neurosurgical intensive care; Intracerebral hemorrhage patients treated in a specialized neuroscience ICU had lower mortality, length of stay, and cost than those treated in a general ICU[24,25]; and from the burn intensive care[26-29]. Does this mean that we have to reorganise all specialized surgical units, even if those units are already working in accordance with the "closed format" setting? Several authors state that we should not reform all of our specialized surgical ICUs[30-33].

Trauma has been called the unnoticed epidemic and the unheeded disease of modern society. Trauma every year impacts hundreds of thousands of individuals and cost billions of dollars in direct financial loss[34]. Trauma care has improved over the past 20 years, largely from improvements in trauma systems, assessment, triage, resuscitation, emergency and intensive care[34]. Trauma is a significant cause of morbidity and mortality throughout the world. Major or severe trauma requires immediate surgical intervention and/or intensive care treatment. Over one quarter of trauma patients are cared for in an ICU during their hospital admission in the United States[33,35]. Modern trauma care has become highly specialized, especially for the critically ill patient with multiple-system injuries[36]. The care provided in this setting plays a major role in ensuring survival following injury and might significantly influence functional outcome[33]. Nevertheless, the function and structure of the ICU has received very little awareness in the literature when examining outcomes from critical injuries[36]. The American College of Surgeons Committee on Trauma, whose criteria is used for the verification of trauma centers, recommends that the surgeon presuming first responsibility for the care of the injured patient should maintain that responsibility all through the acute care phase of hospitalization, including the ICU[37]. Nathens *et al*[30] have concluded that closed ICUs with a surgeon intensivist had the best outcome in the care of the critically injured trauma patient compared with the non-surgeon intensivists. Park *et al*[32] suggested that improved clinical outcomes, lower costs and reduced length of stay are directly related to a separate closed trauma unit. And the most recent study of Duane *et al*[36] concludes that severely injured patients require the years of experience in complex trauma care that only a surgery/trauma ICU can organise. These patients air a number of exceptional challenges for the ICU physician including the need for ongoing resuscitation, drive of resuscitation endpoints, and treatment of early post-resuscitation complications. How well these are addressed may have critical implications for long-term outcome and survival[38]. Timing in treatment (especially re-operations in the first 48 h) of the critically injured patient is of great importance; and who is better to understand these circumstances than the surgeon intensivist (with experience in trauma surgery)? In a perfect world, should a trauma center have the capability of a separate specialized ICU for trauma patients ("closed format") next to its standard general mixed ICU? Critically injured patients requiring admission to the ICU often have multi-system injuries that require technically advanced medicine including resuscitation from shock. The ICU care of the trauma patient differ from that of other intensive care patients in many ways, one of the most important being the need to continuously combine operative and non-operative treatment. Though, development in the care of the injured has been made, death due to uncontrolled bleeding, severe head injury, or the development of multiple organ dysfunction syndrome remains all too common in this patient population. Additionally, due to the potential nature of the injuries, the problem not seldom arises that the optimum therapy for one injury or organ system, such as preoperative permissive hypotension in actively bleeding patients, may result in suboptimal or even harmful therapy in the existence of an other injury (such as traumatic brain injury)[39]. In addition, trauma leads to a state of relative immunosuppression with decreased humoral and cell mediated immunity[40-45].

Trauma surgery critical care teams often consult multiple specialists to provide the complex care necessary to treat the most severely injured. It is true that this kind of advanced medicine is indeed available at each Level I trauma center general ICU. However, would the experience of highly trained personnel (trauma nurses, senior surgical residents, trauma fellows) contribute even more to a better patient outcome? With this kind of highly trained and experience personnel the possibility exists to perform small operations on the unit itself without having to wait and transport the critically injured patient to an operation theatre. Complex, high skilled nursing interventions such as volume replacement, correction of coagulopathy and hypothermia, invasive monitoring and the management of "damage-control" conditions demand understanding and experience that are not able to be gauged. These skills are obtained on a daily basis in Trauma ICUs where there is an excess of "hands-on" learning possibility. The development of such skills is critical for optimal results in life-threatening

blunt and penetrating trauma. An identical care is hard to attain even from staff that is experienced and exceptional in their non-surgical fields[36]. Even in our own intensive care patient organisation (concerning surgical patients and the critically injured patients on outcome), a difference in the dimensions of crude ICU outcome (short-term mortality/length of ICU stay and ICU readmission) was seen after the reorganization to a general ICU[46]. Should there not be an organised survey among different trauma centers to analyse the critically injured patient outcome. This should give critical care physicians and surgeons specialized in trauma insight in the question whether patient outcome could gain from separate trauma units or give us the conclusive information whether we should continue combining all specialized care units together.

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Severe scrub typhus infection: Clinical features, diagnostic challenges and management

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Abstract

Scrub typhus infection is an important cause of acute undifferentiated fever in South East Asia. The clinical picture is characterized by sudden onset fever with chills and non-specific symptoms that include headache, myalgia, sweating and vomiting. The presence of an eschar, in about half the patients with proven scrub typhus infection and usually seen in the axilla, groin or inguinal region, is characteristic of scrub typhus. Common laboratory findings are elevated liver transaminases, thrombocytopenia and leukocytosis. About a third of patients admitted to hospital with scrub typhus infection have evidence of organ dysfunction that may include respiratory failure, circulatory shock, mild renal or hepatic dysfunction, central nervous system involvement or hematological abnormalities. Since the symptoms and signs are non-specific and resemble other tropical infections like malaria, enteric fever, dengue or leptospirosis, appropriate laboratory tests are necessary to confirm diagnosis. Serological assays are the mainstay of diagnosis as they are easy to perform; the reference test is the indirect immunofluorescence assay (IFA) for the detection of IgM antibodies. However in clinical practice, the enzyme-linked immuno-sorbent assay is done due to the ease of performing this test and a good sensitivity and sensitivity when compared with the IFA. Paired samples, obtained at least two weeks apart, demonstrating a $\geqslant$ 4 fold rise in titre, is necessary for confirmation of serologic diagnosis. The mainstay of treatment is the tetracycline group of antibiotics or chloramphenicol although macrolides are used alternatively. In mild cases, recovery is complete. In severe cases with multi-organ failure, mortality may be as high as 24%.

Key words: Rickettsia; Diagnosis; Management; Outcome; Multi-organ failure

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Core tip: Scrub typhus is an important differential diagnosis in patients who present with acute undifferentiated fever in South East Asia. Since the presentation may be non-specific, with features of organ failure in those with severe infection, early diagnosis and appropriate management is crucial. The presence of an eschar suggests scrub typhus infection. The diagnosis may be confirmed on serological assays, the reference test being the indirect immunofluorescence test for the detection of IgM antibodies. In those with mild infection, fever defervescence occurs in about 2-d with Doxycycline therapy.

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INTRODUCTION

Scrub typhus infection is an important aetiology of acute undifferentiated fever in south-east Asia and India[1,2]. It is a zoonotic rickettsial illness caused by *Orientia tsutsugamushi* and is endemic in the "Tsutsugamushi triangle" that extends from northern Japan and far eastern Russia to northern Australia in the south and Pakistan in the west[3]. The reservoirs for infection are the chiggers (larva of trombiculid mite) and rats and humans are accidentally infected. It is transmitted by trombiculid mites in long grasses and in dirt-floor homes, with infection characterized by a flu-like illness of fever, headache and myalgia lasting approximately one week. In some, the illness progresses to multi-organ dysfunction syndrome and death.

DISTRIBUTION OF DISEASE

Scrub typhus is seen in several parts of South-East Asia including India[4-11], Bangladesh[12], China[13], Taiwan[14], South Korea[15], Japan[16] and Northern Australia[17]. Although scrub typhus has been reported from isolated parts of these countries[2,5,9,13,14], it is likely that this disease is ubiquitous. The majority of cases are from the rural areas given that these mites thrive in those environments. However acute infection as well as serological evidence of infection has been published from metropolitan cities[10,11,13]. Outbreaks generally occur during the cooler months of the year after monsoons[12].

In the endemic Asia-Pacific region, one billion people are estimated to be at risk of infection and one million cases of scrub typhus occur every year[18]. The disease is responsible for nearly 1/4th of the febrile episodes in endemic areas[19]. Mortality in severe case or with improper treatment may be as high as 30%[20,21].

PATHOPHYSIOLOGY

The pathophysiological hallmark of scrub typhus is disseminated vasculitis[22] with subsequent vascular injury that involves organs such as skin, liver, brain, kidney, meninges and the lung. The organism multiplies at the site of inoculation that progresses on to necrosis and evolves into an eschar with regional lymphadenopathy[22]. Within a few days, patients develop rickettsemia with infection of the vascular endothelium resulting in vascular injury in several organs. The injury causes disseminated intravascular coagulation (DIC) with platelet consumption, vascular leak, pulmonary edema, shock, hepatic dysfunction and meningoencephalitis[23-26].

MOLECULAR CHARACTERISTICS

O. tsutsugamushi expresses a type-specific protein, the 56-kDa protein, which is unique and not expressed by other bacteria or Rickettsiae. Since this protein sequence is unique, and contains cross-reacting epitopes, variations in this have resulted in the genetic diversity of *O. tsutsugamushi*[27]. This protein has also been explored in the development of vaccines[28]. Commonly reported strains include the prototype Karp strain and closely related strains (Karp-like strains), which are most frequent in endemic areas, as well as Gilliam, Kato, Kawasaki, TA763 and others[28,29].

CLINICAL FEATURES

Scrub typhus presents as an acute undifferentiated fever. The incubation period for symptoms is between six and twenty-one days from exposure[30]. The clinical picture is characterized by sudden onset fever with chills, headache, backache and myalgia, profuse sweating, vomiting and enlarged lymph nodes[30]. In some patients, an eschar may develop at the site of chigger feeding, usually at sites where the skin surfaces meet, such as axilla, groin and inguinal areas[31]. Although the eschar is reported to be less frequently observed in South Asian patients than in East Asian or Caucasians[31], 55% of patients had an eschar in a recent study from South India[27]. In a large retrospective analysis of 418 patients with confirmed scrub typhus and an eschar, a significant difference in the distribution of eschar was noted between males and females[32]. In females it was primarily present in the chest and abdomen (42.3%), while in males it was present in the axilla, groin and genitalia (55.8%). Unusual sites of eschar were reported to be in the cheek, ear lobe and dorsum of the feet[32].

Five to eight days after the onset of fever, a macular or maculopapular rash may appear on the trunk and later extend to the arms and the legs in a small proportion of patients[31]. Complications of scrub typhus infection include pneumonia[33], acute respiratory distress syndrome (ARDS) like picture[34,35],

myocarditis[36], encephalitis[37], hepatitis[38], DIC[39], hemophagocytic syndrome[40], acute kidney injury[41], acute pancreatitis[42], transient adrenal insufficiency[43], subacute painful thyroiditis[44] and presentation as an acute abdomen[45].

Several neurological manifestations have been observed in the setting of scrub typhus infection. The most common neurological presentation in scrub typhus is as meningitis, meningoencephalitis or encephalitis[46]. Others include cerebral venous thrombosis[47], Guillain-Barre Syndrome[48], transient Parkinsonism and myoclonus[49], opsoclonus[50], cerebellitis[51], transverse myelitis[52], polyneuropathy[53], facial palsy[54], abducens nerve palsy[55] and bilateral optic neuritis[56].

Multi-organ dysfunction is not uncommon in severe scrub typhus infection. In a recently published study of 116 patients admitted to an intensive care unit with severe scrub typhus infection, the admission Acute Physiology and Chronic Health Evaluation (APACHE) II score was 19.6 ± 8.2[20]. Ninety-one patients in this cohort had dysfunction of 3 or more organs and 16 patients (15%) had evidence of dysfunction of all six organs. Respiratory dysfunction was predominant (96.6%) with ventilatory support required in 87.9%. Cardiovascular dysfunction was present in 61.7% and hepatic dysfunction in 63.8%. Thirteen patients (11.2%) were dialyzed. Hospital mortality in this ICU cohort was 24.1%[20]. On logistic regression analysis, APACHE-II score and duration of fever were independently associated with mortality.

DIAGNOSIS

Acute febrile illness (AFI) may be categorized as differentiated fever, where there is an obvious focus of infection (*e.g.*, respiratory tract, urinary tract) or an undifferentiated fever. In an undifferentiated fever, where there is no obvious focus of infection and the symptoms and signs are quite nonspecific, several diagnostic possibilities are considered, particularly in the tropics[2]. This includes scrub typhus, malaria, enteric fever, dengue, leptospirosis, spotted fever rickettsioses and Hanta virus[2]. Thus, in this setting, it is particularly important that a detailed clinical history and examination are done and relevant diagnostic tests performed to diagnose the cause of AFI. The presence of an eschar makes the diagnosis of scrub typhus highly likely and this should be carefully looked for.

The diagnostic methods available for laboratory confirmation include identification of the organism in cell culture, detection of the antigen by immunehistochemical methods or the antibodies by the indirect immunofluorescence assay (IFA) and finding specific nucleic acid targets using molecular methods. The success of a test in confirming the diagnosis of scrub typhus is dependent on the type of sample taken[57] and the timing of the specimen. Cell culture or molecular assays performed using eschar (when present) or buffy coat are more likely to be positive in the first two weeks of illness[58]. Antibody levels reach detectable levels by day seven; paired sera obtained at least two weeks apart are necessary for serologically confirming the diagnosis by demonstration of a ⩾ 4 fold rise in titre[59].

Isolation of *Orientia tsutsugamushi* in culture is definitive and can be performed using cell culture[60]. Cell lines like HeLa cells, L929 cells (mouse fibroblast cells), Vero cells, BHK-21 cells have been used to cultivate *Orientia tsutsugamushi*. The L929 mouse fibroblast cell line is commonly used for the isolation of *O. tsutsugamushi* from the blood. Isolation of *Orientia tsutsugamushi* is not routinely done as it requires a cell culture facility, trained personnel, strict bio-safety precautions and a BSL (Bio Safety level) Ⅲ facility. As the organism doubling time is 9-18 h[61], it takes an average of four weeks for identification by culture[57]. This further precludes the use of culture as a routine diagnostic test. Currently, reference laboratories use culture techniques for isolation of *Orientia tsutsugamushi* for definitive identification, research and for obtaining antigen for immunofluorescence[62].

Since antigen detection tests have low sensitivity/specificity and require biopsy specimens, in the clinical setting, serological assays are the mainstay of diagnosis[63] as they are simple and comparatively easy to perform[64]. The serological reference test is the indirect IFA for the detection of IgM antibodies. This assay has drawbacks which include retrospective nature, requirement of well trained personnel and equipment which may not be available in many diagnostic laboratories[65]. Currently most diagnostic laboratories use the enzyme-linked immunosorbent assay (ELISA) for the detection of IgM antibodies in scrub typhus as it provides an objective result and has sensitivity similar to that of IFA[64]. Detection of IgM antibody is considered to be diagnostic of an acute infection when compared to IgG antibodies which suggest a previous infection especially in endemic areas[66]. Rapid tests to detect IgM antibodies to scrub typhus have sensitivity ranging from 34.7% to 96.7% and specificity between 93.3% and 99.7%[66-68].

PCR assays, either conventional or real-time, targeting the 56 kDa gene, 47 kDa gene, *16 S rRNA* and *groEL* gene have also been explored and reported to have specificity approaching 100%[24]. Sensitivity of the nested PCR assays using 56 kDa or the *16 S rRNA* genes can be as low as 22.5% to 36.1%[9]. Real-time PCR assays show a better sensitivity ranging from 45%[69] to 82%[70]. In recent times, LAMP assays targeting the *GroEl* and the 47 kDa gene have been described[71,72]. The LAMP assay has the advantage that it can be performed using simpler equipment. In addition it is not inhibited by heme as is the case with PCR[73].

In the clinical setting, a diagnosis of scrub typhus is considered when a patient with an AFI has an eschar and a positive IgM ELISA for scrub typhus and other causes of fever excluded[74]. In the absence of an eschar, a positive IgM ELISA in the appropriate clinical setting with defervescence within 48-h of initiation of

Table 1 Commonly used antimicrobial agents in scrub typhus infection

Name of drug	Dose and administration in adults	Comments
Doxycycline[75,77]	100 mg twice daily for 7 d	Drug of choice Intravenous preferred for sicker patients Rapid defervescence within 48 h
Tetracycline[76]	500 mg four times daily	No difference between doxycycline and tetracycline
Azithromycin[75,77]	Mild infections: 500 mg single dose Severe infections: 500 mg once daily for 3 to 5 d; 1 g loading dose may be given	Preferred drug in pregnancy In mild cases symptom duration similar when compared with doxycycline Recommended when doxycycline resistance is present
Telithromycin[80]	800 mg daily for 5 d	As effective as doxycycline
Chloramphenicol[75,77]	500 mg every 6 h for 7 d	Most common alternative to tetracycline Contraindicated in pregnancy Risk of aplastic anemia
Rifampicin[78]	600 to 900 mg daily for 7 d	Combination with doxycycline not more efficacious than either Rifampicin or doxycycline in mild scrub typhus Shorter duration of fever with Rifampicin in Northern Thailand when compared with Doxycycline Caution in tuberculosis endemic areas

doxycycline or scrub IgM ELISA seroconversion on convalescent sera with other etiologies of AFI ruled out with appropriate investigations also suggests scrub typhus infection[2].

TREATMENT

Supportive treatment

Patients with mild disease presenting with fever without organ dysfunction may require only antipyretics along with antibiotics. Patients presenting with organ dysfunction would need organ support depending on the nature and extent of organ dysfunction[20]. Patients with respiratory failure could be supported either by means of non-invasive or invasive mechanical ventilation based on standard criteria in the management of respiratory failure. Those with circulatory shock can be treated with fluid resuscitation and vasoactive therapy if the blood pressure does not improve with fluids. Acute kidney injury, which is not uncommon in scrub typhus, may need renal replacement therapy. Those with DIC with clinical bleeding would require transfusion of blood products depending on the nature of coagulation derangement.

Specific treatment

The drug treatment options in scrub typhus have been evaluated and summarized in a recent meta-analysis[75]. In the 17 studies that were included in the meta-analyses, six antibiotics were used and included doxycycline, chloramphenicol, azithromycin, rifampicin, roxithromycin and tetracycline. Conventionally, the treatment of scrub typhus involves the use of the tetracycline group of antibiotics[76] or chloramphenicol[75]. Since these drugs are contraindicated in pregnancy and in children, alternative agents such as quinolones and macrolides are used for the treatment of scrub typhus in this setting[75].

In the four studies that compared azithromycin with chloramphenicol, chloramphenicol treatment was associated with significantly shorter median time to clearance of fever and lower adverse events when compared with azithromycin[75]. Six studies compared doxycycline with chloramphenicol; symptom clearance time was significantly shorter with doxycycline[75]. No significant differences were observed in symptom duration comparing azithromycin with doxycycline (3 studies), roxithromycin with doxycycline (3 studies) and doxycycline with either rifampicin or tetracycline (2 studies each)[75].

Doxycycline is the preferred drug in the treatment of scrub typhus. A therapeutic response to doxycycline therapy is used as a diagnostic test[2]. In less sick patients oral doxycycline can be administered at 100 mg twice daily. The duration of treatment is 7 d. In critically ill patients, particularly those in shock, the absorption of enterally administered doxycycline may be problematic. In such situations, intravenous doxycycline should be used; where unavailable, intravenous azithromycin may be used in isolation or combined with enteral doxycycline[20,74]. Azithromycin is also the recommended drug for treatment of scrub typhus in pregnancy[77]. Rifampicin may be considered where doxycycline resistance is present[77]. In one trial of patients with mild scrub typhus, Rifampicin was found to have shorter defervescence time when compared with doxycycline[78]. However, in tuberculosis endemic countries, rifampicin should be avoided for the treatment of scrub typhus. Although there is some evidence for the use of quinolones in scrub typhus, recent reports of quinolone resistance suggests that this treatment should not be used in critically ill patients[79]. Preliminary reports suggest that Telithromycin is a promising new antibacterial agent for patients with mild to moderate scrub typhus[80]. The different anti-microbial agents used in scrub typhus are summarized in Table 1.

COURSE

Patients with mild disease usually recover fully. In a

study of 261 patients from Taiwan, no mortality was observed[81]. In a recently published large cohort of 623 patients hospitalized with scrub typhus of varying illness severity from mild to critically ill, the mortality was 9%[35]. Reducing mortality over a 4-year period was reported in this study. Favourable maternal and fetal outcome may be expected in appropriately managed patients with scrub typhus complicating pregnancy[82]. In sicker patients admitted to the ICU with multi-organ failure, the mortality is 24%[20]. These observations should encourage clinicians to approach scrub typhus infection with optimism.

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ORIGINAL ARTICLE

Clinical Trials Study

Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at masaki46228@m-kanazawa.jp.

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Abstract

AIM: To investigate whether landiolol, an ultra-short-acting β1-antagonist, can safely and effectively control heart rate in septic patients with supraventricular tachyarrhythmias.

METHODS: We reviewed all patients with sepsis who admitted to our intensive care unit between January 2006 and December 2011. Sixty one septic patients suffered from supraventricular tachyarrhythmias (heart rate ⩾ 120 bpm for > 1 h). Among 61 patients, 39 patients were treated with landiolol (landiolol group) and 22 patients were not treated with landiolol (control group). Arterial pressure, heart rate, cardiac rhythm, pulmonary arterial pressure and cardiac output (if a pulmonary arterial catheter was inserted) were compared between the 2 groups at 1, 8 and 24 h after the initiation of tachyarrhythmias.

RESULTS: Mean age and Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores were similar between the 2 groups. Paroxysmal atrial fibrillation/flutter (87%), paroxysmal atrial tachycardia (10%), and paroxysmal supraventricular tachycardia (3%) were observed. The initial landiolol dose administered was 6.3 ± 5.8 g/kg per minute. Rapid and substantial reduction of heart rate was observed in the landiolol group without any

deterioration of hemodynamics. Landiolol significantly reduced heart rate (from 145 ± 14 bpm to 90 ± 20 bpm) compared to the control group (from 136 ± 21 bpm to 109 ± 18 bpm, $P < 0.05$). The conversion to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point ($P < 0.01$ at 8 h; $P < 0.05$ at 1 and 24 h).

CONCLUSION: Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmias.

Key words: Landiolol; Supraventricular tachyarrhythmias; Sepsis; Rate control; Conversion to sinus rhythm

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Core tip: The management of tachyarrhythmia is important but it is often difficult because of unstable hemodynamics in septic patients. Landiolol is an ultra-short-acting β1 selective adrenoceptor antagonist. It exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other β blockers. In fact, landiolol significantly reduced heart rate without any deterioration of hemodynamics in this study. The most impressive finding is high conversion rate to sinus rhythm immediately after landiolol administration. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias. Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

Okajima M, Takamura M, Taniguchi T. Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. *World J Crit Care Med* 2015; 4(3): 251-257 Available from: URL: http://www.wjgnet.com/2220-3141/full/v4/i3/251.htm DOI: http://dx.doi.org/10.5492/wjccm.v4.i3.251

INTRODUCTION

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The incidence of paroxysmal atrial fibrillation/flutter (PAF) has been reported to be 31% in critically ill patients with sepsis[1]. Tachyarrhythmias have been identified as a major source of morbidity in critically ill patients[2,3]. Therefore, controlling tachyarrhythmia should be important in such patients.

Measurements of serum catecholamine level and direct measurements of renal sympathetic nerve activity have revealed that severe infection activates the sympathetic nervous system[4-9]. This activation may trigger supraventricular tachyarrhythmias in the presence of severe infection[10]. Therefore, we believed that β blockers can be used to control heart rate (HR) in patients with severe infection. However, it is difficult to use β blocker in patients with severe sepsis because of hemodynamic instability.

Landiolol (ONOACT; Ono Pharmaceutical, Osaka, Japan), a newly developed commercially available agent, is an ultra-short-acting β-adrenoceptor antagonist with a half-life of 4 min in healthy subjects. Landiolol also has high β_1 selectivity (β_1/β_2 = 255) and is 8 times more cardioselective than esmolol[11-14]. Moreover, landiolol exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol in rabbits[15,16]. In clinical situations, landiolol has been used to treat perioperative tachyarrhythmias in Japan. Landiolol reduced HR significantly without reducing blood pressure and stabilized hemodynamics in postsurgical patients[11,17-20].

Considering these characteristics, landiolol could be valuable and suitable for managing tachyarrhythmias in patients with severe infection. Therefore, we investigated whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in patients with severe sepsis.

MATERIALS AND METHODS

Study design and patients selection

This historical cohort, single-center, interventional, and inter-subjective comparison study was approved by the Institutional Review Board of the Kanazawa University Hospital and was registered under ISRCTN number 70831305. Informed consent was obtained from all patients.

Medical records of all patients were screened and followed for sepsis with supraventricular tachyarrhythmia by a single intensivist in the intensive care unit (ICU) of the Kanazawa University Hospital from January 2006 to December 2011, were reviewed. Patients were included in this study if they met the following criteria: (1) systemic inflammatory response syndrome score ⩾ 2 with infection; (2) ⩾ 18 years of age; (3) supraventricular tachyarrhythmias with HR ⩾ 120 bpm for >1 h; (4) no history of chronic supraventricular tachyarrhythmias; and (5) no supraventricular tachyarrhythmias at the time of ICU admission. Patients were divided into 2 groups: those treated with landiolol (landiolol group) and those not treated with landiolol (control group) to control HR of supraventricular tachyarrhythmias.

Measurements

Arterial pressure and HR were compared between the 2 groups at 1, 8, and 24 h after the initiation of tachyarrhythmia. We also investigated heart rhythm and the conversion to sinus rhythm. Pulmonary arterial pressure, central venous pressure (CVP), cardiac output, and cardiac index (CI) were measured if a pulmonary arterial catheter was inserted. Systemic vascular resistance index (SVRI) was calculated as follows: SVRI

Table 1 Patients' characteristics

	Landiolol	Control
n	39	22
Age, yr	70.7 ± 12.3	70.8 ± 12.5
Underlying disease		
Cardiovascular disease	16 (41.0%)	11 (50.0%)
Malignancy	11 (28.2%)	3 (13.6%)
Immunological disorder	3 (7.7%)	2 (9.1%)
Others	9 (23.1%)	6 (27.2%)
Infected site		
Respiratory tract	17 (43.6%)	14 (63.6%)
Intra-abdominal	13 (33.3%)[a]	2 (9.1%)
Blood	5 (12.8%)	0 (0%)
Skin/soft tissue	2 (5.1%)	0 (0%)
Urinary tract	1 (2.6%)[a]	4 (18.2%)
Others	1 (2.6%)	2 (9.1%)
APACHE II	22.8 ± 5.4	22.1 ± 7.7
SOFA	8.8 ± 4.0	9.1 ± 3.9

[a]$P < 0.05$ *vs* control. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

Table 2 Hemodynamics

	Landiolol	Control
Heart rate, bpm	145 ± 14[a]	136 ± 21
Systolic arterial pressure, mmHg	113 ± 34[a]	137 ± 39
Diastolic arterial pressure, mmHg	60 ± 17	66 ± 13
Mean arterial pressure, mmHg	78 ± 21	86 ± 28
Diastolic pulmonary arterial pressure, mmHg	19 ± 6	20 ± 7
Cardiac output, L/min	3.9 ± 1.7	5.8 ± 1.5
Cardiac index, L/min per square meter	2.5 ± 1.1[a]	4.0 ± 1.3
SVRI, dyne·s/m^5 per square meter	2068 ± 795	1615 ± 399
Arrhythmia		
Paroxysmal atrial fibrillation/flutter	34 (87%)	13 (60%)
Paroxysmal atrial tachycardia	4 (10%)	8 (36%)
Paroxysmal supraventricular tachycardia	1 (3%)	1 (5%)
Concomitant drugs to control arrhythmia		
Calcium-channel blocker	3 (8%)	5 (22%)
Other β blockers	0 (0%)	3 (14%)
Disopyramid phosphate	0 (0%)	1 (5%)
Amiodarone	0 (0%)	1 (5%)

[a]$P < 0.05$ *vs* control. SVRI: Systemic vascular resistance index.

(dyne·s/cm^5 per square meter) = 80 (mean arterial pressure-CVP)/CI.

Endpoints

The primary endpoint was HR reduction of the supraventricular tachyarrhythmias without a decrease in arterial pressure. The secondary endpoint was the frequency of conversion to sinus rhythm.

Statistical analysis

Continuous variables are expressed as mean ± SD. Patient characteristics and hemodynamics of the 2 groups were compared using an independent *t* test for continuous variables and with either Fisher's exact test or a chi-square test for categorical variables. Differences of conversion rates were analyzed with Fisher's exact test or the chi-square test as appropriate. Other data were analyzed by repeated-measures analysis of variance. In all analyses, $P < 0.05$ was considered statistically significant. The statistical methods of this study were reviewed by Masayuki Takamura, PhD from Kanazawa University Graduate School of Medicine.

RESULTS

A total of 188 septic patients were admitted to the ICU in this period. Among them, 23 patients were excluded from analysis because of less than 18 years of age. Two patients were excluded because of atrial fibrillation at the time of ICU admission. Supraventricular tachyarrhythmias occurred in 61 patients (37.4%) in leaving 163 septic patients. Among 61 patients, 39 patients were treated with landiolol and 22 patients were not treated with landiolol.

Patient characteristics are indicated in Table 1. There were no significant differences between the 2 groups with respect to age, underlying disease, Acute Physiology and Chronic Health Evaluation Ⅱ score and Sequential Organ Failure Assessment. Intra-abdominal infection was more ($P < 0.05$) and urinary tract infection was less ($P < 0.05$) in landiolol group than in control group. Respiratory tract infection was the most frequent disease in both groups.

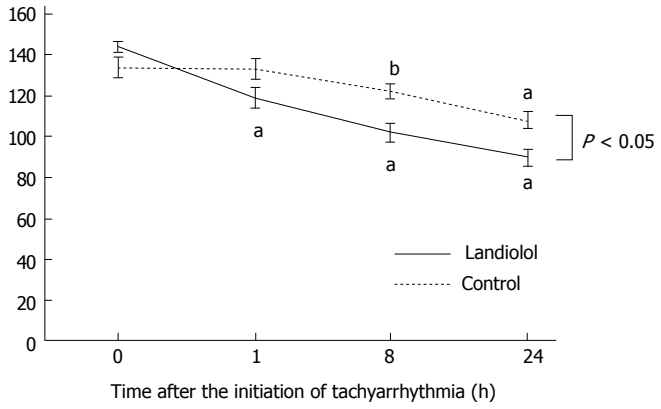
Baseline hemodynamics are summarized in Table 2. Baseline HR was higher in the landiolol group. Systolic arterial pressure and CI were lower in the landiolol group. PAF was the most frequent observation in both groups. Calcium channel blockers and antiarrhythmic agents were used to control HR or cardiac rhythm in the control group.

The initial dose of landiolol was 6.3 ± 3.3 g/kg per minute. Landiolol significantly reduced HR from 145 ± 14 bpm to 119 ± 28 bpm ($P < 0.01$) without reducing arterial pressure at 1 h after the initiation of tachyarrhythmia (Figures 1 and 2). At that time, HR did not change significantly in the control group (from 136 ± 21 bpm to 135 ± 21 bpm) (Figure 1). The conversion rate to sinus rhythm was 25.6% in the landiolol group but 0% in the control group (Figure 1, $P < 0.05$).

After that, a substantial reduction in HR was observed in the landiolol group without any deterioration of hemodynamics. At 24 h after the initiation of tachyarrhythmia, landiolol reduced HR dramatically from 145 ± 14 bpm to 90 ± 20 bpm (Figure 1). A lesser degree of HR reduction was seen in the control group (from 136 ± 21 bpm to 109 ± 18 bpm) than in the landiolol group (Figure 1). The conversion from to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point (Figure 1, $P < 0.01$ at 8 h; $P < 0.05$ at 24 h).

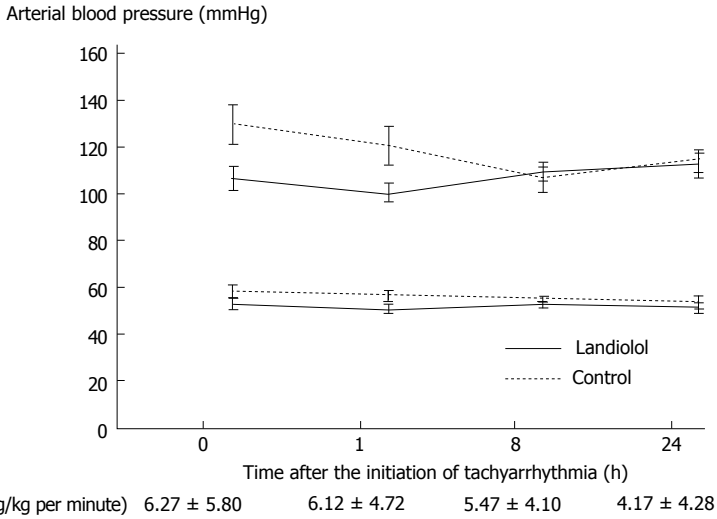
Baseline diastolic pulmonary arterial pressures were similar between groups and did not change (Figure 3). In the landiolol group, baseline CI was lower and did not decrease compared to the control group (Figure 3).

Finally, the duration of landiolol administration was 80.7 ± 78.5 h and the significant bradycardia have



Landiolol (μg/kg per minute)	6.27 ± 5.80	6.12 ± 4.72	5.47 ± 4.10	4.17 ± 4.28
Conversion to sinus rhythm				
Landiolo	25.6%[b]	55.3%[a]	69.7%[b]	
Control	0%	18.2%	36.4%	

Figure 1 Heart rate and sinus rhythm conversion rate. Rapid and substantial reduction of heart rate (HR) was observed in the landiolol group. Reduction in HR was observed in the landiolol group than the control. In addition, the conversion from supraventricular arrhythmia to sinus rhythm was observed more frequently in the landiolol group than in the control group at every point. Results are expressed as mean ± SE. [a]$P < 0.01$, [b]$P < 0.05$ *vs* time 0 h.



Landiolol (μg/kg per minute)	6.27 ± 5.80	6.12 ± 4.72	5.47 ± 4.10	4.17 ± 4.28

Figure 2 Arterial pressure. Landiolol did not change atrial blood pressure. Results are expressed as mean ± SE.

never been observed in any treated patients.

DISCUSSION

This is the first report to investigate the clinical use of landiolol for treating supraventricular tachyarrhythmia in patients with severe sepsis. Its major findings are as follows: (1) low-dose landiolol rapidly and substantially reduced HR in septic patients with supraventricular tachyarrhythmia; (2) low-dose landiolol did not reduce arterial pressure and cardiac output; and (3) low-dose landiolol immediately and significantly converted supraventricular tachyarrhythmias to sinus rhythm in septic patients.

Severe infection or sepsis generally activates sympathetic nervous system. Plasma norepinephrine and epinephrine plasma levels have been reported to be approximately 6 times and 60 times higher in conscious rats with endotoxicosis than in control rats, respectively[5]. In 1 human study, the serum levels of both norepinephrine and epinephrine were significantly higher in postoperative patients with sepsis than in those without sepsis[4]. Moreover, by direct measurement of sympathetic nerve activity, renal sympathetic nerve activity was also increased approximately 3.5 fold by the systemic administration of lipopolysaccharide in rats[6,21].

There is a close association between autonomic nervous system activity and supraventricular tachyarrhythmia. Sepsis-induced activation of the sympathetic nervous system is partially associated with supraventricular tachyarrhythmia in patients with severe sepsis[10]. Sympathetic activation of the heart facilitates

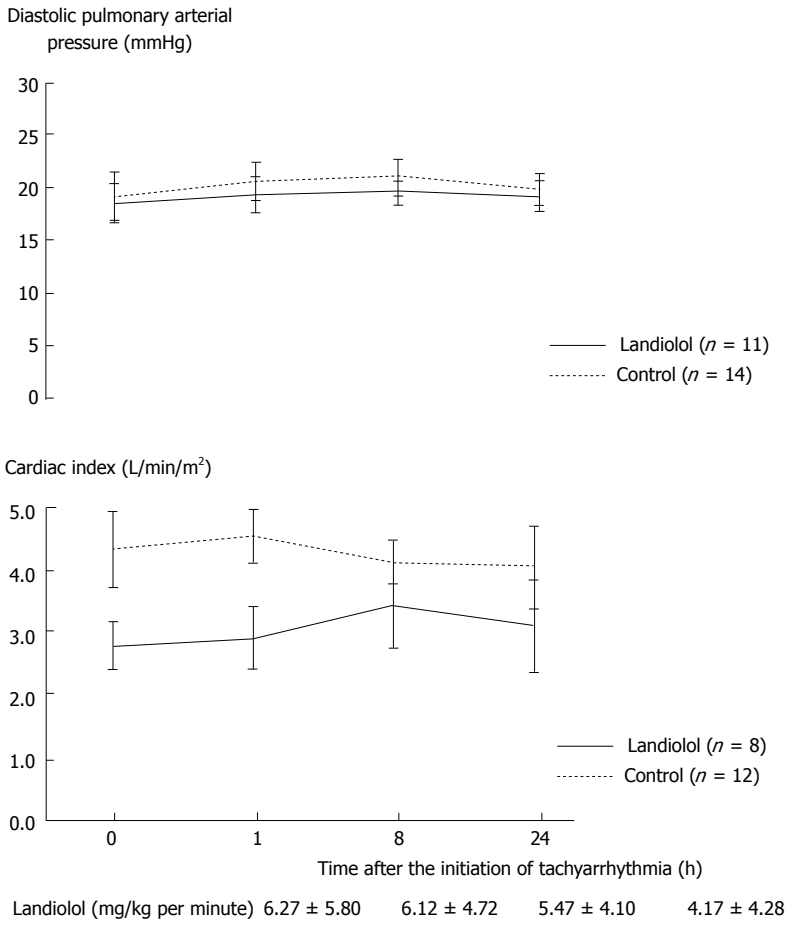


Figure 3 Pulmonary arterial catheter parameters. Landiolol did not affect diastolic pulmonary arterial pressure or cardiac index. Results are expressed as mean ± SE.

arrhythmogenesis by increasing calcium entry and the spontaneous release of calcium from the sarcoplasmic reticulum[22,23]. Therefore, β blockers are the reasonable drug for controlling HR in the presence of supraventricular tachyarrhythmia in septic patients. The landiolol infusion at the dose of 5-10 μg/kg per minute much lower than described dose in the package insert, significantly decreased HR in 82% of postoperative patients with PAF[19]. Consistent with these previous studies, low-dose landiolol rapidly and substantially reduced HR in our septic patients with supraventricular tachyarrhythmia. Therefore, the low dose (6.3 ± 3.3 g/kg per minute) of landiolol administered was enough to inhibit excessive activation of sympathetic nerve activity and to significantly reduce HR in septic patients with tachyarrhythmia.

Landiolol reduced HR significantly without reducing arterial pressure and stabilized hemodynamics in postsurgical patients[11,17-20]. Consistent with these studies, landiolol neither reduces arterial pressure nor deteriorates hemodynamics in our septic patients. Recent prospective, multicenter, single-blind, randomized, parallel-group study showed that low-dose landiolol rapidly decreased HR of atrial fibrillation/flutter without an increase in the incidence of adverse events in patients with LV dysfunction[24]. Landiolol may have more negative chronotropic effect than negative inotropic effect, especially at a low dose. Landiolol has a higher β_1-selectivity (β_1/β_2 = 255) and 8 times more cardioselective than esmolol, which is also short-acting β_1-selective β adrenergic receptor blocker[11-14]. Landiolol exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol in rabbits[15,16]. Consistent with these reports, in our study, landiolol did not decrease CI despite HR reduction. Another reason is that HR reduction by landiolol causes better hemodynamics. The landiolol-induced HR reduction in patients with tachyarrhythmia allows sufficient left ventricular filling time, which subsequently allows more stroke volume. Moreover, the conversion to sinus rhythm, in part, results in sufficient atrial kick, which also creates more stroke volume. Therefore, landiolol did not decrease arterial pressure and stabilized hemodynamics.

The most impressive findings in our study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. A few case studies have reported landiolol-induced conversion to sinus rhythm in patients with atrial fibrillation or flutter[25,26]. Recently, landiolol has been reported to be more effective and safer than diltiazem for conversion to normal sinus rhythm in patients with postoperative atrial fibrillation after open heart surgery[20]. Landiolol-induced reduction of HR improves hemodynamics and converts supraventricular tachyarrhythmias to

sinus rhythm. However, landiolol may function as an antiarrhythmic agent and directly affects the restoration to sinus rhythm. The use of β blockers has recently been reported to have an anti-oxidative and anti-inflammatory effect. However, no study has reported the antiarrhythmic effect of landiolol in supraventricular tachyarrhythmia. As the excessive sympathetic nervous activation caused by sepsis may be associated with maintaining supraventricular arrhythmia, landiolol that has more direct suppressive effect of sympathetic activity than other drugs may cause the conversion to sinus rhythm.

Our study has several potential limitations. First, as this is the historical cohort study, the drug selection for managing tachyarrhythmia was mainly dependent on intensivists or primary doctors examining the patient then. These selection biases might have affected the results observed. However landiolol was administrated in more hemodynamically unstable patients, such as lower systolic blood pressure and lower CI, than control group. Therefore we believe that these selection biases may not overestimate the benefit of landiolol that we observed in results. Second, baseline arterial pressure was relatively high, and diastolic pulmonary arterial pressure was not very low. Because sufficient volume resuscitation was first conducted in our study, few patients with intravascular hypovolemia were observed. Third, the number of patients performed a pulmonary arterial catheter analysis was relatively a few in present study. Therefore, the power of the statistical analysis may be weak. However, we did not need to perform a pulmonary arterial catheter analysis because the patients' hemodynamics did not worsen. Therefore, we are convinced that landiolol did not cause hemodynamic deterioration. Finally, we did not evaluate prognosis such as ICU stay length or mortality. Although ICU stay length was similar between the 2 groups, mortality was higher in the control group than in the landiolol group. We did not perform multivariate analysis of mortality; therefore, this requires further investigation.

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing tachyarrhythmias in patients with sepsis.

ACKNOWLEDGMENTS

We thank patients and staff at Kanazawa University Hospital who participated in this project.

COMMENTS

Background

Supraventricular tachyarrhythmias are frequently observed in patients with sepsis. The management of tachyarrhythmia is important as tachyarrhythmias have been identified as a major source of morbidity in critically ill patients. However it is often difficult because of unstable hemodynamics in septic patients.

Research frontiers

Landiolol, an ultra-short-acting β1 selective adrenoceptor antagonist, exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than other β blockers. The current research hotspots is whether landiolol can safely and effectively control heart rate of supraventricular tachyarrhythmias in septic patients.

Innovations and breakthroughs

Landiolol significantly reduced heart rate without any deterioration of hemodynamics. The most impressive finding in the study is high conversion rate to sinus rhythm immediately after landiolol administration. Surprisingly, within one hour after landiolol administration, conversion to sinus rhythm from supraventricular tachyarrhythmias were observed in more than a quarter of patients treated with landiolol, but in none without landiolol. Landiolol could control not only heart rate but also cardiac rhythm in septic patients with supraventricular tachyarrhythmias.

Applications

Landiolol safely reduced heart rate and, in part, converted to sinus rhythm in septic patients with supraventricular tachyarrhythmia. Landiolol could be a valuable and suitable drug for managing supraventricular tachyarrhythmias in patients with sepsis.

Terminology

Landiolol, a newly developed commercially available agent, is an ultra-short-acting β-adrenoceptor antagonist (a half-life of 4 min), has high β_1 selectivity (β_1/β_2 = 255) and exerts a more potent negative chronotropic effect and a lesser effect on blood pressure than esmolol.

Peer-review

The paper is interesting and well written.

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ORIGINAL ARTICLE

Observational Study

Outcomes of critically ill cancer patients with *Acinetobacter baumannii* infection

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Author contributions: All authors contributed to this manuscript.

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Informed consent statement: This study has been approved by the Bioethics Committee of INCan, and the requirement for informed consent was waived.

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Data sharing statement: Data presented in the manuscript is anonymised and the risk of identifying individual patient is very low. No additional data is available other than stated in the manuscript for this study.

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Abstract

AIM: To describe the intensive care unit (ICU) outcomes of critically ill cancer patients with *Acinetobacter baumannii* (AB) infection.

METHODS: This was an observational study that included 23 consecutive cancer patients who acquired AB infections during their stay at ICU of the National Cancer Institute of Mexico (INCan), located in Mexico City. Data collection took place between January 2011, and December 2012. Patients who had AB infections before ICU admission, and infections that occurred during the first 2 d of ICU stay were excluded. Data were obtained by reviewing the electronic health record of each patient. This investigation was approved by the Scientific and Ethics Committees at INCan. Because of its observational nature, informed consent of the patients was not required.

RESULTS: Throughout the study period, a total of 494 critically ill patients with cancer were admitted to the ICU of the INCan, 23 (4.6%) of whom developed AB infections. Sixteen (60.9%) of these patients had hematologic malignancies. Most frequent reasons for ICU admission were severe sepsis or septic shock (56.2%) and postoperative care (21.7%). The respiratory tract was the most frequent site of AB infection (91.3%). The most common organ dysfunction observed in our group of patients were the respiratory (100%), cardiovascular (100%), hepatic (73.9%) and renal dysfunction (65.2%). The ICU mortality of patients with 3 or less organ system dysfunctions was 11.7% (2/17) compared with 66.6% (4/6) for the group of patients with 4 or more organ system dysfunctions (P = 0.021). Multivariate analysis identified blood lactate levels (BLL) as the only variable independently associated with in-ICU death (OR = 2.59, 95%CI: 1.04-6.43, P = 0.040). ICU and hospital mortality rates were 26.1% and 43.5%, respectively.

CONCLUSION: The mortality rate in critically ill patients with both HM, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a BLL ⩾ 2.6 mmol/L in the first day of stay in the ICU.

Key words: Outcomes; Cancer patients; *Acinetobacter baumannii*; Intensive care; Critical care

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Core tip: Several factors have been associated with poor prognosis among critically ill patients with infections caused by *Acinetobacter baumannii* (AB) in the intensive care unit (ICU) including renal failure, thrombocytopenia, neutropenia, history of prior immunosuppressive therapy use, the need for invasive mechanical ventilation, and development of severe sepsis. In this study the mortality rate in patients with both hematological malignancies, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a blood lactate levels ⩾ 2.6 mmol/L in the first day of stay in the ICU.

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INTRODUCTION

Acinetobacter baumannii (AB) is an aerobic, gram-negative coccobacillary rod that grows at 20 ℃-30 ℃ on standard laboratory media[1]. AB infections may be fatal in patients with suboptimal immune defenses[2]. The mortality attributable to infections caused by AB in critically ill patients ranges from 40.7% to 73%[3-5]. The intensive care unit (ICU) and hospital mortality rate of patients with both hematologic malignancies and AB infection is 83%[6]; however, patients with solid tumors and bacteremia caused by AB have a relatively good prognosis with a mortality rate of 14.5%[7].

Risk factors associated with AB colonization or infection include prolonged hospitalization, admission to the ICU, recent surgical procedures, exposure to antibiotics, use of central venous catheter, hospitalization and nursing home residence before hospital admission[8]. Several factors have been associated with poor prognosis among critically ill patients with infections caused by AB in the ICU, including renal failure, thrombocytopenia[9], low Glasgow coma scale, neutropenia, history of prior immunosuppressive therapy use, the need for mechanical ventilatory support, and development of severe sepsis[6].

In Latin America Acinetobacter spp has been reported as one of the most commonly isolated species (9.6%) from patients with suspected hospital-acquired pneumonia[10]. In Mexico, information on the prevalence and incidence of AB infections is limited[11,12]. The aim of the present study was to describe the ICU outcomes of critically ill cancer patients with AB infection.

MATERIALS AND METHODS

This was an observational study that included 23 consecutive cancer patients who acquired AB infections during their stay at ICU of the National Cancer Institute of Mexico (INCan), located in Mexico City. Data collection took place between January 2011, and December 2012. Data on the characteristics, organization, and recommendations for admission to our ICU have been previously reported[13,14]. Patients who had AB infections before ICU admission, and infections that occurred during the first 2 d of ICU stay were excluded. This investigation was approved by the Scientific and Ethics Committees at INCan (Rev/02/13). Because of its observational nature, informed consent of the patients was not required.

Data were obtained by reviewing the electronic health record of each patient. Data obtained included: the Eastern Cooperative Oncology Group scale for performance status[15] prior to hospitalization, malignancy types, reasons for ICU admission, the need for invasive mechanical ventilation (IMV), the need for vasopressor therapy, durations of vasopressors, length of IMV, the length of stay (LOS) in the hospital before ICU admission, the LOS in hospital wards before ICU, use of antibiotics 30 d before ICU admission, infection sites, and the ICU and hospital mortality rate. The LOS in the ICU was measured by the number of hours or days spent there by the patient. The LOS in the hospital before ICU admission was quantified as the number of days from date of hospital admission until

ICU admission. The AB was categorized as follows: multidrug-resistant (MDR), pandrug-resistant (PDR), and pansensitive (PDS). AB MDR was defined as non-susceptible to ⩾ 1 agent in ⩾ 3 antimicrobial categories. AB PDR was defined as non-susceptible to ⩾ 1 agent in all but ⩽ 2 categories. AB PDS was defined as susceptible to all antimicrobial agents[16]. The Acute Physiology and Chronic Health Evaluation Ⅱ score[17], and the Sequential Organ Failure Assessment (SOFA) score[18] were calculated within the first day ICU stay. In this study we have defined organ dysfunction as a SOFA score ⩾ 1 point[14]. Malignancies were grouped into either hematological malignancies (HM) or solid tumors. Patients were divided into two groups based on their blood lactate levels (BLL): BLL ⩾ 2.6 mmol/L or BLL < 2.6 mmol/L.

Data presentation

The Kolmogorov-Smirnov test was performed to verify the normality of the distributions of the data; all of continuous variables were normally distributed. Data are presented as the mean ± SD. The continuous variables were compared using student's *t* test and the chi-square or the Fisher exact test was used to compare categorical data.

Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve to evaluate the potential for using the lactate levels to discriminate between patients who die from those who survive. The sensitivity and specificity of the BLL cuoffs for predicting ICU mortality were examined. We constructed a multivariable model to identify factors associated with ICU mortality. We entered parameters into the model that were statistically significant on univariate analysis at a level of $P < 0.20$. Results were summarized as odds ratios (OR) with 95%CI. We assessed model discrimination using the area under the ROC curve[19]. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and an adequate fit was assumed if $P > 0.05$[20]. Survival curves were estimated by the Kaplan-Meier method and differences between survival curves were checked with the log-rank test. Statistical analysis was done using the Statistical Package for the Social Sciences version 20.0. All tests were two-tailed, and a $P < 0.05$ was predetermined for statistical significance. All reported *P* values are 2 sided.

Statistical analysis

The statistical methods of this study were reviewed by Silvio A Ñamendys-Silva, Department of Critical Care Medicine, Instituto Nacional de Cancerología, Mexico City 14080, Mexico. Telephone: +52-55-47471020-13015, 13016.

RESULTS

Throughout the study period, a total of 494 patients with cancer were admitted to the ICU of the INCan, 23 (4.6%) of whom developed AB infections. Sixteen (60.9%) of these patients had HM. Most frequent reasons for ICU admission were severe sepsis or septic shock (56.2%) and postoperative care (21.7%). In Table 1 are presented demographic and clinical data of patients. The mean time between the admission to the ICU and the development of AB infection was 13 ± 9.9 d. The respiratory tract was the most frequent site of AB infection (91.3%). The most frequent co-morbidity associated with AB infection was diabetes mellitus 3/23(13%), followed by cardiovascular disease (8.7%).

Table 1 Demographic and clinical characteristics of the study population

Characteristics	Values
No. of patients	23
Age (years), mean ± SD	44.09 ± 17.10
Gender (women), *n* (%)	11 (47.8)
Length of ICU stay (d), mean ± SD	21.9 ± 28.9
Length of hospital stay (d), mean ± SD	23.9 ± 12.3
Need for vasopressors, *n* (%)	23 (100)
Need for invasive mechanical ventilation, *n* (%)	23 (100)
Length of mechanical ventilation (d), mean ± SD	21.4 ± 11.8
In hospital ward time before ICU admission, *n* (%)	20 (86.9)
Length of stay in hospital wards before ICU admission (d), mean ± SD	8.8 ± 10.6
Use of antibiotics 30 days before ICU admission, *n* (%)	17 (73.9)
Infection site, *n* (%)	
Respiratory	21 (91.3)
Blood culture	3 (13)
Surgical site	1 (4.3)
Pansensitive, *n* (%)	2 (8.7)
Pandrug-resistant, *n* (%)	5 (21.7)
Multidrug-resistant, *n* (%)	16 (69.6)
APACHE II score, mean ± SD	13.3 ± 5.8
SOFA score, mean ± SD	8.7 ± 2.4
Performance status 0-2, *n* (%)	22 (95.7)
ICU mortality, *n* (%)	6 (26.1)
Hospital mortality, *n* (%)	10 (43.5)

ICU: Intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IQR: Interquartile range; PEEP: Positive end expiratory pressure.

The most common organ dysfunction observed in our group of patients were the respiratory (100%), cardiovascular (100%), hepatic (73.9%) and renal dysfunction (65.2%). The ICU mortality of patients with 3 or less organ system dysfunctions was 11.7% (2/17) compared with 66.6% (4/6) for the group of patients with 4 or more organ system dysfunctions ($P = 0.021$) (Table 2).

The primary outcome variable of interest was ICU mortality. Univariate analysis indicated that the following three factors were associated with ICU death: BLL, four or more organ dysfunctions, and creatinine level (Table 3). Multivariate analysis identified BLL as the only variable independently associated with in-ICU death. The area under the ROC curve was 0.88 (95%CI: 0.74-0.99), $P = 0.006$, demonstrating a good discriminatory power to predict ICU mortality. The cut-off point was a BLL ⩾ 2.6 mmol/L, with 100% sensitivity and 77% specificity (Figure 1). ICU and hospital mortality rates were 26.1% and 43.5%,

Table 2 Demographic and clinical characteristics of the critically ill cancer patients with *Acinetobacter baumannii* infection on the day of admission to the intensive care unit (initial) according to outcome

Characteristics	Survivors	Nonsurvivors	*P*
Age, years, mean ± SD	42.6 ± 16.6	48.1 ± 19.3	0.510
Women, *n* (%)	8 (47)	3 (50)	0.901
APCAHE II score, mean ± SD	12.7 ± 5.0	15.3 ± 7.9	0.357
SOFA score, mean ± SD	8.4 ± 2.4	9.6 ± 2.6	0.318
PEEP, cmH2O	8.4 ± 2.8	7.3 ± 2.3	0.422
Durations of vasopressors	7.59 ± 4.2	11 ± 4.9	0.122
Leukocytes, × 10^9/L	8.6 ± 6.9	11.6 ± 13.1	0.487
Absolute neutrophil count, cells/mm^3	7.5 ± 6.2	10.2 ± 11.2	0.472
Lymphocytes, cells/mm^3	682 ± 542	666 ± 871	0.959
Platelets, × 10^9/L	184.4 ± 149.2	112.8 ± 105.0	0.291
Sodium, mmol/L	138 ± 5.85	135.3 ± 6.4	0.330
Potassium, mmol/L	3.9 ± 0.51	4.0 ± 0.71	0.800
Chloride, mmol/L	109.1 ± 8.74	109.3 ± 4.2	0.967
Lactate, mmo/L	2.01 ± 1.29	5.2 ± 3.2	0.002
Magnesium, mmol/L	0.93 ± 0.24	0.97 ± 0.13	0.722
Phosphorus, mmol/L	1.33 ± 0.46	1.28 ± 0.66	0.816
Hemoglobin, g/L	91.3 ± 19.2	94.5 ± 18.8	0.739
Creatinine, μmol/L	75.8 ± 39.01	133.2 ± 34.4	0.004
Glucose, mmol/L	8.34 ± 3.5	8.09 ± 2.2	0.877
Bilirubin, total, μmol/L	17.8 ± 12.5	22.5 ± 15.5	0.465
Uric acid, μmol/L	219.0 ± 94.0	189.3 ± 149.0	0.576
ARDS, *n* (%)	13 (76.4)	4 (66.6)	0.632
Number of organ dysfunction (≥ 4)	2 (11.7)	4 (66.6)	0.021
Malignancies			
Hematological malignancy, *n* (%)	8 (47)	6 (100)	0.030
Solid tumor, *n* (%)	9 (52.9)	0 (0)	

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; IQR: Interquartile range; PEEP: Positive end expiratory pressure; ARDS: Acute respiratory syndrome distress.

respectively. ICU survival by BLL is presented in Figure 2, indicating that the patients who had a BLL ≥ 2.6 mmol/L in the first day ICU stay were less likely to survive.

DISCUSSION

In this study, the incidence of AB infection in cancer patients who were admitted to the ICU was 4.6%, and ICU and hospital mortality rates were 26.1% and 43.5%, respectively, which is lower than the mortality rates reported by other authors[4,6]. All of the patients who died had HM. Patients who had four or more organ system failures at the time of admission to the ICU had a high mortality rate. In the multivariate analysis, the only variable independently associated ICU mortality was a BLL ≥ 2.6 mmol/L. Patients with a BLL ≥ 2.6 mmol/L in the first day ICU stay were less likely to survive.

The overall ICU mortality rate found in our study could be related to the implementation of medical management protocols. Patients with severe sepsis and septic shock had received standard guidelines-based treatment[21]. Patient care rounds were performed daily

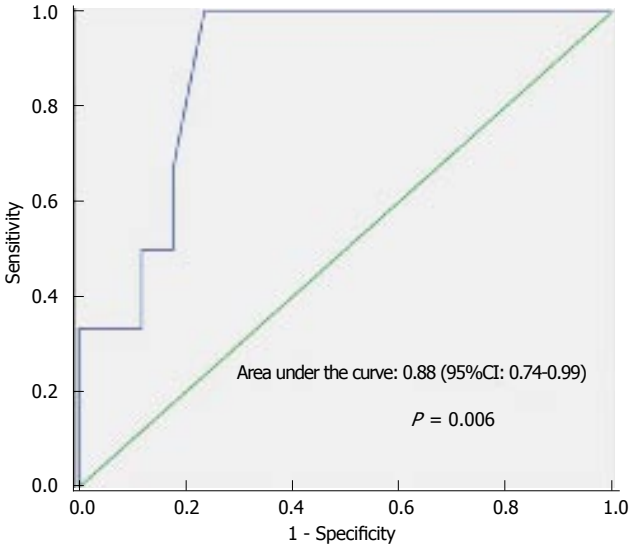

Figure 1 Receiver operator characteristic curve for lactate. The area under the Receiver operator characteristic curve is 0.88 (95%CI: 0.74-0.99), demonstrating a good discriminatory power for intensive care unit mortality.

with an infectious diseases attending physician[22]. Levy and collaborators[23] reported that the implementation of guidelines for management of severe sepsis and septic shock is associated with sustained, continuous quality improvement in sepsis care, and with a significant reduction in hospital mortality among patients with severe sepsis and septic shock.

The patients with HM admitted to our ICU had higher ICU mortality rates than those with solid tumors (21.4% *vs* 46.1%)[13,14]. Sepsis remains a frequent complication in patients with cancer, and is associated with high mortality[24]. Immune dysfunction has been documented in patients with cancer. Predisposing factors for infection include the tumor site, intravenous devices, neutropenia because of an underlying disease, corticosteroids, monoclonal antibodies, and treatment with chemotherapy or radiation therapy[25].

Risk factors for developing AB infections in patients with HM include advancing age, prior exposure to aminoglycosides, central venous catheterization, and the presence of nasogastric tube[6]. Turkoglu *et al*[6] reported that a low Glasgow coma scale, neutropenia, history of prior immunosuppressive therapy use, the need for IMV, and development of severe sepsis were associated with mortality in patients with HM. Infection with AB an APACHE Ⅱ score ≥ 21 points are variables associated with a poor clinical outcomes for patients with solid tumors and AB complex bacteremia[7]. In our study all of the patients who died in the ICU had HM, and required vasopressors. Univariate analysis primarily identified three factors that were related with ICU mortality; BLL, four or more organ dysfunctions, and creatinine levels. Multivariate analysis identified BLL as an independent prognostic factor for in-ICU death. The patients with BLL ≥ 2.6 mmol/L in the first day of stay in the ICU were less likely to survive. Increased BLL

Table 3 Univariate and multivariate logistic regression analysis for identifying independent risk factors for mortality in the intensive care unit

Variables	Univariate		*P*	Multivariate		*P*
	OR	95%CI		OR	95%CI	
Age (yr)	1.02	0.96-1.08	0.491			
Gender (male)	1.12	0.17-7.24	0.901			
APACHE II score	1.07	0.92-1.25	0.345			
SOFA score	1.23	0.82-1.84	0.308			
Length of stay in hospital wards before ICU admission (d)	0.76	0.51-1.12	0.171			
Duration of vasopressors (d)	1.18	0.95-1.48	0.129			
Blood lactate level (mmol/L)	2.59	1.04-6.43	0.04	2.59	1.04-6.43	0.04
Number of organ dysfunction (≥ 4)	15.00	1.58-142.1	0.018			
Creatinine (μmol/L)	1.03	1.004-1.064	0.024			
Total bilirubin (μmol/L)	1.02	0.95-1.10	0.449			
Albumin g/L	1.06	0.89-1.27	0.494			
Platelets ($\times 10^9$/L)	0.99	0.98-1.00	0.295			
Absolute neutrophil count/μL	1.04	0.92-1.17	0.459			
Absolute lymphocytes count/μL	1.03	0.93-1.15	0.479			

Goodness-of-fit (Hosmer-Lemeshow) $\chi^2 = 4.42$, $P = 0.817$, AUC = 0.88 (0.74-0.99), $P = 0.006$. APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval; AUC: Area under receiver operator characteristic curve.

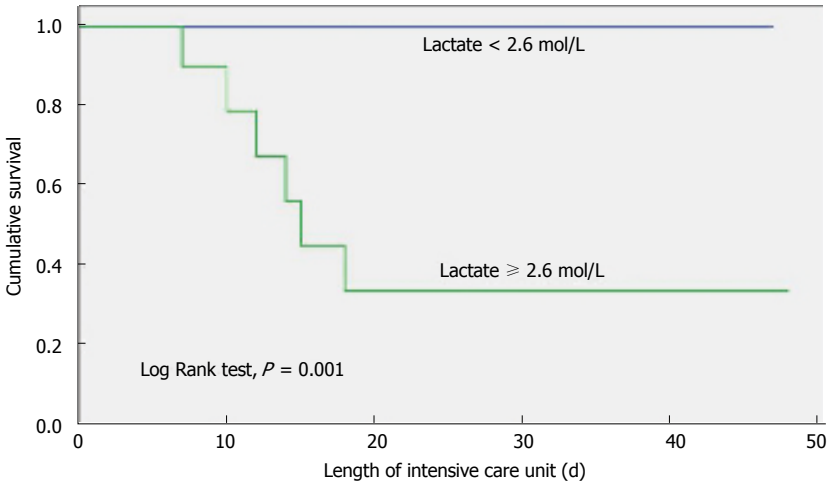

Figure 2 Overall survival with respect to blood lactate level in the first 24 h of intensive care unit stay.

have been related to morbidity and mortality[26]. BLL are frequently elevated in critically ill patients and correlate well with disease severity. Hyperlactatemia (> 2 mmol/L) is observed in shock states when oxygen consumption becomes critically dependent on oxygen delivery[27]. The results of the current study suggest that in critically ill patients with cancer, and sepsis caused by AB, BLL may be used to identify patients at an increased risk of an adverse outcome. This may help to identify patients who may benefit from early admission to ICU. This report confirms that BLL is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection. There have been no new cases reported since July 2014 in our ICU.

This study has the following limitations: (1) The clinical data were obtained from a single institution; and (2) A small number of patients was included.

The mortality rate in critically ill patients with both HM, and AB infections who are admitted to the ICU is high. The variable most associated with increased mortality was a BLL ≥ 2.6 mmol/L in the first day of stay in the ICU.

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We thank the nurses and medical staff of the intensive care unit at INCan, Mexico City who were involved in the care of these patients for their assistance.

COMMENTS

Background

The mortality attributable to infections caused by *Acinetobacter baumannii* (AB) in critically ill patients ranges from 40.7% to 73%. The intensive care unit (ICU) and hospital mortality rate of patients with both hematologic malignancies and AB infection is high. Risk factors associated with AB colonization or infection include prolonged hospitalization, ICU admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization and nursing home residence. Several factors have been associated with poor prognosis among critically ill patients with infections caused by AB in the ICU, including renal failure, thrombocytopenia, the presence of neutropenia, prior immunosuppressive therapy, the need for invasive mechanical ventilation, and development of severe sepsis.

Research frontiers

In Latin America Acinetobacter spp has been reported as one of the most frequent species isolated from patients hospitalized with suspected pneumonia. In Mexico, information on the prevalence and incidence of AB infections is limited.

Innovations and breakthroughs

Blood lactate level (BLL) is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection and thereby the importance of providing ICU treatment.

Applications

The results of our study suggest that in critically ill cancer patients with sepsis caused by AB, BLL may be used to identify patients at an increased risk of an adverse outcome. This may help to identify patients who may benefit from early admission to ICU.

Peer-review

The manuscript is well conceived and indicates that lactate is a valuable biomarker in the treatment of critically ill cancer patients with septic shock caused by AB infection and thereby the importance of providing ICU treatment.

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