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ORIGINAL ARTICLE

Basic Study

Effects of mineralocorticoid receptor antagonists on responses to hemorrhagic shock in rats

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Abstract

AIM

To evaluate the effects of mineralocorticoid receptor (MR) antagonists on mortality and inflammatory responses after hemorrhagic shock (HS) in rats.

METHODS

One hundred and two male Sprague–Dawley rats were randomly assigned to one of the following three groups: Control, spironolactone (SPL), and eplerenone (EP) groups. HS was induced by the removal of blood. One half of rats were evaluated to determine mortality, hemodynamics, plasma tumor necrosis factor-alpha (TNF-α) concentrations, and arterial blood gas at 8 h after

HS recovery. In the remainder of rats, the expression levels of genes encoding cytokines were evaluated in liver tissue samples at 1 h after HS recovery.

RESULTS

The survival rates 8 h after HS recovery were 71%, 94%, and 82% in the control, SPL, and EP groups, respectively. There were no significant differences in survival rates among the three groups (P = 0.219). Furthermore, there were no significant differences in gene expression levels in the liver or plasma TNF-α concentrations among the three groups (P = 0.888).

CONCLUSION

Pretreatment with MR antagonists did not improve mortality or cytokine responses in the liver after HS recovery in rats.

Key words: Hemorrhagic shock; Mortality; Inflammatory response; Mineralocorticoid receptor antagonist; Cytokine

Core tip: Mineralocorticoid receptor (MR) antagonists have anti-inflammatory effects in models of ischemic and reperfusion injury, suggesting potential clinical value in patients with hemorrhagic shock. However, our findings indicate that pretreatment with MR antagonists does not improve mortality rates or cytokine responses in the liver after recovery from hemorrhagic shock in rats.

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INTRODUCTION

Hemorrhagic shock (HS), a frequent and dangerous complication of trauma and massive intraoperative bleeding, is associated with high mortality and morbidity. HS causes ischemic injury in vital organs and tissues, and resuscitation for HS causes reperfusion injury in these tissues. Ischemic and reperfusion injury (IRI) causes the release of numerous pro-inflammatory mediators, such as cytokines and nitric oxide, and results in multiple organ dysfunction (MOD), a leading cause of death in HS patients[1-5]. Mineralocorticoid receptor (MR) antagonists, such as spironolactone (SPL) and eplerenone (EP), have anti-inflammatory effects *in vitro*[6-8]. In particular, SPL inhibits inflammatory responses, such as the attenuation of cytokine and NF-kappa B responses, *in vitro*[6-8]. Moreover, in several animal models, MR antagonists protect against IRI in various organs, including the kidney, liver, intestine, heart, and brain[9-13]. These observations suggest that MR antagonists have beneficial effects during HS and after recovery from HS. In clinical settings, MR antagonists are often administered to hypertensive patients to control blood pressure (BP)[14,15]. However, it is not clear whether MR antagonists have beneficial effects when administered before reaching the HS state caused by trauma and massive intraoperative bleeding. We hypothesized that pretreatment with MR antagonists has beneficial effects on MOD after HS. Accordingly, we evaluated the effects of pretreatment with SPL and EP on mortality and inflammatory responses after HS in rats.

MATERIALS AND METHODS

All procedures involving animals were reviewed and approved by the Committee on Animal Experimentation of Kanazawa University (AP-153421).

Experimental protocol

Effect of MR antagonists on mortality and inflammatory responses in HS rats: Fifty-one male Sprague–Dawley (SD) rats (body weight, 350–400 g) were randomly divided into the following 3 groups (n = 17 per group): Control (no medication), SPL (oral administration of SPL at 10 mg/kg per day for 5 d), and EP (oral administration of EP at 100 mg/kg per day for 5 d). The rats received SPL and EP with food. Rats in the SPL and EP groups received powder medicine with powder feed for 5 d. The doses of EP and SPL were selected based on previous studies in rats[16,17].

After medication for 5 d, all rats were anesthetized with pentobarbital sodium (intraperitoneal injection of 50 mg/kg)[18]. Rats underwent tracheostomy, and a cannula was inserted into the trachea. The tracheal cannula was attached to a respirator after a cannula was inserted into the carotid artery. Ventilation was performed by administering oxygen (100%, 1 L/min) at a frequency of 32 breaths/min with an inspiratory/expiratory ratio of 1:1 using a small animal respirator. Then, the femoral artery and vein were cannulated. After the operation, lactate Ringer's solution containing muscle relaxant (rocuronium bromide 0.75 mg/mL) and an anesthetic (pentobarbital sodium 0.98 mg/mL) were continuously infused through the cannula of the femoral vein at 10 mL/kg per hour. The femoral artery catheter was connected to a pressure transducer to monitor the arterial blood pressure and heart rate (HR). Rats were placed on a warming pad and maintained at 36-38 ℃, as measured using a rectal thermometer.

After the stabilization of rats for 30 min, their blood was drawn *via* the carotid artery cannula to induce HS. Systolic arterial pressure (SAP) was maintained at less than 40 mmHg for 40 min. Removal blood volume were 13 ± 0.4 mL, 13 ± 0.5 mL, and 13 ± 0.4 mL in the control group, SPL group, and EP group, respectively. The

removed blood was diluted two-fold in lactate Ringer's solution and an equal volume was returned through the femoral vein cannula. The methods for this experiment were described in a previous study[19].

The survival rate, SAP, and HR were observed for up to 8 h after HS recovery. The arterial blood sample (0.25 mL) was obtained before HS and at 0, 1, 2, 3, 4, and 5 h after HS recovery. And then PH, Lactate, BE and Hb were measured immediately by The ABL800 FLEX blood gas analyzer. Furthermore, arterial blood samples (1.5 mL) were obtained before HS and at 2, 4, and 5 h after HS recovery to measure plasma tumor necrosis factor (TNF)-α. The TNF-α concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits (Boster Biological Technology, Pleasanton, CA, United States).

Effects of MR antagonists on gene expression in the liver after recovery from hemorrhagic shock: An additional 51 male SD rats were randomly divided into the following 3 groups (n = 17 per group): Control group (no medication), SPL group (oral administration of SPL at 10 mg/kg per day for 5 d), and EP group (oral administration of EP at 100 mg/kg per day for 5 d).

As described above, all animals were anesthetized and HS was induced. At 1 h after recovery from HS, the organization of the liver was examined in the three groups. Liver tissue samples were obtained at 1 h after recovery from HS; the time was established based on previous studies[20]. Each sample was placed in a container, frozen in liquid nitrogen, and stored at -80 ℃.

Total RNA was isolated from liver tissues using the High Pure RNA Tissue Kit (Roche Diagnostics, Mannheim, Germany). The quality and quantity of RNA was determined using a NanoDrop (NanoDrop Technologies, Wilmington, DE, United States). The RNA was reverse-transcribed to cDNA using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, United States). Quantitative real-time detection polymerase chain reaction (RTD-PCR) was performed using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). The following primers and TaqMan probes (Applied Biosystems) were used: interleukin (IL)-6 (Rn01410330_m1), TNF (Rn01525859_g1), IL-1β (Rn00580432_m1), intercellular adhesion molecule (ICAM) 1 (Rn00564227_m1), and 18S rRNA (18S,4319413E). The following standard protocol was followed for all reactions: 30 s at 95 ℃ (initial denaturation), 40 cycles of 5 s at 95 ℃ and 30 s at 60 ℃. mRNA levels were standardized against 18S rRNA expression levels[21].

Animal care and use statement

The protocol was designed to minimize pain or discomfort. Before operation all rats were anesthetized with pentobarbital sodium (intraperitoneal injection of 50 mg/kg). Ventilation was performed by administering oxygen (100%, 1 L/min) using a small animal respirator during experiment. Lactate Ringer's solution containing muscle relaxant (rocuronium bromide 0.75 mg/mL) and an anesthetic (pentobarbital sodium 0.98 mg/mL) were continuously infused through the cannula of the femoral vein at 10 mL/kg per hour during experiment. All rats were euthanized by intravenous injection KCl under general anesthesia for tissue collection.

Statistical analysis

At a sample size analysis, one-sided Fisher's exact tests with a significance level of 5% and a power of 85% showed that a minimum of 17 rats per group was needed to detect a difference in the survival ratio of at least 40% between control and treatment groups. It was based on the result of the preliminary experiment. All data are expressed as means ± standard error (SE). At survival rate analysis, the death was defined as an event. The observation period was defined as eight hours since HS recovery. If an event did not occur at the time of the end during an observation period, it was censored. Survival rates for the three groups were compared using the Kaplan–Meier and Log Rank (Mantel–Cox) tests. Significance was defined as $P < 0.01$. Differences between groups in hemodynamic properties, including blood gas analysis (BGA) and plasma TNF-α, were analyzed using two-way repeated measure ANOVA, followed by post-hoc tests (Bonferroni's method). Differences in gene expression levels between groups were analyzed by one-way ANOVA. Significance was defined as $P < 0.01$. Data analyses were implemented in SPSS v.23 (SPSS Inc., Chicago, IL, United States).

RESULTS

Mortality rate and hemodynamics

The survival rates 8 h after recovery from HS were 71%, 94%, and 82% in the control group, SPL group, and EP group, respectively. There were no significant differences in survival rate among the three groups (Figure 1).

SAPs gradually decreased after HS recovery in all groups. SAPs of the control group decreased more in comparison with SAPs of the MR antagonists treatment group. SAPs of the EP treatment group did not decrease very much in comparison with the SAP of the control group. There were significant differences among three groups in SAP ($P < 0.01$). There were significant differences between EP group and control group in SAP at 5-8 h after the HS recovery (EP *vs* control; $P < 0.01$, Figure 2).

Inflammatory responses

The lactate concentrations increased immediately after HS, but recovered in all groups. There were no significant differences among the three groups in lactate concentration, Hb, PH, and BE (Figure 3).

The plasma TNF-α concentration in all groups increased slightly after the recovery from HS. There were no significant differences in plasma TNF-α concentrations among the three groups (Figure 4).

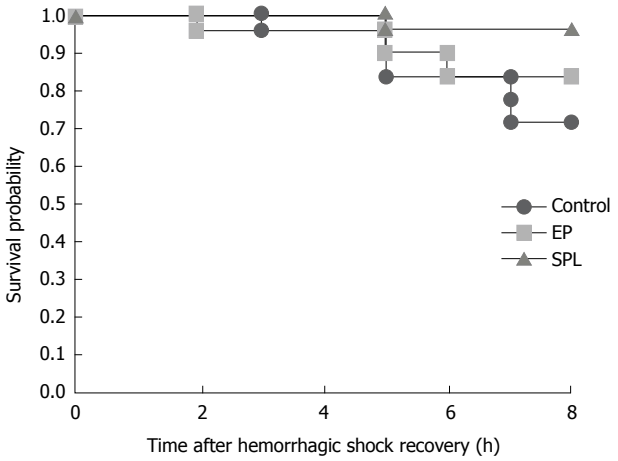

Figure 1 Kaplan–Meier survival analysis. The survival rates 8 h after recovery from HS were 71%, 94%, and 82% in the control group, SPL group, and EP group, respectively. There were no significant differences in survival rate among the three groups (P = 0.219). HS: Hemorrhagic shock; EP: Eplerenone; SPL: Spironolactone.

Gene expression in the liver at 1 h after recovery from hemorrhagic shock

The mRNA expression levels of *TNF-α, IL-6, IL-1β,* and *ICAM-1* did not exhibit significant differences in the liver at 1 h after HS recovery among the three groups (Figure 5).

DISCUSSION

HS induced by partial exsanguination in rats caused metabolic acidosis and increased TNF-α concentrations immediately after the return of blood. Metabolic acidosis deteriorated immediately after the recovery from HS, but was gradually re-aggravated. As a result, the survival rate was low. HS with the oral administration of SPL and EP, MR antagonists, also resulted in similar to HS of the control. These were no significant differences between the control and MR antagonist-treated groups in the responses after HS recovery. Cytokine gene expression in the liver tissue 1 h after HS recovery did not differ among groups. Thus, our results showed that the oral administration of MR antagonists does not affect the mortality rate and inflammatory responses after HS recovery in rats based on comparisons with control rats after HS recovery.

MR antagonists are often used to treat hypertensive patients and have beneficial effects in patients with chronic heart failure and ischemic heart diseases[14,15,22,23]. Many recent investigations have demonstrated the beneficial effects of MR antagonists with respect to inflammatory responses and IRI *in vitro* and *in vivo*[6-13]. Kato *et al*[6] showed that SPL inhibits the production of pro-inflammatory mediators, such as TNF-α and nitric oxide, in response to lipopolysaccharides *in vitro*. Ozacmak *et al*[11] showed that pretreatment with SPL reduces intestinal injury induced by IR, including the inhibition of inflammatory responses, in rats. These studies suggest that the early and continuous administration of MR antagonists has beneficial effects

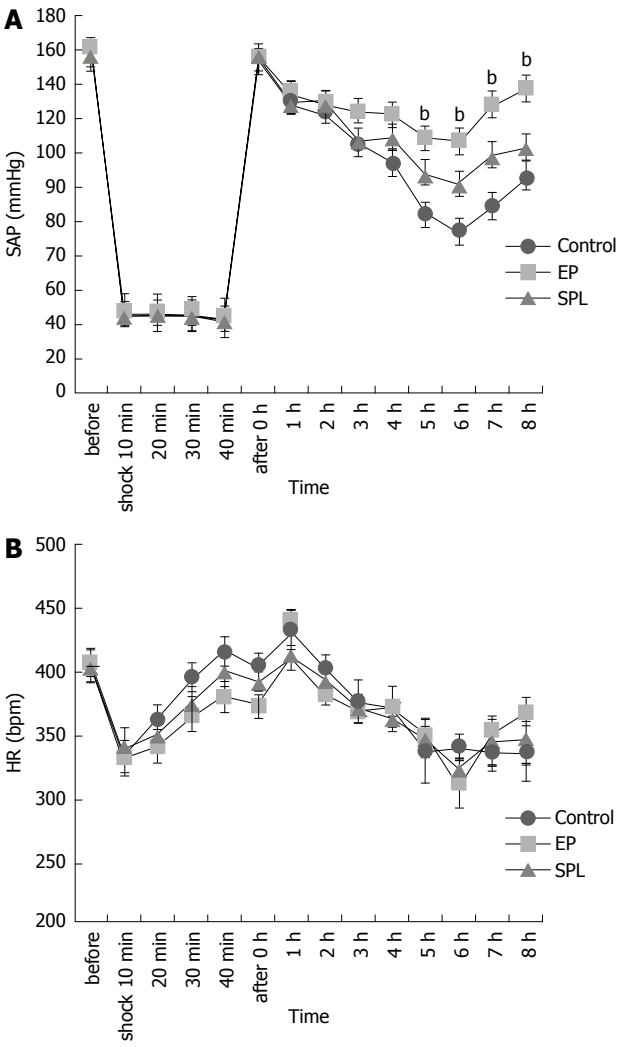

Figure 2 Changes in systolic arterial pressure and heart rate over an 8-h period after hemorrhagic shock recovery. Changes in (A) SAP and (B) HR in three groups. SAPs gradually decreased after HS recovery in all groups. There were significant difference among three groups in a change of the SAP (P < 0.01). There were significant difference between EP group and control group in SAP at 5-8 h after the HS recovery. EP *vs* control; P < 0.01(5-8 h). Data represent means ± SE. ^bP < 0.01 compared with controls. SAP: Systolic arterial pressure; HR: Heart rate; HS: Hemorrhagic shock; EP: Eplerenone.

in critical patients with MOD after HS. However, the effects of pretreatment with MR antagonists on MOD after HS are unclear. Therefore, we evaluated the effects of the pretreatment of MR antagonists on mortality and inflammatory responses after HS in rats. Contrary to our expectations, pretreatment with MR antagonists did not have beneficial effects after HS in rats.

Many investigations have demonstrated that activated Kupffer cells release inflammatory cytokines, such as TNF-α or IL-1, soon after liver IRI. TNF-α increases the expression of ICAM-1 and promotes the adhesion of neutrophils[24-26]. Liver failure is recognized after liver IRI, and many other organs (*e.g.,* the myocardium, pancreas, small intestine, kidney, adrenal gland, and lungs) seem to be damaged by inflammatory reactions and oxidation[27]. Therefore, it is important to evaluate cytokine production in the liver at an early stage after

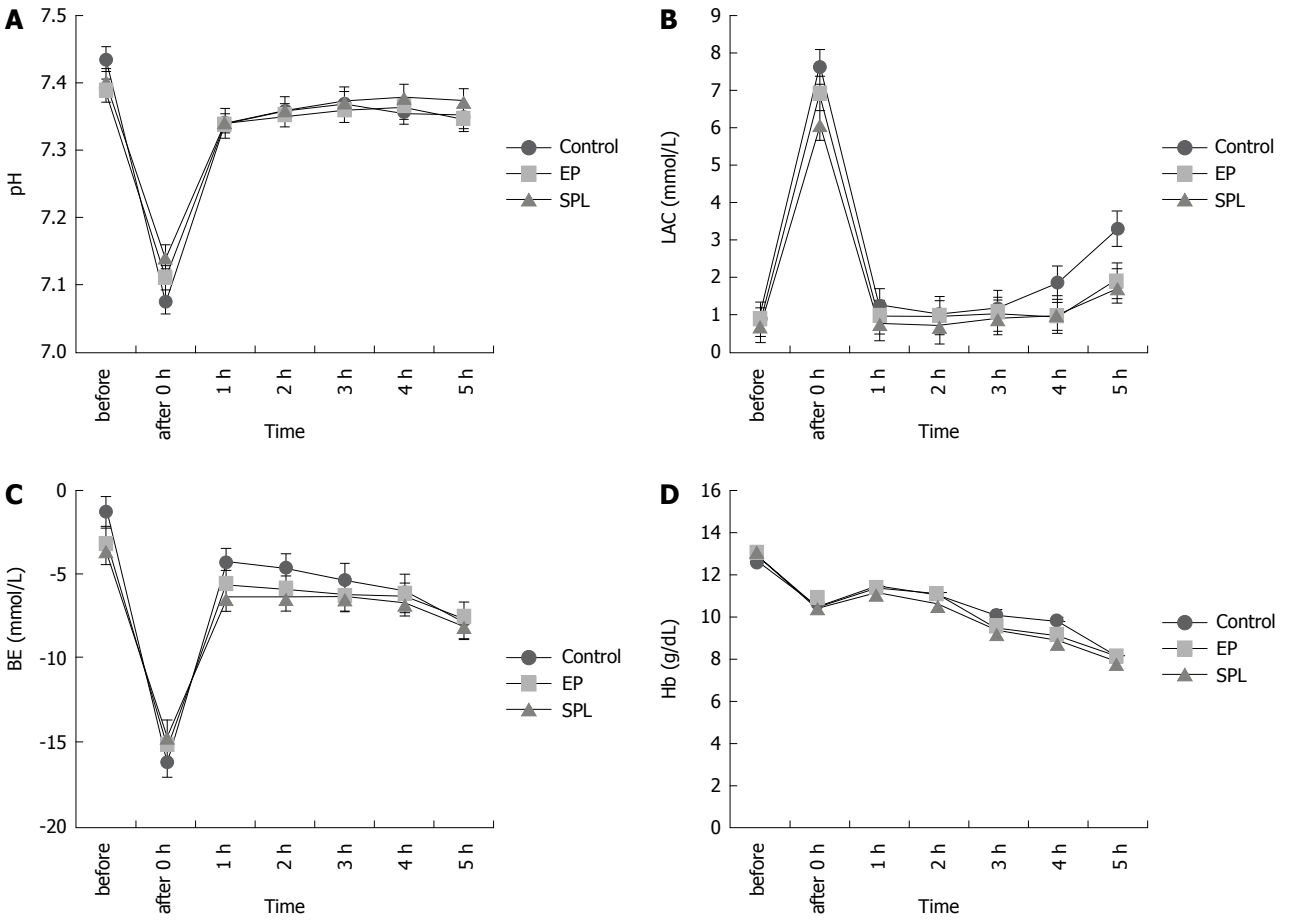

Figure 3 Blood gas analysis results for a 5-h period after hemorrhagic shock recovery. Changes in (A) PH, (B) LAC, (C) (BE), and (D) Hb in three groups. The lactate concentrations increased immediately after HS, but recovered in all groups. There were no significant differences among the three groups in PH, LAC, BE, and BE. Data represent means ± SE. LAC: Lactic acid; BE: Base excess; Hb: Hemoglobin; HS: Hemorrhagic shock.

HS recovery. Several reports have suggested that MR antagonists modulate the production of cytokines, such as TNF-α, IL-6, and IL-1β, in various organs after IRI[9-13]. Pérez *et al*[10] showed that SPL reduces liver damage caused by IRI induced by increases in catalase activity in the liver. Therefore, we hypothesized that pretreatment with MR antagonists has beneficial effects on the expression of genes encoding cytokines, such as TNF-α, IL-6, IL-1β, and ICAM-1, in the liver after recovery from HS. However, we did not detect beneficial effects of MR antagonist pretreatment on cytokine gene expression after HS in rats.

There are several potential explanations for the differences between our results and those of previous studies. First, it is possible that these differences are explained by the relatively short period of ischemia in this study. Suzuki *et al*[28] reported that the activation of Kupffer cell depends on the duration of liver ischemia. The short duration of ischemia may explain lower plasma TNF-α concentrations in this study than in past reports. Further studies are needed to examine long-term ischemic models. Second, the differences among studies may be explained by differences in the dose and duration of the administration of MR antagonists. Ikeda *et al*[9] used a high SPL dose and long period of administration (100 mg/kg per day and 12 wk) in rats. Ozacmak *et al*[11] used a high SPL dose and short period of administration (20 mg/kg/day and 3 d) in rats. Further investigations are needed to clarify the dose- and time-dependent effects of MR antagonists. Finally, the present study used normal SD rats. In clinical settings, MR antagonists are generally administered to hypertensive patients. Further investigations of hypertensive rats are needed to establish the general relevance of the results.

In this study, SAPs of the EP treatment group did not decrease in comparison with the SAP of the control group, however it did not affect the survival rate. In a previous study, Kajihara *et al*[29] showed that blood aldosterone and cortisol levels were rapidly increased after hemorrhage in dog. After recovery of hemorrhagic shock, arterial blood pressure and blood cortisol decreased, however the blood aldosterone level remained relatively high. Rushing *et al*[30] showed that serum corticosterone was stimulated in hemorrhagic shock model of rats. The blood corticosterone and aldosterone in rat can be related to the blood pressure change after the hemorrhagic shock. However, we did not evaluate the change of the blood pressure and the relations of blood aldosterone and corticosterone, in this study. The difference between

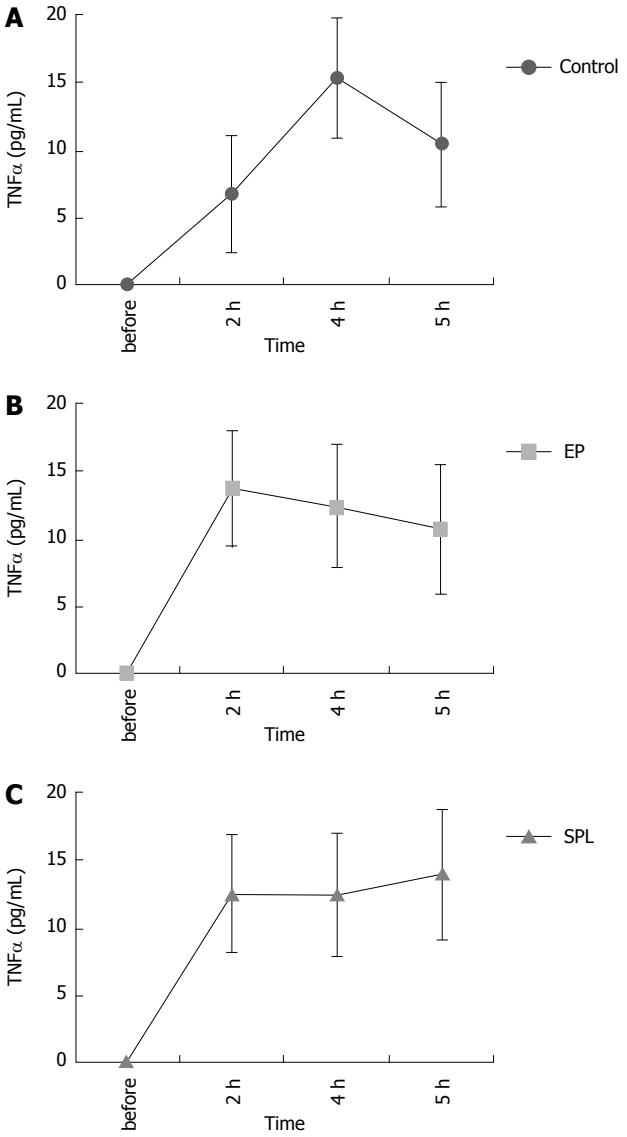

Figure 4 Concentration of plasma tumor necrosis factor-alpha after hemorrhagic shock recovery. Changes of plasma TNF-α concentration in (A) control, (B) EP and (C) SPL group. The plasma TNF-α concentration in all groups increased slightly after the recovery from HS. There were no significant differences in plasma TNF-α concentrations among the three groups. Data represent means ± SE. SPL: Spironolactone; HS: Hemorrhagic shock; EP: Eplerenone; TNF-α: Tumor necrosis factor-alpha.

EP and SPL is selectivity to MR. So further studies are needed to estimate blood corticosterone and aldosterone in hemorrhagic shock by using rats which MR antagonists were administered.

Clinically, it is important to determine whether MR antagonists have beneficial effects when they are administered before reaching the HS state after trauma and massive intraoperative bleeding. We previously showed that the oral administration of a beta antagonist, carvedilol, increases the mortality rate and worsens inflammatory responses to severe HS in rats[19]. Our previous findings suggest that beta antagonists worsen the recovery from severe HS. In the present study, MR antagonists did not worsen HS recovery.

The present study was limited by the number of rats

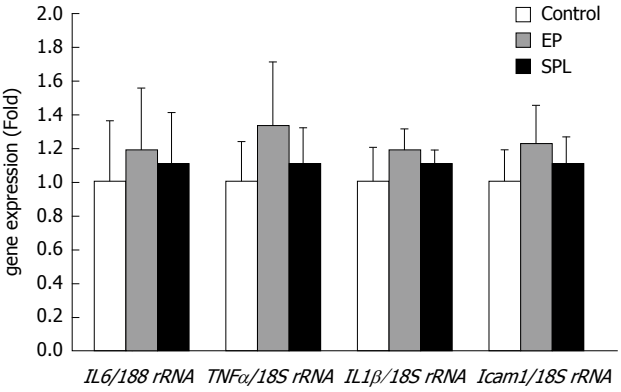

Figure 5 Liber gene expression levels 1 h after hemorrhagic shock recovery. The relative mRNA expression levels of *IL-6/18S rRNA*, *TNFα/18S rRNA*, *IL-1β/18S rRNA*, and *ICAM-1/18S rRNA*. These did not exhibit significant differences in the liver at 1 h after hemorrhagic shock recovery among the three groups. Data represent means ± SE.

and the method for inducing HS. It may be necessary to evaluate a larger sample of rats to increase power in the analysis of survival rate, but this is difficult in animal experiments. Blood was removed by the carotid artery rapidly and a low blood pressure was maintained. This HS model may not be representative of clinical situations. Accordingly, additional studies should examine the MR antagonists using different methods for HS induction.

In conclusion, the present study showed that pretreatment with MR antagonists, such as SPL and EP, does not decrease the mortality rate and does not attenuate inflammatory responses to HS in rats. These findings suggest that MR antagonists did not worsen HS recovery.

ARTICLE HIGHLIGHTS

Research background

Clinically, mineralocorticoid receptor (MR) antagonists such as spironolactone (SPL) and eplerenone (EP) are often administered to hypertensive patients to control blood pressure. However, it is not clear whether MR antagonists have beneficial effects when patients administered MR antagonists become hemorrhagic shock (HS) state caused by trauma and intraoperative bleeding.

Research motivation

It is very important for perioperative management to clarify the influence of MR antagonist administration before HS state caused by trauma and intraoperative bleeding.

Research objectives

The effects of pretreatment of MR antagonists on mortality and inflammatory responses after HS were evaluated in rats.

Research methods

HS was induced by the removal of blood by using rats which MR antagonists were administered or were not administered. The effects of pretreatment of MR antagonists were evaluated by mortality, hemodynamics, plasma TNF-α concentrations, arterial blood gas and liver TNF-α, IL-6, IL-1β and ICAM-1 mRNA expression after HS recovery.

Research results

There were no significant differences among the three groups in survival rate, plasma TNF-α concentrations, arterial blood gas and liver TNF-α, IL-6, IL-1β and ICAM-1 mRNA expression. Systolic arterial pressure (SAP) after HS

recovery did not decrease in rats of EP group in comparison with control groups. After HS recovery, the reason why blood pressure was maintained in rats of EP group is the problems that remain to be solved, in this research.

Research conclusions

Pretreatment with MR antagonists did not improve mortality or cytokine responses in the liver after HS recovery in rats. The HS model in the present study was made during general anesthesia after pretreatment of MR antagonists. This model is similar to the clinical situation when patients administered MR antagonists become HS state during operation. The present study suggested that MR antagonists may not be worsen the recovery of HS state and may not need to be withdrawn before the operations.

Research perspectives

The present study used normal SD rats. In clinical settings, MR antagonists are generally administered to hypertensive patients. Further investigations by using hypertensive rats which MR antagonists were administered will be needed. The present study, SAPs of the EP treatment group did not decrease in comparison with the SAP of the control group, so further studies are needed to evaluate relations of blood corticosterone or aldosterone and blood pressure in hemorrhagic shock by using rats which MR antagonists were administered.

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ORIGINAL ARTICLE

Retrospective Study

Adverse events in critical care: Search and active detection through the Trigger Tool

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Abstract

AIM

To investigate the incidence of disadvantageous events by using the Global Trigger Tool in an intensive care unit (ICU).

METHODS

A retrospective descriptive study was performed in a 12-bed university ICU in the city of Medellin, Colombia. Clinical charts of hospitalized patients were reviewed, between January 1 and December 31, 2016, with the following inclusion criteria: subjects aged over 18 years, with at least 24 h of hospitalization and who had a complete medical history that could be accessed. Interventions: Trained reviewers conducted a retrospective examination of medical charts searching for clue events that elicit investigation, in order to detect an unfavorable event. Measurements: Information was processed through SPSS software

version 21; for numerical variables, the mean was reported with standard deviation (SD). Percentages were calculated for qualitative variables.

RESULTS

Two hundred and forty-four triggers occurred, with 82.4% of subjects having presented with at least one and an average of 3.37 (SD 3.47). A total of 178 adverse events (AEs) took place in 48 individuals, with an incidence of 52.1%. On average, four events per patient were recorded, and for each unfortunate event, 1.98 triggers were presented. The most frequent displeasing issues were: pressure ulcers (17.6%), followed by complications or reactions to medical devices (4.3%), and lacerations or skin defects (3.7%); the least frequent was delayed diagnosis or treatment (0.56%). Thirty-eight point four percent of mishap events caused temporary damage that required intervention, and 48.9% of AEs were preventable. Comparison between AEs and admission diagnoses found that hypertension and sepsis were the only diagnoses that had statistical significance (P = 0.042 and 0.022, respectively).

CONCLUSION

Almost half of the unfavorable issues were classified as avoidable, which leaves a very wide field of work in terms of preventative activities.

Key words: Adverse events; Critical care; Trigger Tool; Complications; Security

Core tip: The Global Trigger Tool is a type of active detection of adverse events (AEs). Three studies carried out in intensive care units (ICUs), which included only patients who died in the following 96 h or 7 d prior to ICU admission. The importance of our study is that it was performed during the entire hospital stay in the ICU. The incidence of AEs was 52.1%, and 48.9% of these were preventable. The most frequent were pressure ulcers (17.6%) and complications related to medical devices (4.3%). The three main triggers were skin defects, excitation or drowsiness, and unscheduled withdrawal of surgical catheter, probes, or drains.

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INTRODUCTION

In 2000, the publication of "To Err is Human: Building a Safer Health System" from the United States Institute of Medicine marked a before and after in the awareness of this issue and has made security research become a fundamental pillar[1]. In 2004, the World Health Organization (WHO) created the Global Alliance for Patient Safety, in order to coordinate, disseminate and accelerate improvements in patient safety worldwide.

Patient safety is defined as the absence of unnecessary or potential harm associated with health care. This damage is represented as a functional, structural or any detrimental effect derived from medical care. Adverse events (AEs) can be classified as preventable or nonpreventable. The causality model raises many factors that influence avoidable unfavorable event sequence. The system produces errors when several weaknesses occur momentarily, allowing the opportunity for accident. Risk management is a discipline the objective of which is study of unfavorable issues derived from assistance through its detection and analysis, with the ultimate goal of designing strategies for its prevention. Risk is defined as the combination of the probability of occurrence of an event and its consequences. In the United Kingdom, an organizational model of causation of errors and AEs, known as the London Protocol, was developed.

In a study by Resar *et al*[2] conducted between 2001 and 2004 in 62 intensive care units (ICUs) of 54 hospitals, the authors described an incidence of 11.3 AEs. Rothschild *et al*[3], for a year under direct observation, found 120 AEs in 79 subjects (20.2%), including 66 (55%) not avoidable and 54 (45%) avoidable; the rate per 1000 patient-days was 80.5. Forster *et al*[4], in an academic ICU with 207 individuals being monitored daily, found AEs in 40 patients (19%), being preventable in 21 subjects (10%); these AEs were associated with an increase in hospital stay.

There are two types of AE detection: passive, where events are voluntarily reported; and active, where retrospectively or prospectively, a comprehensive assessment is performed to actively detect issues. The passives do not reach the absolute detection of the events, compared to the active review[5]. As described previously, only between 10% to 30% of AEs are voluntarily reported[6]. In one study, nurses were able to create a nonpunitive atmosphere which increased the spontaneous and voluntary reporting 10 to 20 times more[2]. Another survey assessing different methods of notification in Hospital Monte Naraco, revealed that 30% of the events were reported by voluntary means[6].

In the active methodology, there is a tool known as Global Trigger, which is based on a retrospective revision of the clinical chart performed by trained reviewers which seeks hints that will serve as indications for the evaluators to investigate the records in depth. This tool enables data acquisition and subsequent analysis and management through time of the causes of AEs[7,8]. This tool has facilitated the detection of, at least, 10 times more events than those reported by passive search methods, such as voluntary reports[2]. It has been reported that only between 10% to 20% of errors

Table 1 Triggers

Trigger	*n*	%
Skin defects or lacerations	36	14.75
Excitation or drowsiness of the patient	34	13.93
Unscheduled withdrawal of surgical catheter, probes, drains or other devices	34	13.93
Hypotension	33	13.52
Initiation of antibiotics after 48 h of admission	28	11.48
Abrupt fall in hemoglobin or hematocrit by more than 25%	24	9.84
Hypoglycemia	19	7.79
Pneumonia	9	3.69
Reintubation in less than 48 h	6	2.46
Unscheduled surgical reintervention	5	2.05
Chest tube insertion during ICU hospitalization	4	1.64
Initiation of dialysis during ICU hospitalization	4	1.64
Accidental extubation	3	1.23
Adverse drug reaction events	3	1.23
Cardiac arrest	1	0.41
Protamine use	1	0.41
Total	244	100.00

ICU: Intensive care unit.

are reported; and, of those, 90% to 95% do not cause harm to patients[9]. We intend to establish the incidence of AEs by using the Global Trigger Tool (GTT) in a high-complexity academic ICU.

MATERIALS AND METHODS

A retrospective descriptive study was conducted in a 12-bed ICU, belonging to a university center in the city of Medellin, Colombia. This service is attended by intensivists, with a ratio of 6 patients per doctor at daytime and 12 patients per doctor at night. Nursing staff keeps a ratio of 6 patients per nurse during 24 h, and there is 1 nursing assistant for every 2 patients. There is an available respiratory therapist 24 h a day. Clinical charts of hospitalized patients were taken, between January 1 and December 31, 2016, with the following inclusion criteria: subjects aged over 18 years, with at least 24 h of hospitalization who had a complete medical history that could be accessed. This study was approved by the ethics committee of the Universidad Pontificia Bolivariana.

Techniques and data collection instruments

After the ethical and institutional endorsement, we proceeded to train the team of reviewers, constituted by nurses with expertise and experience in Quality of Health Services, and medical specialists in intensive care who were standardized in review(ing) criteria, established(ing) times and process(ing) order(s). Each team analyzed the medical records in the event of a trigger; the chart was sent to one of two intensive care specialists to define the presence of this AE. Sixteen triggers were used to detect AEs (Table 1). These triggers were initially extracted from the literature, and then corroborated by each of the service intensivists, and subsequently, a consensus was obtained at a group meeting.

In case of an AE, a consensus was reached between the two intensivists. If this was proven positive, the specialist analyzed the preventability and severity of the AE, which was carried out with the classification of the The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), which stipulates the following criteria on a scale from A to I. Criteria from A to D are considered incidents. From the E and on, they are considered events, as follows: E: Temporary harm requiring intervention; F: Temporary harm requiring prolonged hospitalization; G: Permanent harm; H: Injury that demands intervention to sustain life; Y: Harm that contributes to death.

Statistical analysis

Data processing was done using SPSS version 21. Quantitative variables were analyzed by grouping (mean and median) and dispersion measures [standard deviation and interquartile range (IQR), according to their distribution type]. Categorical variables were analyzed as proportions. Bivariate analysis was performed to search for association between AE and admission diagnoses. χ^2 hypothesis tests were used for categorical variables and Student's *t*-test for continuous variables with normal distribution or Mann-Whitney *U*-test for those variables with a different distribution[10]. A significant association was considered if a *P* value of less than 0.05 was obtained.

RESULTS

Data were collected from 134 patients. Forty patients were excluded for the following reasons: 12 subjects aged under 18 years and 28 patients remained less than 24 h in hospitalization; finally, 94 clinical charts were analyzed. General characteristics of the patients were: the mean age of the individuals was 56.77 years (standard deviation: 20.72; minimum: 10 and

Table 2 Adverse events

Adverse event	*n*	(%)
Pressure ulcers	62	17.6
Complications or reactions to medical devices	15	4.3
Lacerations	13	3.7
Drug-induced hypotension	10	2.8
Poor glycemic control	9	2.6
Nosocomial pneumonia	9	2.6
Injury during procedure	8	2.3
Phlebitis	7	2.0
Hemorrhage or hematoma related to surgery or procedure	7	2.0
Acute lung disease or respiratory failure	5	1.4
Operative site infection	5	1.4
Another event	5	1.4
Drug-induced neurological disorders	4	1.1
Sepsis and septic shock	4	1.1
Burns, erosion, bruises and fractures	3	0.9
Pneumothorax	2	0.6
Pruritus, rash or dermal lesions, reactive to drugs or dressings	2	0.6
Adhesion and functional alterations after surgical intervention	1	0.3
Bacteremia associated with device	1	0.3
Error in medication delivery	1	0.3
Events attributable to internal failures in timeliness or continuity of evaluation	1	0.3
Failures attributed to quality	1	0.3
Opportunistic infection by immunosuppressive treatment	1	0.3
Nosocomial urinary tract infection	1	0.3
Delay in diagnosis or treatment	1	0.3
Total	178	100

maximum: 87). Sixty-two point eight percent (*n* = 59) of patients were female, and 37.2% (*n* = 35) were male. Of the subjects who suffered AEs, 62.8% were women and 37.2% were men. APACHE Ⅱ was 18 (IQR 14-24), and 12 of the 94 patients died (12.5%), with only one death related to an AE. The average patient stay was 8.05 d, with a standard deviation of 11.8 d (with a minimum of 1 d and a maximum of 66 d). The reasons for admission were: 22 (23.4%) patients were postsurgical, 18 (19.14%) came from the obstetric service, 14 (14.9%) from emergencies, 28 (29.78%) from hospitalization and 12 (12.76%) came from other institutions. Of the assessed patients, 43/94 (45.7%) had at least one comorbidity on admittance to the ICU; among the main ones were acute myocardial infarction (84%), sepsis (15%), cranioencephalic trauma (5%), pneumonia (5%) and cerebrovascular accident (4%). Other causes of lower frequency included: Urinary tract infection, heart failure and rheumatologic disease with 4%, 3% and 2%, respectively. Eighty-eight point three percent of the individuals had health system affiliation due to their job, and 11.7% were subsidized by the State.

Table 1 shows the triggers, totaling 248, concentrated in 69 subjects; the most frequent of which were: skin defects or lacerations (14.75%), excitation or somnolence of the patient through the RASS scale (+3 or -3) (13.93%) and hypotension (13.52%). The least frequent was the use of protamine (0.41%).

The Triggers found elicited further investigation into the medical records in order to look for unfavorable issues. This search yielded a total of 178 AEs in 49 subjects, with an incidence of 52.1%; on average, 3.6 events per patient were recorded, and 1.98 triggers for each AE.

Table 2 shows the AEs detected; the most predominant were pressure ulcers (17.6%), followed by complications or reactions to medical devices (4.3%), lacerations or skin defects (3.7%). The least presented was delayed diagnosis or treatment (0.56%).

One part of the analysis of displeasing events is prevention; almost half of the AEs were preventable (48.9%), 28% were incidents, 1.2% were nonpreventable and 21.9% were a complication of the underlying disease.

The 38.4% of severity of AEs were classified in category E (temporary harm that required intervention), 10.8% classified in category H (harm that required an intervention to sustain life), 0.9% were rated in category F (temporary harm demanding prolonged hospitalization), and finally, categories Y (harm that contributed to death) and G (permanent harm), accounted for 0.3%.

Another comparison between AEs and admission diagnoses found that hypertension and sepsis were the only diagnoses that had statistical significance (*P* = 0.042 and 0.022, respectively).

When reviewing the patient's age and preventability, the most striking findings indicated that 172 patients had preventable AEs, who were at least 17 years of age and had a maximum age of 87 years, with a median of 69 years and a 75th percentile of 77 years. On the contrary, 6 patients developed nonpreventable AEs, with a minimum age of 64 and a maximum of 87 years; the median was 69 and the 75th percentile was 75 years.

Table 3 Comparison between the different studies in ICU using the Trigger Tool methodology

Ref.	Patients	No. of ICUs	Sample	Incidence or prevalence of AEs
Resar *et al*[2]	During ICU stay	62	12074	11.3/100 patient d
Nilsson *et al*[12]	Those who die in less than 96 h of ICU admission	1	128	32/100 ICU admissions 19.5%
PREVENT[13]	Within 7 d prior to ICU admission	5	280	27.1% (80% related to reason for admission)
UPB (Molina *et al*)	During ICU stay	1	94	52.1% 3.6 AEs per patient

AEs: Adverse events; ICU: Intensive care unit.

The statistical significance was a Kruskal-Wallis *P* value of 0.012.

DISCUSSION

The main finding of our study is that the incidence of AEs in the ICU is 52.1%. The most frequent triggers were skin defects or lacerations (14.7%), excitation or somnolence of the patient according to the RASS scale (+3 or -3) (13.9%), and hypotension (13.5%). The most predominant AEs were pressure ulcers (17.6%), followed by complications or reactions to medical devices (4.3%), and lacerations or skin defects (3.7%). On average, 3.6 events per patient were recorded, and 1.98 triggers for each AE.

The largest study to identify the occurrence of displeasing issues was conducted by the Institute for Healthcare Improvement in 62 ICUs from 54 hospitals, between 2001-2004. The prevalence of AEs observed in 12.074 admissions in the ICU was 11.3 AEs/100 patient d; in a subgroup of 1.294 charts of 13 ICUs, which were reviewed in detail, 1.450 unpleasant events were identified, with a prevalence of 16.4 events/100 ICU d[2]. The Institute used, for the first time as a method of detecting AEs in ICU, records related to medications linked to pharmacy, finding 120 AEs in 79 patients (20.2%), with a rate of 8.05 AEs/100 patient d. This incidence is lower than ours, but with two differences: the Institute did not use the Tool, and it was prospective for a year, through continuous direct observation. Forster *et al*[4] also monitored patients daily by a multidisciplinary team; they evaluated 207 critical patients, with AEs in 40 patients (19%).

In a systematic review of the GTT by the end of 2016, in the different specialties, only three studies carried out in ICUs were found. Apart from the aforementioned[11], which shares similarity to ours, investigating triggers in subjects during hospital stay, the other two studies differ in their admission criteria. The first, Nilsson *et al*[12], included only patients who upon admission to the hospital's ICU or in the following 96 h died. The second, the PREVENT trial[13], reviewed clinical charts 7 d prior to ICU admission. Table 3 shows the methodological characteristics of these surveys, including our own. Table 4 shows the most frequent triggers and AEs in the different studies performed with GTT in ICU.

Of the findings of these investigations, we can highlight the following. Firstly, that AEs are preventable in a high proportion (between 48.9% and 77% of cases). Secondly, in all studies, except PREVENT, AEs in their severity were more temporal (E or F). Thirdly, in spite of using the GGT methodology, only Resar *et al*[2] and ours describe the most conventional triggers. And, lastly, the most common AEs in the different studies are distinct, perhaps they do resemble in that they are related to skin care.

In our study, the most extensive trigger was skin laceration, which is consistent with the most prevalent AE: pressure ulcer; this event is consistent with other studies, such as IBEAS[14] in hospitalization, which considers it as the most common in Latin America. This event is largely associated with the presence of patients' comorbidities, such as physical dependence, poor nutritional status, high hospital stay and the need to be in bed, distinctive of subjects hospitalized in an ICU.

In terms of severity and age, it was evident that as the patient was older, the likelihood of developing an AE increased, a fact that is consistent with a study conducted in Spain, where it was observed that age over 65 years was associated with the presence of AE[15]. Our knowledge indicates a higher frequency of unpleasant issues in females, in contrast to a survey performed in an ICU in Sao Paulo, which revealed a higher incidence of AE in males 52.3%. Sex differences could be attributed to the fact that the institution included in this research serves primarily maternal patients[16].

This study had several limitations. First, it was performed in a single center. Second, since it is retrospective, there may be bias in the lack of information from medical and nursing records. The third limitation was the inclusion of the unit's own intensivists within the research team; however, this fact strengthened their competencies in the use of the methodology and facilitated that they self-evaluated the AEs presented. The fourth limitation was the difficulty that existed in our environment for the unification in the administrative criteria of hospitalization in intensive care; that is to say, there may be special care patients. The fifth limitation was selection bias for interobserver variability, despite treatment and use of the same tool.

In the future, it will be worthwhile to carry out a multicenter study, given the shortage of these, and with the clearance of the most frequent triggers found in this study and Resar *et al*[2]. In addition, a prospective cohort study, after identifying the triggers, can be done to see how many AEs are prevented.

Table 4 Triggers and adverse events among the different studies in ICU using the Trigger Tool methodology

Ref.	Most frequent triggers	Adverse event	Severity	Preventability
Resar *et al*[2]		Triggers led to an AE in:		Not reported
	1 Proceeding	1 17.8%	E = 58.2%	
	2 Hemoglobin fall	2 65%	F = 24.3%	
	3 Intubation or reintubation	3 54%	G = 2%	
	4 Pneumonia	4 67%	H = 11.4%	
	5 Positive blood cultures	5 83%	Y = 4.1%	
Nilson *et al*[12]	Not reported	1 Nosocomial infection (22%)	E = 49%	54%
		2 Hypoglycemia (19%)	F = 10%	
		3 Pressure ulcer (17%)	G = 2.4%	
		4 Complication by procedure (15%)	H = 4.8%	
			Y = 33.8%	
PREVENT[13]	149 triggers. Does not report frequencies	1 Delay/failure in medical management (14.4%)	E = 5.5%	77%
		2 Surgical tissue damage (11.5%)	F = 31%	
		3 Failure to monitor scales by nursing (96%)	G = 32%	
		4 Error in medication prescription (8.6%)	H = 21%	
			Y = 10.5%	
UPB (Molina *et al*)	248 triggers			48.9%
	1 Skin defects or lacerations (14.7%)	1 Pressure ulcers (17.6%)	E = 38.4%	
	2 Excitation or drowsiness of the patient (13.9%)	2 Complications or reactions to medical devices (4.3%)	F = 0.9%	
	3 Hypotension (13.5%)	3 Lacerations (3.7%)	G = 0.3%	
	4 Unscheduled removal of surgery catheter, probes, drains or other devices (13.9%)	4 Drug-induced hypotension (2.8%)	H = 10.8%	
	5 Initiation of antibiotics after 48 h of admission (11.5%)	5 Poor glycemic control (2.6%)	Y = 0.3%	

The main conclusions of our study were: we had an incidence of 52.1%; on average, 3.6 events per patient were recorded, and for each AE we had 1.98 triggers; and, the main AEs were related to skin lesions (pressure ulcers, lacerations) and the use of medical devices. Almost half of the AEs were classified as preventable, which leaves a very broad field of work in terms of preventing the occurrence of such events. We propose that each ICU identify its triggers, so that it can actively prevent the AEs.

ARTICLE HIGHLIGHTS

Research background

The Global Trigger Tool (GTT) enables data acquisition and subsequent analysis and management through time of the causes of adverse events (AEs). This tool has facilitated the detection of, at least, 10 times more events than those reported by passive search methods. GTT is a type of active detection of AEs. Just three studies carried out in intensive care units (ICUs), which included only patients who in the following 96 h died or 7 d prior to ICU admission. The importance of our survey is that it was performed during the entire hospital stay in ICU.

Research motivation

The main motivations for the study were the low amount of reports on AEs and the issue that the search and report systems do not detect all events that could present in our institution. Although there is a high incidence of AEs in hospitalized patients in the ICU, current search and report systems fail to detect them all. For this reason, we are inclined to the GTT methodology. One of the problems was that these triggers were initially extracted from the literature, and then corroborated by each of the service intensivists, and subsequently, a consensus was obtained at a group meeting. Therefore, it is essential that the medical team of each ICU in the world defines which would be the most useful triggers. Another difficulty we had was the review of all the patients' records to identify the triggers. One solution is to carry out prospective studies that include data for the detection of triggers in each patient's evolution chart. In the future, it will be worthwhile to carry out a multicenter study in this sense.

Research objectives

The authors intended to establish the incidence of AEs by using the GTT in a high-complexity academic ICU. The authors determined which were the most frequent triggers and AEs, along with their severity, which was carried out with the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) classification, that stipulates criteria on a scale from A to I, and from A to D. In addition, analysis was performed to explore the association between AEs and admission diagnoses. For future prospective multicenter research, the association of triggers with AEs should be evaluated.

Research methods

A retrospective descriptive study was conducted in a 12-bed ICU. The inclusion criteria were subjects aged over 18 years, with at least 24 h of hospitalization, and who had a complete medical history that could be accessed. A training team of reviewers (nurses and intensivists) were standardized in review criteria, established times and process order. Each team analyzed the medical records in the event of a trigger. Sixteen triggers were used to detect AEs. These triggers were initially extracted from the literature, and then corroborated by each of the service intensivists; subsequently, a consensus was obtained at a group meeting.

Research results

The main finding of this study was that the incidence of AEs in the ICU is 52.1%. The most frequent triggers were skin defects or lacerations (14.7%), excitation or somnolence of the patient according to the RASS scale (+3 or -3) (13.9%), and hypotension (13.5%). The most predominant AEs were pressure ulcers (17.6%), followed by complications or reactions to medical devices (4.3%), and lacerations or skin defects (3.7%). This search yielded a total of 178 AEs in 49 subjects, with an incidence of 52.1%; on average, 3.6 events per patient were recorded, and 1.98 triggers for each AE. One of the problems of this retrospective study was the detection of the severity of AEs. For this reason, the authors sent the data to two intensivists to agree on the severity of these AEs; we think that this aspect could be better solved in a prospective research study.

Research conclusions

The Global Trigger Detection Tool is a useful instrument to detect AEs in an ICU. As a descriptive study, no theory could be generated from our findings. In this survey, the clinical chart review methodology, suggested by the IHI,

was taken as a reference, although the research team made variations in the manner of selecting patients (systematic randomized sampling), along with the review time of clinical records (review all charts), which allowed the detection of more triggers and AEs that could be useful for future investigations. Including GTT methodology to the study implies an increase in the frequency of AEs, and thus adopts measures that reduce their incidence in the future.

Research perspectives

The authors suggest the adoption of the methodology in the institution with a trained team in this tool. In future investigations, it is recommended to determine the effectiveness of the tool through analytical studies (cases and controls) that show statistically significant differences between passive and active methods of AE detection. The authors suggest prospective projects that validate the methodology to verify that they could anticipate the presentation of AEs.

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ORIGINAL ARTICLE

Prospective Study

Spectrum of cardiac manifestations and its relationship to outcomes in patients admitted with scrub typhus infection

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Abstract

AIM

To study the spectrum of cardiac manifestations in scrub typhus infection and assess its relationship to outcomes.

METHODS

Demographic data, electrocardiographic (ECG) changes, left ventricular (LV) systolic and diastolic function, myocardial injury (defined as troponin T > 14 pg/mL), and pericardial effusion were documented. Myocarditis was diagnosed when myocardial injury was associated with global LV systolic dysfunction. The relationship between myocarditis and outcomes was assessed using logistic regression analysis and expressed as odds ratio (OR) with 95%CI.

RESULTS

The cohort (*n* = 81; 35 males) aged 49.4 ± 16.1 years (mean, SD) presented 8.1 ± 3.1 d after symptom onset. The APACHE-Ⅱ score was 15.7 ± 7.0. Forty-eight (59%) patients were ventilated, and 46 (56%) required vasoactive agents. Mortality was 9.9%. ECG changes were non-specific; sinus tachycardia was the most common finding. Myocardial injury was evident in 61.7% of patients and LV systolic dysfunction in 30.9%. A diagnosis of myocarditis was made in 12.3%. In addition, seven patients with regional wall motion abnormalities had LV systolic dysfunction and elevated cardiac enzymes. Mild diastolic dysfunction was observed in 18 (22%) patients. Mild to moderate pericardial effusion was seen in 51%. On multivariate logistic regression analysis, patients with myocarditis tended to be older (OR = 1.04, 95%CI: 0.99-1.09), had shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98), and tended to stay longer in hospital (OR = 1.17, 95%CI: 0.98-1.40). Myocarditis was not associated with increased mortality.

CONCLUSION

In scrub typhus infection, cardiac manifestations are frequent and associated with increased morbidity but not mortality.

Key words: Scrub typhus; Myocarditis; Outcome

Core tip: This study characterizes the cardiac manifestations in scrub typhus using a combination of clinical parameters, biomarkers, and echocardiography. In this prospective cohort study, 81 patients admitted with scrub typhus infection were enrolled. A wide range of cardiac manifestations were observed from non-specific electrocardiographic changes to pericarditis, myocarditis, and circulatory shock. Myocarditis occurred in 12.3% of the patients. Patients with myocarditis had significantly shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98) and tended to stay longer in hospital (OR = 1.17, 95%CI 0.98-1.40). An effect on mortality was not demonstrable.

Karthik G, Sudarsan TI, Peter JV, Sudarsanam T, Varghese GM, Kundavaram P, Sathyendra S, Iyyadurai R, Pichamuthu K. Spectrum of cardiac manifestations and its relationship to outcomes in patients admitted with scrub typhus infection. *World J Crit Care Med* 2018; 7(1): 16-23 Available from: URL: http://www.wjgnet.com/2220-3141/full/v7/i1/16.htm DOI: http://dx.doi.org/10.5492/wjccm.v7.i1.16

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi,* is endemic in the "tsutsugamushi triangle". It accounts for nearly 50% of the cases of acute, undifferentiated febrile illness in some settings[1], and is associated with significant morbidity. Although the overall case fatality rate of patients admitted with scrub typhus infection is reported to be 9%[2], in those presenting with severe illness and requiring intensive care unit (ICU) admission, mortality may be as high as 24%[3]. There are reports that scrub typhus can cause myocarditis and myocardial dysfunction[4-7]. However, the magnitude of this problem and its impact on outcome are unclear.

Myocarditis is postulated to occur as a result of disseminated endothelial infection of the small vessels or secondary immune mediated mononuclear inflammation[5]. In a study of 31 patients who died of scrub typhus infection during World War Ⅱ, post-mortem findings showed varying degrees of myocardial inflammation in 25 cases[6]. In a recent study of 35 children with scrub typhus infection[5], myocarditis with cardiogenic shock was reported in 34%. In a systematic review of 76 articles on scrub typhus involving 19644 patients, only four studies reported data on myocarditis[8]. Pooled analysis of these four studies[8] suggested a strong association between myocarditis and mortality (24% *vs* 4%; $P < 0.001$). There is a paucity of prospective studies that have systematically characterized cardiac manifestations in scrub typhus. This study detailed the spectrum of cardiac manifestations in scrub typhus infection and assessed its relationship to outcomes.

MATERIALS AND METHODS

Patients and setting

Adult patients admitted with an acute febrile illness (AFI) between June 2012 and January 2014 to the medical ward, medical ICU, or high dependency unit (HDU) of a tertiary care teaching hospital in India were considered for inclusion. Since a majority of patients with scrub typhus infection manifest thrombocytopenia, only patients with AFI and thrombocytopenia (platelet count < 150000/cmm) were screened. This was done because the study protocol required an echocardiographic assessment within 48 h of admission as well as additional serological tests. Given that the serological tests are batched for analysis and are not done daily, and since the institution handles a large number of patients with AFI, the additional screening criteria ensured that patients with a low probability of scrub typhus infection were not subject to additional tests and echocardiographic evaluation.

A diagnosis of scrub typhus was made when a patient with an AFI had a positive IgM enzyme-linked immunosorbent assay (ELISA) for scrub typhus, with or without an eschar and other causes of fever were excluded[5,8]. Patients with an alternative diagnosis and those unwilling to participate in the study were excluded.

Ethical approval and funding

The study was approved by the local Institutional Review

Board (No. 8104) and supported by an institutional research grant (Fluid Research Fund). Written informed consent was obtained from all the patients or from their next of kin if the patient was critically ill and unable to consent.

Diagnostic tests

All patients underwent routine tests that included complete blood count, liver function test, renal function test, electrolyte test, chest radiograph, and appropriate cultures and serological tests. Scrub Typhus detect IgM ELISA (InBios International Inc., Seattle, United States) was used for serological diagnosis. An optical density ⩾ 0.5 was diagnostic of scrub typhus.

Cardiac enzymes, creatinine kinase muscle brain isoenzyme (CK-MB), and troponin T were determined for all the patients. CK-MB was measured using COBAS e411 from ROCHE diagnostics. The reference range for CK-MB in our laboratory is < 6.7 pg/mL for males and < 3.8 pg/mL for females. Troponin T was measured by electrochemiluminescence immunoassay using COBAS e-411 modular analytics (ROCHE). The reference range for troponin T is < 14 pg/mL. As troponin T is a sensitive marker of myocyte injury[9], this test was used for screening and diagnosis of myocarditis; troponin T > 14 pg/mL was considered as evidence of myocardial injury.

All patients had an electrocardiogram (ECG) at recruitment; heart rate, ST-T changes, and rhythm abnormalities were documented. A transthoracic echocardiography was performed within 48 h of admission, using a Sonosite Micromax unit with a 1 to 5 MHz phased array transducer probe. Left ventricular (LV) systolic and diastolic function and presence of pericardial effusion were assessed. LV systolic function was assessed by ejection fraction (EF), cardiac index (CI), and stroke volume index (SVI). LV ejection fraction (LVEF) < 50% determined by M mode in the parasternal long axis view was considered as myocardial dysfunction. The CI and SVI were determined using the measured LV outflow diameter from the parasternal long-axis view and LV outflow tract velocity time integral in apical 5 chamber view. A diagnosis of myocarditis was made when global LV systolic dysfunction (LVEF < 50%) was associated with cardiac enzyme elevation (Troponin T > 14 pg/mL).

LV diastolic dysfunction was assessed using the mitral inflow wave pattern measured on pulsed wave Doppler (PWD) ultrasound. The ratio between heights of early and late diastolic flow velocity peaks E and A was obtained. The early diastolic peak velocity of the medial mitral annulus was also measured by tissue Doppler imaging and designated as e'. Diastolic dysfunction was diagnosed when the E/A ratio was < 1 and / or E/e' was > 15[10-12].

Shock was classified as cardiogenic, septic, or mixed, based on echocardiograhic parameters, where measures of preload [central venous pressure (CVP) and inferior vena cava (IVC) variability], cardiac contractility (cardiac index), and afterload [vasular resistance-systemic vascular resistance index (SVRI)] were used. Since CVP is not a reliable measure of preload[13], non-invasive measurements of the IVC diameter and IVC variability (calculated by measuring the difference between the maximum and minimum diameters on the M-mode and dividing it by the mean of the two) were used for assessing preload. IVC variability was present when it was > 18% for ventilated patients with no spontaneous breaths and was > 50% in a spontaneously breathing patient. Patients with a low CI and high SVRI were categorized as having cardiogenic shock, while those with a high CI and low SVRI were categorized as the ones with septic shock. Patients with a clinical picture of septic shock but a low CI were considered with mixed shock.

Severity of illness

Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE-Ⅱ) score[14]. Organ dysfunction was evaluated using the Sequential Organ Failure Assessment (SOFA) score[15]. Organ dysfunction was present when the organ specific SOFA score was ⩾ 1 and organ failure when SOFA score was ⩾ 3[16].

Patient management and outcome parameters

All patients were managed with appropriate antibiotics and supportive therapy (hemodynamic support, ventilation, and renal replacement therapy) as indicated. In less sick patients, oral doxycycline was administered at 100 mg twice daily. In critically ill patients, particularly those in shock, intravenous azithromycin 500 mg once daily was used either alone or in combination with enteral doxycycline since intravenous doxycycline was not available at the time of study. In pregnant patients, only azithromycin was administered.

The primary outcome that was assessed was the incidence of myocarditis. Other outcomes that were evaluated included mortality, need for ventilation and dialysis, type of ventilatory support (invasive or non-invasive), and duration of ICU and hospital stay.

Validation

Three investigators (KP, TIS, and KG), trained in critical care sonology, did the echocardiographic assessments. Inter-observer variability validation studies were done at the start of the study on 20 randomly chosen patients. The agreement among the investigators was measured using kappa and interclass correlation co-efficient. The kappa for the categorical variable regional wall motion abnormality was 0.57, and the interclass correlation coefficients for non-categorical variables such as LVEF, E/a, left ventricular outflow tract (LVOT) diameter, IVC diameter, and E/e' were 0.76, 0.86, 0.87, 0.76, and 0.88, respectively. During the study, echocardiogram images of all the recruited patients were stored and reviewed by a certified sonologist (KP).

Table 1 Demographics, symptoms, co-morbidities, and laboratory parameters in patients with and without myocarditis

Characteristic	With myocarditis (n = 10)	No myocarditis (n = 71)	P value
Demographic			
Age, mean (SD), yr	56.5 (13.7)	48.4 (16.2)	0.14
Gender (female:male)	41:30:00	5:05	0.64
Illness duration, mean (SD), d	6.8 (3.1)	8.3 (3.0)	0.16
Symptom, n (%)			
Fever	10 (100)	71 (100)	1.00
Cough	2 (10)	27 (38)	0.27
Breathlessness	8 (80)	54 (76)	0.78
Altered mental status	3 (30)	12 (16.9)	0.32
Myalgia	5 (50)	25 (35.2)	0.36
Vomiting	3 (30)	19 (27.8)	0.83
Co-morbidity, n (%)			
Diabetes	0	16 (22.5)	0.09
Hypertension	1 (10)	14 (19.7)	0.46
Pregnancy	0	5 (7)	0.39
Coronary artery disease	0	2 (2.8)	0.59
Smoking	1 (10)	2 (2.8)	0.26
Laboratory parameter, mean (SD)			
Hemoglobin, g %	12.9 (3.6)	11.3 (2.2)	0.06
Total white cell count, cmm	11360 (5484)	10649.3 (4879)	0.67
Platelets, cmm	47400 (36039)	65376 (62668)	0.38
Creatinine, mg %	1.6 (1.1)	1.7 (1.5)	0.76
Total bilirubin, mg %	1.7 (1.1)	2.1 (2.0)	0.49
Direct bilirubin, mg %	1.3 (1.0)	1.6 (1.7)	0.55
Serum albumin, mg %	2.3 (0.7)	2.6 (0.5)	0.20
AST, U/L	173 (143)	142 (92)	0.37
ALT, U/L	69 (53)	71.7 (51)	0.88
Alkaline phosphatase, U/L	196 (105)	203 (108)	0.84
SOFA score	10.6 (2.8)	8.7 (4.0)	0.16
APACHE Ⅱ score	17.1 (8.3)	15.5 (6.8)	0.50

n: Number of patients; SD: Standard deviation; AST: Serum aspartate aminotransferase; ALT: Serum alanine transaminase; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit.

Statistical analysis

Assuming an incidence of myocarditis in scrub typhus as 30%, with 10% precision, the sample size was calculated to be 84. Descriptive statistics were obtained for all variables in the study. Categorical and continuous variables were compared for outcome using the Fisher's exact test and Student's t-test, respectively. All continuous data are expressed as the mean with standard deviation (SD) unless the data are not normally distributed. A P-value < 0.05 was considered statistically significant. The presence of myocarditis was correlated with mortality and expressed as odds ratio (OR) with 95% confidence interval (CI). A bivariate logistic regression analysis was performed to identify factors associated with myocarditis. Clinically relevant factors with a P-value < 0.2 on bivariate logistic regression analysis were incorporated into a multivariate logistic regression analysis. Statistical analyses were done using SPSS version 15 and Stata 11 statistical package (Statacorp, College Station, Texas, United States).

RESULTS

Baseline characteristics

During the study period, 122 patients with suspected scrub typhus were screened for myocarditis; 103 patients were diagnosed with scrub typhus based on presentation as AFI, a positive IgM ELISA for scrub typhus, and exclusion of other diagnoses. Nineteen patients were excluded due to poor echo window and three patients were excluded because they did not consent for the study. Therefore, the study cohort comprised of 81 patients (35 males) with a mean (± SD) age of 49.4 ± 16.1 years, who presented 8.1 ± 3.1 d after symptom onset. All patients presented with fever; dyspnea was present in 52 (76.5%) patients. Diabetes mellitus was the most common co-morbid condition (23.5%). Baseline characteristics are summarized in Table 1.

On examination, an eschar was present in 62 (77%) patients. Involvement of two or more organ systems was present in 79 (97.5%), and 7 (8.6%) had involvement of all six organ systems. Respiratory and cardiovascular system involvements were present in 90.1% and 62.9%, respectively. Forty-eight (59%) patients required mechanical ventilatory support and three (3.7%) patients required dialysis.

Cardiac parameters

Cardiac parameters are summarized in Table 2. Sinus tachycardia was the most common ECG finding (46.9%). Fourteen patients had two abnormal findings in the ECG and 18 (22.2%) had a normal ECG. Twenty-five (30.9%) patients had myocardial dysfunction, and 50

Table 2 Comparison of cardiac parameters in patients with and without myocarditis

Parameter	With myocarditis (n = 10)	No myocarditis (n = 71)	P value
Electrocardiography finding, n (%)			
Sinus tachycardia	3 (30)	35 (49.3)	0.25
ST-T changes	2 (20)	8 (11.3)	0.43
T wave inversion	3 (30)	5 (7)	0.023[1]
QRS morphology changes	5 (50)	6 (8.5)	< 0.001[1]
Supraventricular tachycardia	0	1 (1.4)	0.70
Atrial fibrillation	0	3 (4.2)	0.51
Wide QRS tachycardia	0	1 (1.4)	0.71
Sinus bradyarrhythmia	1 (10)	4 (5.6)	0.59
Cardiac biomarker, mean (SD)			
CK-MB (ng/mL)	14.1 (18.1)	5.9 (7.1)	0.009[1]
Troponin T (pg/mL)	235.9 (475.2)	61.6 (136.5)	0.014[1]
Echocardiography finding, mean (SD)			
LVEF	41.6 (8.8)	59.8 (13.3)	< 0.001[1]
Cardiac index	2.7 (1.1)	2.6 (0.9)	0.79
Systemic vascular resistance	2417 (1280)	2354 (891)	0.85
E/A	0.9 (0.2)	1.2 (0.4)	0.06
E/e′	9.9 (4.0)	9.8 (3.4)	0.94
CVP, cm	13.5 (5.3)	10.9±5.2	0.15

[1]Significant value. SD: Standard deviation; CK-MB: Creatinine kinase muscle brain iso-enzyme; LVEF: Left ventricular ejection fraction; E/A: The ratio between heights of early and late diastolic flow velocity peaks; E/e′: The ratio between early mitral inflow velocity and mitral annular early diastolic velocity; CVP: Central venous pressure.

(61.7%) patients had myocardial injury. Myocarditis was diagnosed in ten (12.3%) patients. In addition, 12 patients had regional wall motion abnormality (RWMA) with seven patients manifesting myocardial injury and an LVEF of < 50%. Eighteen (22%) patients had evidence of diastolic dysfunction. Mild to moderate pericardial effusion was seen in 41 (51%) patients.

Sixty-seven patients had hypotension at recruitment; however, only 46 (56.8%) patients required vasoactive agents. In these 67 patients, echocardiographic parameters of cardiac index, SVRI and CVP calculated from IVC variability were used to categorize shock. In patients with myocarditis (n = 10), the clinical picture was cardiogenic shock in four patients, septic (vasoplegic) shock in two patients, and mixed shock in four patients. In the seven patients with RWMA with myocardial dysfunction, four had features of cardiogenic shock, two had features of septic shock, and and one had mixed shock. Of the remaining patients, 22 had features of cardiogenic shock and six had features of septic shock while mixed type of shock was seen in 22.

Outcomes

Forty-nine (60.5%) patients required intensive care; 48 were mechanically ventilated. Thirty-nine patients required invasive ventilation, 15 required non-invasive ventilation, and seven were treated with both invasive and non-invasive ventilation. The mean (± SD) durations of ICU and hospital stay were 4.2 ± 4.4 and 9.2 ± 4.7 d, respectively. The overall hospital mortality, which included two patients discharged at request, was 9.9%. Myocarditis was associated with a significantly higher (P = 0.024) number of patients requiring vasoactive agents. The need and duration of ventilation, length of stay, and mortality were not significantly different between those who developed myocarditis and those who did not (Table 3).

Factors associated with myocarditis

On bivariate logistic regression analysis (Table 4), patients with myocarditis tended to have shorter duration of symptoms prior to presentation to hospital (P = 0.16), higher organ dysfunction scores as assessed by SOFA (P = 0.16), and a longer stay in hospital (P = 0.10) when compared with those who did not develop myocarditis. Myocarditis was not associated with mortality (P = 0.99).

On multivariate logistic regression analysis incorporating age, duration of symptoms, SOFA score, and hospital length of stay, myocarditis was independently associated with shorter duration of symptoms (OR = 0.69, 95%CI: 0.49 to 0.98, P = 0.04). However, age and longer hospital stay only tended to be associated with myocarditis (Table 4). The "goodness of fit statistic" (Hosmer Lemeshow test, P = 0.238) was used to validate the regression analysis.

DISCUSSION

Scrub typhus is a common cause of AFI with multi-organ dysfunction in India. There is a paucity of literature on the spectrum of cardiac manifestations and its impact on outcome in scrub typhus. In this prospective study of 81 patients admitted with scrub typhus infection, cardiac manifestations ranged from non-specific ECG changes to pericarditis, myocarditis, and circulatory shock.

We observed, in our cohort, that ECG changes were non-specific. The most common ECG finding was sinus tachycardia (46.9%). Three patients had atrial fibrillation, while five had sinus bradycardia and one

Table 3 Outcomes in patients with and without myocarditis in scrub typhus infection

Characteristic	With myocarditis (n = 10)	No myocarditis (n = 71)	P value
Outcome variable, n (%)			
Needing ventilation	7 (70)	41 (57.7)	0.46
Non-invasive ventilation	3 (30)	12 (16.9)	0.32
Invasive ventilation	5 (50)	34 (47.9)	0.90
Duration of ICU stay, mean (SD), d	5.0 (4.8)	4.0 (4.4)	0.53
Length of hospital stay, mean (SD), d	11.6 (5.7)	8.9 (4.5)	0.10
Needing dialysis	1 (10)	2 (2.8)	0.26
Needing vasoactive agent	9 (90)	37 (52.1)	0.024[1]
Mortality	1 (10)	7 (9.9)	0.99

[1]Significant value. SD: Standard deviation; *n*: Number of patients; ICU: Intensive care unit.

Table 4 Bivariate and multivariate logistic regression analyses of factors associated with myocarditis in scrub typhus infection

Variable	Bivariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.03 (0.99-1.08)	0.14	1.04 (0.99-1.09)	0.08
Gender	0.73 (0.19-2.76)	0.64		
Symptom duration	0.84 (0.65-1.07)	0.16	0.69 (0.49-0.98)	0.04
APACHE-Ⅱ score	1.03 (0.94-1.13)	0.49		
SOFA score	1.13 (0.95-1.34)	0.16	1.12 (0.89-1.41)	0.32
Need for ventilation	1.71 (0.41-7.15)	0.46		
Hospital length of stay	1.11 (0.98-1.27)	0.10	1.17 (0.98-1.40)	0.09
Mortality	1.02 (0.11-9.25)	0.99		

Variables with a P-value < 0.2 were incorporated into the multivariate logistic regression analysis; on multivariate logistic regression analysis, age and hospital length of stay tended to be associated with myocarditis while symptom duration was associated with myocarditis. Hosmer-Lemeshow goodness-of-fit test, P = 0.238. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment.

patient had a wide QRS tachycardia. ST-T and QRS morphology changes were observed in 12.3% and 13.6%, respectively. The ECG findings in our cohort are similar to the study by Watt *et al*[17], where findings were predominantly minor and non-specific.

Troponin T was used as the biomarker to indicate myocyte injury, since it is a more sensitive marker in patients clinically suspected to have myocarditis[18]. Myocardial injury was diagnosed in 50 (61.7%) patients. Since troponin can be elevated in several conditions other than myocardial injury in critically ill patients[19], the incidence of myocardial injury may have been overestimated in our cohort, particularly in patients with renal failure (n = 16). However, myocarditis was presumed only if myocardial injury coexisted with global myocardial dysfunction. Thus, it is unlikely that the prevalence of myocarditis in our study (12.3%) was affected by a possible overestimation of myocardial injury. It is also interesting to note that troponin T was elevated in 17 patients without any evidence of myocardial dysfunction or renal failure.

Echocardiogram is a key non-invasive tool in detecting impaired LV function in suspected myocarditis, even when subclinical[7,18]. Depressed LVEF was observed in 25 (30.9%) patients. RWMA was seen in 12 patients, of whom seven had a LVEF of < 50%. Although the presence of new RWMA with myocardial injury would suggest myocardial infarction, it is possible that in this clinical setting, it could also indicate focal myocarditis in these seven (8.6%) patients. However, this was not explored further.

LV diastolic dysfunction has not been previously described in scrub typhus. Eighteen patients had evidence of diastolic dysfunction; however, only two had E/e' > 15. Pericardial involvement has been reported in autopsy studies, case reports[7,20], and case series[21]. We observed mild to moderate pericardial effusion in 41 (51%) patients. However, none developed cardiac tamponade requiring intervention.

Forty-nine (60.5%) patients required intensive care admission. The proportion of patients presenting in shock in our study (56.8%) was higher than those of the earlier reports by Varghese *et al*[2] and Chrispal *et al*[1] (23.1% and 13.8%, respectively). This is likely due to selection bias of possibly excluding less sick patients, as outlined in the methods. However, it is interesting to note that the mortality in our cohort (9.9%) is similar to an earlier study (9%)[2] and much lower than that of a study that included only critically ill patients (24.1%)[3].

The frequency of occurrence of myocarditis in our adult cohort of patients with scrub typhus (12.4%) is lower than the 34% reported in the pediatric subset[5]. The high frequency of occurrence in the pediatric study[5] was attributed to the late presentation. In our study, myocarditis was associated with a trend to shorter duration of symptoms and higher SOFA score (Table 4). However,

APACHE-Ⅱ score was not associated with myocarditis. There was no gender predilection to the development of myocarditis. On the other hand, there was a trend of increasing occurrence of myocarditis with increasing age. Myocarditis was not associated with an increased need for mechanical ventilatory support but tended to be associated with longer period of hospital stay. Further, myocarditis was not associated with increased mortality. On multivariate logistic regression analysis, myocarditis was associated with shorter duration of symptoms prior to presentation and prolonged hospitalization. Generally, myocarditis is thought to be a rare but serious complication of scrub typhus resulting in high mortality and presenting later[1,2,8]. The shorter duration of symptoms in those with myocarditis in our study may indicate earlier presentation in those who develop more severe symptoms.

The lack of association between myocarditis and mortality in our study contradicts the observations of Taylor *et al*[8], who in a systematic review pooling data of four studies showed a significant association between myocarditis and mortality. The low mortality in our relatively small cohort (n = 81) may explain this difference. Further, as described in that review[8], the diagnosis of myocarditis was made in the majority of studies based on clinical parameters and was not based on echocardiographic evaluation and cardiac enzyme elevation. This could have resulted in misclassification and a higher incidence of myocarditis. It is also likely that our study was not powered adequately to detect an association between myocarditis and mortality, since the sample size was calculated assuming an incidence of myocarditis of 30%. The smaller sample size also limited our ability to incorporate all clinical symptoms in the multivariate logistic regression analysis.

In scrub typhus infection, cardiac manifestations are frequent and are associated with increased morbidity but not mortality. Early recognition and focused management of cardiac complications may help reduce morbidity and mortality associated with scrub typhus infection. Histopathological studies may further clarify the understanding of the pathophysiology of cardiac manifestations in scrub typhus infection.

ARTICLE HIGHLIGHTS

Research background

Scrub typhus, a rickettsial infection caused by *Orientia tsutsugamushi*, is endemic in India, with mortality rates of up to 24% in critically ill cohorts. Although cardiac involvement has been described in scrub typhus infection, the literature is devoid of prospective studies on the nature and extent of cardiac involvement and its impact on outcomes. This study characterizes the cardiac manifestations in scrub typhus infection. Myocarditis was associated with shorter symptom duration but not with mortality.

Research motivation

Scrub typhus is endemic in the southern states of India, with a high case burden next only to malaria and dengue in the list of tropical infections. Disease occurrence is seasonal with peak during monsoons. It is associated with significant morbidity and mortality. Organ dysfunction is common and necessitates intensive care admission. This subject being tropical was considered for study.

Research objectives

The primary objectives were to study the spectrum of cardiac manifestations in scrub typhus infection and to estimate the incidence of myocarditis. The authors planned to compare the outcomes in scrub typhus patients with and without myocarditis and further to identify the factors contributing to the occurrence of myocarditis. This would help understand the disease process better and enable more focused research and treatment.

Research methods

This was a prospective observational study where all patients suspected to have scrub typhus were considered. Those patients with proven scrub typhus were enrolled and clinical characteristics, cardiac biomarkers, and electrocardiographic and echocardiographic findings were noted. Standard definitions were used for the diagnosis of myocardial injury, left ventricular dysfunction, and myocarditis. Myocarditis was correlated with outcomes.

Research results

Myocardial injury was evident in 61.7% of patients and LV systolic dysfunction in 30.9%. A diagnosis of myocarditis was made in 12.3%. On multivariate logistic regression analysis, patients with myocarditis tended to be older (OR = 1.04, 95%CI: 0.99-1.09), had shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98), and tended to stay longer in hospital (OR = 1.17, 95%CI: 0.98-1.40). Myocarditis was not associated with increased mortality.

Research conclusions

In scrub typhus infection, cardiac manifestations are frequent and are associated with increased morbidity but not mortality.

Research perspectives

Myocarditis was diagnosed clinically in many of the previous reported studies. The use of biomarkers and echocardiography might improve the robustness of the definitions. Scrub typhus patients with myocarditis presented early to the hospital and tended to stay longer. Further insight into pathogenesis needs to be addressed by histopathological studies.

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SYSTEMATIC REVIEWS

Respiratory mechanics, ventilator-associated pneumonia and outcomes in intensive care unit

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Abstract

AIM

To evaluate the predictive capability of respiratory mechanics for the development of ventilator-associated pneumonia (VAP) and mortality in the intensive care unit (ICU) of a hospital in southern Brazil.

METHODS

A cohort study was conducted between, involving a sample of 120 individuals. Static measurements of compliance and resistance of the respiratory system in pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV) modes in the 1st and 5th days of hospitalization were performed to monitor respiratory mechanics. The severity of the patients' illness was quantified by the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ). The diagnosis of VAP was made based on clinical, radiological and laboratory parameters.

RESULTS

The significant associations found for the development of VAP were APACHE Ⅱ scores above the average (P = 0.016), duration of MV (P = 0.001) and ICU length of stay above the average (P = 0.003), male gender (P = 0.004), and worsening of respiratory resistance in PCV mode (P = 0.010). Age above the average (P < 0.001), low level of oxygenation on day 1 (P = 0.003) and day 5 (P = 0.004) and low lung compliance during VCV on day 1 (P = 0.032) were associated with death as the outcome.

CONCLUSION

The worsening of airway resistance in PCV mode indicated the possibility of early diagnosis of VAP. Low lung compliance during VCV and low oxygenation index were death-related prognostic indicators.

Key words: Respiratory mechanics; Respiratory tract infection; Ventilator-associated pneumonia

Core tip: The results show that the respiratory function is a prognostic measure, and is strongly associated with mortality. Low oxygen and low lung compliance during volume-controlled ventilation demonstrate this fact. Worsening of respiratory system resistance during pressure-controlled ventilation, associated with the development of ventilator-associated pneumonia, indicates the possibility of early diagnosis. Based on this assumption, this procedure should be performed routinely in the intensive care unit environment, providing the intensive care physician and the physiotherapist with additional prognosis and diagnosis variables, in addition to the clinical, laboratory and radiological data.

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INTRODUCTION

Factors influencing the outcomes in intensive care unit (ICU) enable behaviors that can benefit the patient and reduce hospital costs[1,2]. Monitoring of respiratory mechanics in the admission of patients may provide an additional parameter for the monitoring of cases with possible epidemiological implications[3]. Invasive ventilatory support is a resource frequently used in extremely critical care, either to rescue breathing in patients unable to maintain the ventilatory demand, or as a strategy for energy saving in seriously ill patients[4]. Knowledge about respiratory mechanics may facilitate the detection of changes in the respiratory status of the patient and enable appropriate adjustment in ventilatory parameters, as well as support an appropriate therapeutic intervention to improve his or her clinical condition[5,6].

Few studies use these variables as prognostic measures in ICU[7]. The main applications of monitoring respiratory mechanics are performed on well-established cases, such as in patients with obstructive lung disease[8] and in patients with acute respiratory distress syndrome (ARDS)[9]. Some studies discuss the importance of these measures in patients with pulmonary fibrosis[10] or with the human immunodeficiency virus (HIV) infection and pneumonia[11].

The measurements of respiratory mechanics most frequently used are compliance and resistance of the respiratory system. Compliance is associated with distensibility of the respiratory system, which is resulting from the tidal volume variation divided by the peak inspiratory pressure. Resistance is related to the conduction of air, obtained mathematically from the variation between the peak and plateau pressures divided by the inspiratory airflow[12].

Ventilator-associated pneumonia (VAP) is the most common infection in ICU. This pulmonary condition may change the respiratory mechanics. Beyond the importance of the bundles of care for the prevention of VAP[13], information of compliance and resistance of respiratory system can provide additional data for an early diagnosis. The aim of this study was to assess the risk of changes in respiratory mechanics for determination of outcomes: development of VAP, and mortality in ICU.

MATERIALS AND METHODS

A cohort study was performed on adults in the intensive care unit of the of the Hospital Nossa Senhora da Conceição, located in Tubarão, State of Santa Catarina, Brazil. Individuals hospitalized between February and September 2013 who required invasive ventilatory support and whose family signed the informed consent were selected. The study was approved by the Human Research Ethics Committee of the University of Southern Santa Catarina (number 12.460.4.08.Ⅲ).

As this is a study of diagnostic and prognostic accuracy, the sample size was dimensioned for a prevalence of mortality[14] and VAP[15] of 20% (P = 0.2), with a 12% error (e = 0.12) in the 95% confidence interval ($Z_{\alpha/2}$ = 1.96). Sensitivity was defined 90% (Sens = 0.9). The equation[16] used is described below:

$$n_{sens} = \frac{(Z_{\alpha/2})^2\ Sens.(1\text{-}Sens)}{e^2.P} \approx 120$$

The following subjects were excluded from the study: Patients who were hospitalized in the ICU for cardiac surgery, those who developed pneumonia, died, or were extubated within 48 h of the onset of mechanical ventilation, those who were reintubated and those whose cause of orotracheal intubation was respiratory infection. The patients who were transferred to another ICU were excluded as well.

The following procedures were performed for the data collection: Day 1 (D1) - First 24 h of mechanical ventilation. APACHE Ⅱ[17] scoring, assessment of oxygenation index obtained from the PaO_2/FiO_2 ratio[18], and assessment of the respiratory system compliance and resistance were performed. The patients should score 5-6 in the Ramsay sedation scale[19] for measuring airflow compliance and resistance. Respiratory mechanic was measured in volume-controlled ventilation (VCV) and pressure-controlled ventilation (PCV)[20]. The equations for calculating respiratory mechanics were these:

Volume Control Ventilation (VCV)[20]

$$C_{RS} = \frac{V_T}{P_{Plat} - PEEP} \qquad R_{RS} = \frac{P_{Peak} - P_{Plat}}{F}$$

Pressure Control Ventilation (PCV)[16]

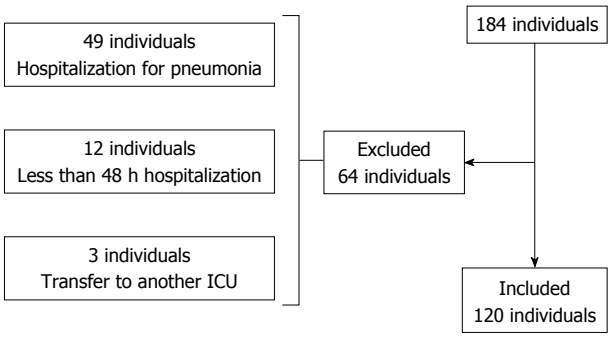

Figure 1 Flow chart of sample characterization.

Table 1 Characteristics of the sample

Sample characteristics (n = 120)	Results
Age (yr)	
Mean ± SD	58.5 ± 19.4
Minimum-maximum	15-91
Gender *n* (%)	
Male	69 (57.5)
Female	51 (42.5)
APACHE Ⅱ (score)	
Mean ± SD	27.4 ± 6.7
Minimum-maximum	8-47
Risk of mortality (%)-APACHE Ⅱ	
Mean ± SD	61.8 ± 7.3
Admission diagnoses *n* (%)	
Diseases of the circulatory system	43 (35.8)
Diseases of the respiratory system	15 (12.5)
Lesions, poisoning and other consequences of external causes	14 (11.7)
Gastrointestinal diseases	8 (6.7)
Unclassified signs and symptoms	8 (6.7)
Diseases of the genitourinary system	7 (5.8)
Neoplasia	4 (3.3)
Nervous system disorders	4 (3.3)
Infectious and parasitic diseases	3 (2.5)
Endocrine, nutritional and metabolic diseases	3 (2.5)
Other	11 (9.2)
Mechanical ventilators n (%)	
[1]Servo S	89 (74.2)
[1]Servo 900	203 (16.7)
[1]Dixtal	11 (9.2)

[1]Source: Prepared by the author, 2013.

$$C_{RS} = \frac{V_T}{P_{Insp} - PEEP} \qquad R_{RS} = \frac{P_{Insp} - PEEP}{F_{max}^{1,75}}$$

C_{RS}: Respiratory system compliance (mL/cmH_2O); R_{RS}: Respiratory system resistance (cmH_2O/L/s); PEEP: Positive end-expiratory pressure (cmH_2O); P_{Insp}: Inspiratory pressure (cmH_2O); P_{peak}: Peak inspiratory pressure (cmH_2O); P_{plat}: Plateau pressure (cmH_2O); V_T: Tidal volume (mL); F: Forced inspiratory flow (L/s); F_{max}: Peak inspiratory flow (L/s).

Day 5 (D5) - Assessment of the respiratory system compliance and resistance was performed as described above. If the patient were in the ventilatory weaning process, this measure would not be collected.

Patients were monitored until their discharge from the ICU or death. The duration of mechanical ventilation and length of ICU stay were taken into account, until the emergence of at least one of those outcomes.

VAP was diagnosed by the emergence of new or progressive pulmonary infiltrate on the chest X-Ray, associated with signs and laboratory alterations, such as fever (> 38 ℃), leukocytosis (> 10000/mm^3) or leukopenia (< 4000/mm^3), and purulent tracheal secretions[21].

Early VAP was performed when it was diagnosed within the first 5 d. Late VAP was considered when the diagnosis occurred after the sixth day[15].

Statistical analysis

Data were stored in a database using a Microsoft Excell® software, which was exported to SPSS® Statistics 20.0. They were presented using absolute numbers and percentages, and measures of central tendency and dispersion. The cutoff point for normal respiratory compliance and resistance was defined as the means obtained from the results.

The analysis of numerical data was performed primarily by the Kolmogorov-Smirnov test for normality. The results with normal distribution were compared using Student's *t*-test, and the non-normal distribution results by using the Mann-Whitney test[22]. The Chi-square test was used for categorical data analysis. Variable comparisons were made in relation to the VAP outcomes, mortality, ICU stay and duration of mechanical ventilation. The relative risk was estimated, by univariate analysis, for variables with statistical association. The confidence interval was set at 95% and a $P < 0.05$ was considered statistically significant.

Measurements of the oxygenation index and respiratory mechanics were performed by analyzing the worsening or improvement in these variables between D1 and D5.

A higher airflow resistance in D1 than in D5 was considered a better state. Reversely, a lower airflow resistance, a worse result.

RESULTS

A total of 184 patients who were hospitalized in the ICU of the Hospital Nossa Senhora da Conceição (Tubarão, State of Santa Catarina, Brazil) between February and September 2013 were consecutively monitored (Figure 1).

According to the selection criteria, 120 patients were allocated to participate in the study. Table 1 describes the general characteristics of the sample.

Oxygenation index and respiratory mechanics on days 1 and 5 are shown in Table 2. On the 5th day, only 77 of the 120 patients were monitored, because they were either extubated, weaned from mechanical ventilation, or had died by then.

The incidence of VAP was 31.8% (38 cases), with an infection density of 24/1000 d. The 38 cases of VAP, 19 (50%) were of early 19 (50%) were late. The overall mortality rate was 62 cases (51.7%). The mean length of stay in ICU was 15.2 ± 11.1 d and mean duration of mechanical ventilation was 13.1 ± 10.6 d.

Table 2 Respiratory mechanics and oxygenation index on the 1st and 5th day

Oxygenation index Respiratory mechanics	Mean ± SD	Minimum-maximum
1st day (n = 120)		
PaO_2/FiO_2 (mmHg)	236.0 ± 97.6	47.0-465.7
Compliance-VCV (mL/cm H_2O)	40.9 ± 12.8	15.0-88.0
Resistance-VCV (cm H_2O/L/s)	13.2 ± 4.9	4.1-28.6
Compliance-PCV (mL/cm H_2O)	35.0 ± 10.0	15.0-62.0
Resistance-PCV (cm H_2O/L/s)	27.3 ± 16.2	9.1-131.1
5th day (n = 77)		
PaO_2/FiO_2 (mmHg)	241.7 ± 88.7	58.0-445.0
Compliance-VCV (mL/cm H_2O)	39.7 ± 13.2	18.0-83.0
Resistance-VCV (cm H_2O/L/s)	13.8 ± 6.0	5.3-43.0
Compliance-PCV (mL/cm H_2O)	32.9 ± 9.3	13.5-52.5
Resistance-PCV (cm H_2O/L/s)	26.4 ± 11.8	6.2-73.5

Source: Prepared by the author, 2013. VCV: Volume-controlled ventilation; PCV: Pressure-controlled ventilation.

Table 3 Numeric variables and ventilator-associated pneumonia

Variables	VAP		*P* value
	Yes	No	
APACHE II[1]	29.2 ± 5.6	26.5 ± 7.1	0.026
Age (yr)	57.1 ± 19.1	59.2 ± 19.6	0.565
1st day (n = 120)			
PaO_2/FiO_2 (mmHg)[1]	232.3 ± 79.9	237.8 ± 105.2	0.756
Compliance-VCV (mL/cmH_2O)	43.1 ± 14.9	39.8 ± 11.6	0.365
Resistance-VCV (cmH_2O/L/s)	13.7 ± 5.0	13.0 ± 4.8	0.594
Compliance-PCV (mL/cmH_2O)[1]	34.8 ± 10.4	35.1 ± 9.8	0.879
Resistance-PCV (cmH_2O/L/s)	23.6 ± 10.3	29.0 ± 18.1	0.114
5th day (n = 77)			
PaO_2/FiO_2 (mmHg)[1]	244.1 ± 94.1	240.2 ± 86.1	0.850
Compliance-VCV (mL/cmH_2O)	43.3 ± 14.0	37.6 ± 12.3	0.092
Resistance-VCV (cmH_2O/L/s)	13.9 ± 6.8	13.8 ± 5.5	0.996
Compliance-PCV (mL/cmH_2O)[1]	33.6 ± 8.9	32.5 ± 9.6	0.606
Resistance-PCV (cmH_2O/L/s)	27.1 ± 11.7	25.9 ± 12.0	0.777
(n = 120)			
Duration of MV (d)	18.4 ± 14.9	10.7 ± 6.8	0.001
Length of stay in ICU (d)	20.4 ± 15.3	12.8 ± 7.6	0.003

Mann-Whitney *U*-test; [1]Student's *t*-test. Source: Prepared by the author, 2013. VAP: Ventilator-associated pneumonia; VCV: Volume-controlled ventilation; PCV: Pressure-controlled ventilation; MV: Mechanical ventilation; ICU: Intensive care unit.

Tables 3 and 4 shows the numeric variables compared with VAP rates and outcomes: Mortality.

Table 5 presents the relative risk estimate for the variables that demonstrated statistical association with VAP and the outcomes.

DISCUSSION

The general characteristics of the sample were similar to those of other studies on ICU, *i.e.*, most individuals were male and the mean age exceeded middle age[14,23,24].

Among the surveyed patients, the severity of disease classified by the APACHE II was considered relatively high. A research carried out by Wunsch *et al*[14] analyzed the clinical and epidemiological characteristics of over 170000 patients from 160 ICUs in England and 137 ICUs in the United States. In the United States, the mean APACHE II score was 15.3 ± 8, and for mechanically ventilated subjects, the score was 20.1 ± 8.9. In England, these scores were significantly higher, reaching 20.5 ± 8.5 in the APACHE II score and 22.3 ± 8.2 for individuals undergoing artificial respiration.

A study conducted by Matic *et al*[25] assessed the influence of the APACHE II score on the selection of the mechanical invasive or non-invasive ventilatory support. The median APACHE II score was 24 in the group that received non-invasive mechanical ventilation, and 26 in the group that required invasive support. These data corroborate the findings of the present study, despite the fact that higher APACHE II scores indicate a more severe clinical condition in patients requiring invasive mechanical ventilatory support. However, the disease severity is related to the characteristics of each ICU, and comorbidities may influence the score, and consequently, the outcomes[26].

With respect to the most common causes of hospitalization in the ICU, the results of this study are in line with the research carried out by Wunsch *et al*[14], in which the main reasons were of cardiac origin (44.6% in the United States and 27.1% in England), followed by respiratory (20.2% in the United States and 26.3% in England), neurological (19, 1% in the United States. and 24.1% in England) and gastrointestinal (9.5% in the United States and 10.1% in England) causes. These results may differ according to the characteristics of each ICU[27,28].

The length of stay in the ICU and duration of MV were relatively high. According to a review study by Elliott[29], the length of stay for all patient profiles can vary from 2 to 13 d, according to the ICU and the severity of cases. A study by Esteban *et al*[30] that analyzed the characteristics and outcomes of adult patients requiring mechanical ventilation indicated an average length of stay in the ICU and duration of MV of 13.7 and 7.2 d, respectively. A study by Matic *et al*[25], also in mechanically ventilated patients, found an average duration in MV of 7 d, and length of stay in ICU of 8.5 d. A Brazilian multicenter study sample consisting of 775 adult patients from 45 ICUs showed that the average length of stay in ICU among subjects requiring only non-invasive ventilation was 7 d. Those who required invasive ventilatory support stayed for 13 d on average[31].

The data regarding the incidence of VAP in the present study were similar to those found in the literature. A review conducted by Joseph *et al*[15] demonstrated that the incidence can vary from 6% to 52%. The density of VAP infection described in the systematic review by Arabi *et al*[32] may vary from 10 episodes per 1000 ventilator days, such as in Thailand and Columbia, to 41.7 episodes per 1000 ventilator days in a cancer ICU in Brazil.

By comparing the significant associations of the variables for the development of VAP, it was observed that the APACHE II was a predictor, indicating that

Table 4 Numeric variables and death

Variables	Outcome		*P* value
	High	Death	
APACHE Ⅱ[1]	27.0 ± 7.6	27.7 ± 5.8	0.606
Age (yr)	51.1 ± 19.9	65.4 ± 16.1	< 0.001
1st day (n = 120)			
PaO_2/FiO_2 (mmHg)[1]	263.1 ± 100.9	210.7 ± 87.8	0.003
Compliance-VCV (mL/cm H_2O)	43.5 ± 12.5	38.4 ± 12.6	0.015
Resistance-VCV (cm H_2O/L/s)	13.3 ± 4.3	13.2 ± 5.4	0.935
Compliance-PCV (mL/cm H_2O)[1]	36.6 ± 9.8	33.6 ± 9.9	0.103
Resistance-PCV (cm H_2O/L/s)	25.0 ± 10.5	29.4 ± 20.0	0.416
5th day (n = 77)			
PaO_2/FiO_2 (mmHg)[1]	268.8 ± 81.9	214.7 ± 87.9	0.004
Compliance-VCV (mL/cm H_2O)	40.7 ± 12.7	38.7 ± 13.7	0.356
Resistance-VCV (cm H_2O/L/s)	14.2 ± 5.0	13.5 ± 6.9	0.22
Compliance-PCV (mL/cm H_2O)[1]	34.1 ± 9.4	31.8 ± 9.1	0.282
Resistance-PCV (cm H_2O/L/s) (n = 120)	25.7 ± 10.8	27.1 ± 12.9	0.76
Duration of MV (d)	14.5 ± 12.4	11.9 ± 8.6	0.212
Length of stay in ICU (d)	18.3 ± 12.5	12.4 ± 8.9	< 0.001

Mann-Whitney *U*-test; [1]Student's *t*-test. Source: Prepared by the author, 2013. VCV: Volume-controlled ventilation; PCV: Pressure-controlled ventilation; MV: Mechanical ventilation; ICU: Intensive care unit.

Table 5 Relative risk for ventilator-associated pneumonia and outcomes

Variables	RR	95%CI	*P* value
VAP			
APACHE II above the average	1.62	1.03-2.55	0.016
Male gender	1.56	1.18-2.08	0.004
Resistance worsening-PCV	1.85	1.16-2.94	0.01
Outcome: Death			
Age above the average	2.08	1.34-3.23	0.001
Compliance-VCV below average on 1st day	1.49	1.00-2.21	0.032
ICU stay below the average	2.05	1.28-3.28	0.001

Source: Prepared by the author, 2013. VAP: Ventilator-associated pneumonia; VCV: Volume-controlled ventilation; PCV: Pressure-controlled ventilation; ICU: Intensive care unit.

severe disease in ICU admission favors the occurrence of VAP. Other studies show no association; however, they describe that higher APACHE Ⅱ scores are related to higher mortality when applied at the time of VAP diagnosis[33,34].

A longer ICU stay and VM duration are also associated with VAP as demonstrated in this study, which is commonly presented in other works as well. Guimarães *et al*[35] evaluated 278 patients in a Brazilian university hospital, and reported a significant difference between the group with and without VAP, having stayed in the ICU for 14 and 5 d, respectively. Patients with spinal cord injury who require prolonged mechanical ventilation also had a higher incidence of VAP due to the increased length of ICU stay and MV dependence[36].

As evidenced in this study, the risk for the development of VAP is higher in men than women. According to Tejerina *et al*[37], 2897 patients from 361 ICUs were surveyed in 20 countries, in which it was shown that men have a relative risk of 1.3 for the occurrence of VAP compared with women.

Worsening resistance during PCV was related to VAP, possibly indicating increased airway inflammation and/or an increase in bronchopulmonary secretions, which is consistent with the pathophysiological mechanism of respiratory infection[21]. A worsening of lung compliance in subjects who developed VAP was also expected, but it did not occur. A study by Lorx *et al*[38] analyzed patients admitted to the ICU because of community-acquired pneumonia stratified into mild and severe conditions. Using low frequency forced oscillometry technique, it was observed that elastance, which is inversely proportional to compliance, was significantly higher in patients with severe pneumonia compared with those who had mild pneumonia. This evidence demonstrates the restrictive aspect of pneumonia, which was not found in the present study.

Monitoring of respiratory mechanics can assist the intensive care physician to detect early changes in lung function, associating them with the evolution of the ventilation status, and present scores associated with increased risk of mortality and VAP development. In addition, monitoring of mechanical breathing is performed at the bedside, does not involve patient transport, and has no financial cost to be implemented.

The results of the respiratory mechanics of the present study demonstrated a lower compliance and a higher resistance than the predicted values[3,6,12]. This may demonstrate a reduction in lung function of the participants. Advanced age was statistically associated with death as the outcome, which was also observed in other studies[23,30]. Low levels of oxygenation in the 1st and 5th days was also related to mortality, which corroborates the study by Eastwood *et al*[39] and de Jonge *et al*[40] that found an association between low levels of oxygenation in the first 24 h and mortality rates in their retrospective observational studies. Low pulmonary compliance during VCV on day 1 also indicated a prediction of mortality in individuals with low pulmonary distensibility. A study by Matić *et al*[7] monitored the static pulmonary compliance with intraesophageal balloon before intubation. It was shown that poor lung compliance was associated with high mortality rates.

It was expected that the incidence of VAP and higher APACHE Ⅱ scores were associated with mortality, which was not observed. Generally, VAP is associated with higher mortality rates[15]; however, Tejerina *et al*[37] found no significant differences between the groups with and without VAP, with an incidence of 38.1% and 37.9%, respectively.

The limitation of this study was the monitoring of respiratory mechanics with sedated patients and not with neuromuscular block. This may have a small influence on the results.

In conclusion, monitoring of the mechanical aspects of lung function is already commonly used in well-established groups with chronic obstructive pulmonary disease and ARDS. It is a simple procedure performed at the bedside, without any physical damage and

no additional cost. Based on this assumption, this procedure should be performed routinely in the ICU environment, providing the intensive care physician and the physiotherapist with additional prognosis and diagnosis variables, in addition to the clinical, laboratory and radiological data.

The results show that the respiratory function is a prognostic measure, and is strongly associated with mortality. Low oxygen and low lung compliance during VCV demonstrate this fact. Worsening of respiratory system resistance during PCV, associated with the development of VAP, indicates the possibility of early diagnosis.

ARTICLE HIGHLIGHTS

Research background

The measurements of respiratory mechanics most frequently used are compliance and resistance of the respiratory system. Compliance is associated with distensibility of the respiratory system, which is resulting from the tidal volume variation divided by the peak inspiratory pressure. Resistance is related to the conduction of air, obtained mathematically from the variation between the peak and plateau pressures divided by the inspiratory airflow.

Research motivation

The aim is evaluate the predictive capability of respiratory mechanics for the development of VAP and mortality in the intensive care unit (ICU) of a hospital in southern Brazil.

Research objectives

Respiratory mechanics, ventilator-associated pneumonia.

Research methods

A cohort study was conducted between, involving a sample of 120 individuals. Static measurements of compliance and resistance of the respiratory system in pressure-controlled ventilation (PCV) and volume-controlled ventilation (VCV) modes in the 1st and 5th days of hospitalization were performed to monitor respiratory mechanics. The severity of the patients' illness was quantified by the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ). The diagnosis of VAP was made based on clinical, radiological and laboratory parameters.

Research results

The significant associations found for the development of VAP were APACHE Ⅱ scores above the average (P = 0.016), duration of MV (P = 0.001) and ICU length of stay above the average (P = 0.003), male gender (P = 0.004), and worsening of respiratory resistance in PCV mode (P = 0.010). Age above the average (P < 0.001), low level of oxygenation on day 1 (P = 0.003) and day 5 (P = 0.004) and low lung compliance during VCV on day 1 (P = 0.032) were associated with death as the outcome.

Research conclusions

The worsening of airway resistance in PCV mode indicated the possibility of early diagnosis of VAP. Low lung compliance during VCV and low oxygenation index were death-related prognostic indicators.

Research perspectives

The results show that the respiratory function is a prognostic measure, and is strongly associated with mortality.

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ORIGINAL ARTICLE

Clinical Practice Study

Confidence level of pediatric trainees in management of shock states

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Abstract

AIM

To assess overall confidence level of trainees in assessing and treating shock, we sought to improve awareness of recurrent biases in clinical decision-making to help address appropriate educational interventions.

METHODS

Pediatric trainees on a national listserv were offered the opportunity to complete an electronic survey anonymously. Four commonly occurring clinical scenarios were presented, and respondents were asked to choose whether or not they would give fluid, rank factors utilized in decision-making, and comment on confidence level in their decision.

RESULTS

Pediatric trainees have a very low confidence level for assessment and treatment of shock. Highest confidence level is for initial assessment and treatment of shock involving American College of Critical Care Medicine/Pediatric Advanced Life Support recommendations. Children with preexisting cardiac comorbidities are at high risk of

under-resuscitation.

CONCLUSION

Pediatric trainees nationwide have low confidence in managing various shock states, and would benefit from guidance and teaching around certain common clinical situations.

Key words: Fluid bolus; Shock; Medical education; Central venous pressure; Decision-making; Pediatric advanced life support guidelines

Core tip: Pediatric trainees at all levels of training across the United States express a low degree of confidence in management of various types of shock. Children with cardiac comorbidity are at very high risk of under-resuscitation when presenting with shock. Central venous pressure is often used in isolation for decision-making regarding fluid administration and supersedes other subjective and objective measures of intravascular fluid status and shock state.

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INTRODUCTION

Fluid resuscitation of hypovolemic shock has been hailed as acute medicine's great triumph for children[1]. A fluid bolus is one of the most rapid ways to increase cardiac output and is central in the management of many shock states. Recognition and timely resuscitation of shock with fluid is one of the most important aspects of training in pediatrics, and one that all trainees must be empowered to feel confident managing. It has been well established that appropriate early treatment of shock is associated with improved outcomes[2,3]. Pediatric resident and fellow physicians are often the first responders at the bedside of an acutely ill child. They may be assessing the patient for the first time in the emergency room, or might be called upon to assess a patient for a change in vital signs. We were interested in exploring the grey zone in decision-making - everyone would elect to continue fluid resuscitation in the face of obvious hypotension - however, in practice, the blood pressure drops very late in the evolution of shock in children, and we were interested in finding out how trainees navigate the period before profound shock develops.

Though there is some literature on level of adherence to Pediatric Advanced Life Support (PALS) guidelines and outcomes[4,5], there is a paucity of literature on the ability of pediatric trainees to correctly assess and treat shock states of varying etiologies. Variable heart rates and blood pressure thresholds for varying ages in children make it more challenging to recognize deviations from normal, often confounded by factors such as fever and beta agonist administration. While comorbid cardiomyopathy engenders a more cautious approach to fluid bolus administration, fear of fluid overload might hamper adequate resuscitation. The American College of Critical Care Medicine (ACCM) guidelines[6] recommend resuscitation end-points based on the difference between mean arterial pressure (MAP) and central venous pressure (CVP), mixed venous saturation ($ScVO_2$) and hemoglobin level, along with clinical exam findings. CVP has long been shown to have no utility as a marker of fluid responsiveness, yet continues to be considered as a factor in decision-making. We framed these potential stumbling blocks as clinical situations that may be widely prevalent in clinical practice as a survey for a nationwide sample of pediatric trainees. We sought to assess the confidence level of residents in the assessment and treatment of shock.

Our aim in performing this research was to assess overall confidence level of trainees in assessing and treating shock. We sought to improve awareness of recurrent biases in clinical decision-making to help address appropriate educational interventions. There is extensive literature on cognitive biases affecting decision-making in medicine[7,8], however we are not aware of any studies dealing with decision-making aspects in the management of children in the emergency room or critical care environment. There are situations where closer supervision and clinical guidance may improve earlier detection of shock in the critically ill child.

MATERIALS AND METHODS

We designed a survey tool using REDCap[9], an online electronic survey tool. We obtained approval from the Institutional Review Board at the Children's National Health System and by the American Academy of Pediatrics (AAP) Section on Medical Students, Residents and Fellowship Trainees (SOMSRFT). The survey was then distributed via the AAP SOMSRFT listserv to all members currently having valid email addresses and registered with this section of the AAP, with an additional reminder email after a few weeks. Participation in the survey was voluntary and anonymous.

We collected demographic information including current role (medical student, resident or fellow), level of training based on postgraduate year (PGY-1, 2, 3, *etc.*) and area of specialty (for fellows). This was followed by four hypothetical case scenarios based on the recognition and management of shock. Table 1 details the clinical case presented and expected outcomes. The clinical description was followed by a set of questions including (1) Course of action the trainee would choose: fluid/

vasoactive/neither/other; (2) clinical factors taken into consideration - ranked on a Likert scale for importance; (3) level of confidence in decision ranked on a Likert scale; and (4) comments/reasoning if any. We performed additional analysis after stratification of the respondents into two groups - experts and non-experts. We classified fellows in pediatric critical care, pediatric emergency medicine and pediatric hospital medicine as experts in fluid resuscitation. All other respondents were non-experts.

Statistical analysis

Data were directly available on REDCap, and descriptive statistics were generated using this tool. Additional statistical functions were performed using SPSS v 21.0 (IBM). We used the χ^2 test to detect differences in categorical variables among groups and the Mann Whitney *U* test to detect differences between the distributions among groups.

RESULTS

There were a total of 539 respondents, with demographic characteristics shown in Table 2. For the purpose of this study, we excluded responses from medical students and attending physicians, thus analyzing a total of 490 responses. There was an even distribution of residents and fellows across all levels of training. Of the fellows, pediatric critical care medicine and pediatric emergency medicine fellows accounted for the majority of respondents. Trainees' clinical decisions in each of the four hypothetical scenarios are detailed in Table 3. Table 4 illustrates different choices selected by experts compared to non-experts for all the four scenarios.

In scenario 1, 85% of respondents chose to continue resuscitation of shock, with an even split of respondents choosing fluid (38%) or vasoactive (47%). Most people cited the ACCM/PALS guideline cutoff of 60 mL/kg for fluid administration as the rationale for choosing vasoactives over fluid. Of the remaining 15%, 9% of respondents required additional data before determining course of action - including mental status, urine output, signs of fluid overload and ultrasound measures of fluid status. Six percent of respondents chose to halt resuscitation. The most common reason cited for stopping resuscitation was to give antipyretic and evaluate heart rate response as tachycardia could be due to presence of fever. Other reasons were "normal blood pressure", giving Ⅳ fluids at higher than maintenance rate to treat shock and avoidance of pulmonary edema. Thirty-six percent of respondents said they had only slight confidence in their decision. There was no correlation of low confidence level with primary decision taken.

For scenario 2, 80% of respondents chose to continue resuscitation of shock, with 20% choosing fluid and 60% choosing vasoactives. The most common reason cited for not continuing resuscitation was interpretation of CVP as normal. Other reasons included awaiting chest X-ray to evaluate for pulmonary edema, echocardiogram for assessing cardiac function, and assessing adequacy of urine output. In this case, 65% of respondents were only slightly confident of their decision. Of respondents who chose to halt resuscitation or obtain additional data first, 76% (70 out of 92) expressed low confidence, compared to those who chose to give either fluid or vasoactive, where 60% expressed low confidence.

For scenario 3, 39% of total respondents choose to give additional fluid, 15% would give a vasoactive, and 46% elect to not continue resuscitation. The most common reason by far for not continuing resuscitation is the known cardiac comorbidity, with several trainees requiring an echocardiogram to evaluate for cardiac function first. The next most common factor cited is the presence of fever, and several respondents want to reevaluate the degree of tachycardia after fever has subsided. Other reasons for slowing or halting resuscitation include obtaining a chest X-ray, cultures and antibiotics, and transfer to the pediatric intensive care unit. Sixty-four percent of all respondents express poor confidence in decision. In this case, prevalence of low confidence level is the same - at 64% in all respondents regardless of whether or not they pursue to continue resuscitation or delay/halt resuscitation.

For the patient in scenario 4, 43% of respondents elected to not perform any additional intervention, 29% chose to give a fluid bolus and 20% elected to increase vasoactive support. By far the most common reason for administration of fluid or increasing vasoactive dose was the CVP value. A majority of respondents (61%) expressed low confidence in their decision.

DISCUSSION

Early identification and rapid reversal of shock has been well documented to improve outcomes. We surveyed pediatric residents and fellows to assess how they made decisions regarding treatment of shock, and uncovered some commonly prevalent biases and errors in management.

The first scenario describes a 5-year old who is clearly presenting in shock, with end-organ dysfunction manifested by altered mental status. She has already received the initial 60 mL/kg of fluid. Per the ACCM guidelines[6], fluid resuscitation should be continued until signs of pulmonary overload occur or shock is reversed, defined by achieving threshold heart rate (HR) and MAP-CVP values, which were not yet achieved in this girl. In our experience, the initial 60 mL/kg is given automatically, and then there is some complacency while the patient awaits transfer to the intensive care unit (ICU). This can be thought of in terms of "premature closure" and "representativeness", where a diagnostic category is assigned to the patient and clinical response after 60 mL/kg of fluid is taken for granted, as this amount would suffice for most patients. Ideally, central

Table 1 Clinical case scenarios and outcomes studied

Case	Scenario description	Clinical questions	Key clinical features	Expected interventions	Outcomes studied
1	A 5 yr-old girl is brought into the emergency department with fever, diarrhea and vomiting. She is drowsy and does not answer questions appropriately. Her vitals are as follows: Temp 38.4 ℃, HR 168/min, RR 36/min, BP 90/45 (MAP 60) mmHg. She seems dehydrated with dry mucous membranes, is warm, flushed and has flash capillary refill. You diagnose septic shock and after getting two good Ⅳ lines for access, begin rapid fluid administration. You give her 60 mL/kg crystalloids over a period of 60 min, and one dose of antibiotics. At the end of this time, her vitals are as follows: Temp 38.4 ℃, HR 165/min, RR 32/min, BP 96/40 (MAP 59) mmHg, capillary refill unchanged. What would be your next plan of action?	What would be your next plan of action (1) Do nothing at this point; (2) give an additional 20 mL/kg fluid bolus; (3) start a vasoactive medication; (4) need additional data to decide- please specify; (5) Other What factors were used for decision making? HR/BP/Cap refill/ Response to fluid/ other (specify) How confident are you in decision on a scale of 0 (not confident at all) to 4 (sure of decision)	Severe shock with altered mental status Ongoing shock with HR and MAP not at threshold levels per ACCM-PALS guidelines	Continue resuscitation with either fluid or vasoactive administration evaluate lactate, mixed venous saturations	Rationale in choosing fluid *vs* vasoactive, or vice versa Rationale for withholding resuscitation Confidence level in decision-making
2	You are caring for a 4 yr old in the PICU with severe septic shock due to lobar pneumonia. His first night of admission he received 60 mL/kg of crystalloids and 20 mL/kg of 5% albumin. When you see him this morning, he is barely arousable and has a cap refill time of 5 s. You insert an internal jugular line and a radial arterial line. His vitals at this time are as follows: Temp 37.5 ℃, HR 152/min, RR 35/min, BP 100/45 (MAP 63) mmHg. His CVP is 8 mmHg. You obtain a blood gas from the A-line, and his lactate is 4.5 mmol/L. You decide to intubate to reduce oxygen consumption related to work of breathing. Despite adequate sedation, he persists to have tachycardia; vitals after intubation are as follows: Temp 37.5 ℃, HR 168/min, BP 110/40 (MAP 63) mmHg, CVP 10 mmHg, cap refill time 5 s. You immediately have to escalate to very high ventilator settings with pressure control of 34 and PEEP of 10 to achieve acceptable oxygenation and ventilation. What would your next intervention be?	What would be your next plan of action (1) Do nothing at this point; (2) give an additional 20 mL/kg fluid bolus; (3) start a vasoactive medication; (4) need additional data to decide- please specify; (5) Other What factors were used for decision making? HR/BP/CVP/Cap refill/Response to fluid/other (specify) How confident are you in decision on a scale of 0 (not confident at all) to 4 (sure of decision)	Worsening hemodynamics after initiation of positive pressure ventilation	Resuscitate shock with fluid or vasoactives	Recognition of decrease in preload caused by initiating of positive pressure ventilation Interpretation of CVP in conjunction with higher intrathoracic pressures
3	While rotating through the Hematology Oncology unit, you are called to the bedside of a 12-yr old receiving maintenance chemotherapy for AML. She has developed a temperature of 39.3 ℃. On exam she has a HR of 160/min, RR 32/min, BP 110/40 (MAP 63) mmHg, and cap refill of 3 s. She is known to have anthracycline-induced cardiomyopathy. You palpate her abdomen and notice that her liver is 3-4 cm, similar to earlier, she has no murmur or gallop, and a CVP transduced through her broviac is 6 mmHg. In the last 4 h, her urine output has reduced from 1.5 mL/kg·h to 0.3 mL/kg·h. You decide to cautiously give her a 10 mL/kg fluid bolus over half an hour to see the response. At the end of the bolus, her HR is now 154/min, BP is 106/46 (MAP 66) mmHg, CVP has increased to 8 mmHg. What would your next step be?	What would be your next plan of action (1) Do nothing at this point; (2) give an additional fluid bolus; (3) start a vasoactive medication; (4) need additional data to decide- please specify; (5) Other What factors were used for decision making? HR/BP/Cap refill/ Response to fluid/ other (specify) How confident are you in decision on a scale of 0 (not confident at all) to 4 (sure of decision)	Known cardiomyopathy with onset of shock Low CVP and absence of hepatomegaly Good response to fluid bolus	Continue fluid resuscitation	Rationale for halting or slowing resuscitation

4	You are caring for a 6 yr old girl admitted to the PICU after anaphylactic shock from a bee sting. She has required a lot of fluid in the 4 h since admission-a total of 60 mL/kg, and is currently on dopamine at 7 mg/kg per minute. She has a urine output of 1 mL/kg per hour. She is on 2 L NC, and her vitals are as follows: Temp 36.8 ℃, HR 115/min, RR 16/min, BP 95/65 (MAP 75) mmHg, with flushed extremities and cap refill of 2 s. You insert an internal jugular line and when you transduce it, you get a CVP of 3 mmHg. What would you do next?	What would be your next plan of action (1) Do nothing- continue maintenance fluids; (2) give an additional 20 mL/kg fluid bolus; (3) increase vasoactive medication; (4) need additional data to decide- please specify; (5) other What factors were used for decision making? HR/BP/Cap refill/ Response to fluid/ other (specify) How confident are you in decision on a scale of 0 (not confident at all) to 4 (sure of decision)	Vital signs not suggestive of shock Incidentally transduced CVP level of 3 mmHg	Do not continue any further resuscitation	Percentage continuing fluid resuscitation based on isolated CVP value

ACCM: American college of critical care medicine; PALS: Pediatric advanced life support; MAP: Mean arterial pressure; CVP: Central venous pressure.

Table 2 Demographics of respondents

Demographics of respondents	*n* (%)
Total respondents	539 (100)
Medical students	37 (7)
Residents	393 (73)
Fellows	97 (18)
Attending physicians	12 (2)
Level of training- residents	367[1] (100)
PGY-1	120 (33)
PGY-2	110 (30)
PGY-3	121 (33)
PGY-4	16 (4)
No response	26
Level of training- fellows	901 (100)
PGY-4	25 (28)
PGY-5	32 (35)
PGY-6	29 (32)
PGY-7	4 (4)
No response	7
Pediatric fellows' specialty (97)	
Pediatric critical care medicine 25 (26)	
Pediatric emergency medicine 22 (23)	
Neonatology 14 (14)	
Pediatric hospital medicine 5 (5)	
Pediatric cardiology 4 (4)	
Other 27 (28)	

[1]Total number of respondents to this question from all survey takers.

venous access should be obtained and vasoactive medications made available to be started immediately if needed, while assessment of shock should proceed with the same urgency as at initial presentation, especially in the presence of ongoing losses. We found that most respondents were appropriately aggressive, opting to continue either fluid or vasoactive. While most respondents explicitly cited that they were basing their decision on ACCM guidelines, most also interpreted the blood pressure as normal, although the MAP was below the threshold recommended in the ACCM guidelines. It would be interesting to study how prevalent is this departure from the guidelines while treating shock, and whether the thresholds recommended by the ACCM are actually achieved in practice.

Scenario 2 dealt with a more complex situation where positive pressure ventilation had just been initiated. While advanced cardiopulmonary interactions are beyond the scope of general pediatric training, the ACCM guidelines mention that fluid loading might be necessary with the initiation of positive pressure ventilation due to a resultant reduction in the preload. The scenario describes florid shock with altered mental status, tachycardia despite adequate sedation, a heart rate of 168 and a diastolic blood pressure of 40 mmHg in a 4-year old child. The CVP of 10 mmHg in the face of very high intrathoracic pressures does not reflect in any way on intravascular volume status. The most common reason for inadequate resuscitation was the CVP value. Interestingly, a low confidence level was correlated with inaction in this scenario. This can be seen as a form of "omission bias"-one of the commonest biases in clinical medicine, where events occurring through the natural progression of a disease are more acceptable than those that may be directly attributed to the action of the physician.

In the third scenario, though the patient is known to have chemotherapy-induced cardiomyopathy, her liver size is not enlarged from baseline, CVP is low, and heart rate improves with an initial 10 mL/kg bolus. The probability that fluid administration will be harmful given these clinical attributes is inflated, and the far more likely possibility that there is ongoing shock in an immunocompromised host is minimized. This is a form of "base rate neglect"-clinicians conflate probabilities to rule out the worst case scenario.

Table 3 Responses to clinical scenarios

Scenario	Fluid bolus	Vasoactive	No further intervention/ need more data/other	Factors cited as important for decision-making	Percentage with low confidence
1-septic shock s/p 60 mL/kg fluid	38%	47%	15%	Capillary refill, response to fluid	36%
2-hemodynamic instability s/p initiation of positive pressure ventilation	20%	60%	20%	CVP, lactate	65%
3-shock with comorbid cardiomyopathy	39%	15%	46%	HR, BP	64%
4-anaphylaxis with resolved shock	29%	20%	51%	CVP	61%

s/p: Status post; CVP: Central venous pressure; HR: Heart rate; BP: Blood pressure.

Table 4 Preferences of non-experts *vs* experts

Scenario	Role	Bolus (% of total)	Vasoactive (% of total)	Other (% of total)	*P* value
1-septic shock with ongoing losses	Non-experts[1] (n = 438)	40	47	13	0.02
	Experts[1] (n = 52)	25	50	25	
2-worsening hemodynamics after intubation	Non-experts (n = 438)	21	59	20	0.08
	Experts (n = 52)	11	73	16	
3-shock in a child known to have cardiomyopathy	Non-experts (n = 438)	39	15	46	0.77
	Experts (n = 52)	42	17	41	
4-recovering anaphylactic shock with low CVP	Non-experts (n = 438)	29	21	50	0.01
	Experts (n = 52)	25	8	67	

[1]Experts: Fellows in pediatric critical care, pediatric emergency medicine, and pediatric hospital medicine; Non-experts: All other respondents.

In scenario 4 - the patient has required a fair amount of fluid and vasopressor, but has an adequate urine output and normal vitals. Again in this case, CVP of 3 mmHg takes precedence in decision-making and half of all respondents elect to give additional fluid or increase vasoactives.

We uncovered some common themes across the scenarios. The presence of fever can act as a confounding factor in the attribution of tachycardia to the shock state. This leads to delay in treatment for shock while treating with antipyretics and awaiting fever to subside before assessing degree of tachycardia. It is important to emphasize to trainees that while awaiting antipyretics to take effect, it is vital to continue resuscitative measures for shock. Although several clinical studies have widely disproven the utility of CVP both as a marker of intravascular volume state as well as an indicator of fluid responsiveness[10,11], CVP is still widely used in decision-making regarding fluid status, often taking primacy over other signs. This approach is not only not useful, it can be potentially harmful as we have shown, where the contribution of factors such as intrathoracic pressure and diastolic function to CVP is not considered, and a normal CVP value leads to a premature halt to resuscitation. Conversely, a CVP of 3 mmHg is normal in a spontaneously breathing child with normal cardiac function and does not indicate hypovolemia[12]. Interpretation of a given CVP value should take into account these aforementioned factors, with recent expert opinion suggesting that extreme values of CVP may still be useful to guide resuscitation[13]. Though some respondents mentioned using ultrasound measures to ascertain for fluid status, markers of fluid responsiveness such as respiratory variation in peak aortic velocity require the absence of spontaneous breathing in a mechanically ventilated patient, as well as some expertise to obtain[14]. Furthermore, although echocardiography might give a general idea as to cardiac function, it does not yield any information on systemic vascular resistance or intravascular volume. Myocardial depression often coexists with septic shock[15], yet these children need to be resuscitated with either fluid or vasopressors, and clinical exam for response to fluid, hepatomegaly and rales is usually the only tool available at bedside. As such, it is not appropriate to await results of echocardiographic imaging to make decisions on fluid resuscitation. Experts were more likely than non-experts to prefer vasoactive medication to fluid in all instances except for scenario 4, and were uniformly more confident.

Our study has several limitations. Answering questions on a survey does not replicate the experience of examining a patient and assessing the evolution of disease in real time. In practice, each patient is immeasurably complex and there are multiple sources of clinical input - both conscious and subconscious. For sake of keeping the question stem at a reasonable length, we had to handpick what we considered the most relevant information. There is also the inevitable introduction of the Hawthorne effect here-respondents are aware that they are completing a survey on fluid management practices and this knowledge might further add to the

inaccuracy of survey responses compared to actual decisions made. Thus the survey-based methodology is far less rigorous than conducting a prospective study and debriefing pediatric trainees in real time.

To conclude, while pediatric trainees are most confident when following ACCM guidelines to treat shock, they face a high degree of decisional conflict and lack of confidence when encountering alternative etiologies and comorbidities. Educational interventions targeting the biases outlined in our study could be of benefit.

ARTICLE HIGHLIGHTS

Research background

Pediatric trainees are often the first responders at the bedside for evaluation and ongoing management of children presenting with various shock states, yet there is little data on how they navigate through these decisions or how confident they feel in making these decisions. We conducted a survey of pediatric trainees all over the United States. Our study is the first study to survey in the literature studying fluid administration practices of trainees.

Research motivation

The motivation for performing this research was to uncover common situations where pediatric trainees faced a significant decisional conflict when treating shock. We also aimed to uncover some common situations where under-resuscitation was common and to highlight cognitive biases and fallacies of trainees while assessing and treating children with shock.

Research objectives

One of the study objectives was to assess level of adherence and confidence level with American College of Critical Care Medicine (ACCM) guidelines which are universally followed in the United States for treatment of septic shock. Additionally, we wanted to assess degree of reliance on central venous pressure, resuscitation in children with ongoing cardiac comorbidity. We also sought to discover if there were significant differences in treatment practices of more advanced level trainees such as pediatric critical care, hospital medicine and emergency medicine fellows. All these objectives were realized, and can help in training and supporting pediatric residents for management of shock.

Research methods

We conducted a nationwide survey of all pediatric trainees in the United States. This included residents at all levels of training, and fellows training in one of the subspecialties of pediatrics. The survey was voluntary and anonymous. Statistics were primarily descriptive, and SPSS was used for performing additional statistical testing.

Research results

We found that pediatric trainees across all levels of training faced a high degree of uncertainty and lack of confidence while they were making decisions regarding fluid administration in children presenting with shock. ACCM guidelines are frequently cited, yet blood pressure goals cited in the ACCM guidelines are often not met, nor is a suboptimal blood pressure recognized. Children with coexisting cardiac comorbidities may be prone to severe under-resuscitation for fear of cardiac failure causing pulmonary edema. Fever is an important confounding factor often delaying recognition of shock. This study sheds light on these important observations, and further prospective observational studies are warranted which study decision-making of trainees.

Research conclusions

This study is the first study on how trainees in pediatrics make decisions for treatment of shock. It is vital that shock be recognized and treated rapidly, yet there are no studies looking at how confident trainees feel in their judgment. This study points to a very low level of confidence when treating shock, and some common situations which should be highlighted to trainees while caring for patients or in simulated scenarios.

Research perspectives

Pediatric trainees should be supported adequately and provided focused teaching related to treatment of shock states in children. Children with malignancy and cardiac comorbidity who present with septic shock are a uniquely vulnerable population prone to under-resuscitation and should be managed by expert physicians. Central venous pressure should be interpreted with caution and not used in isolation without entire clinical picture.

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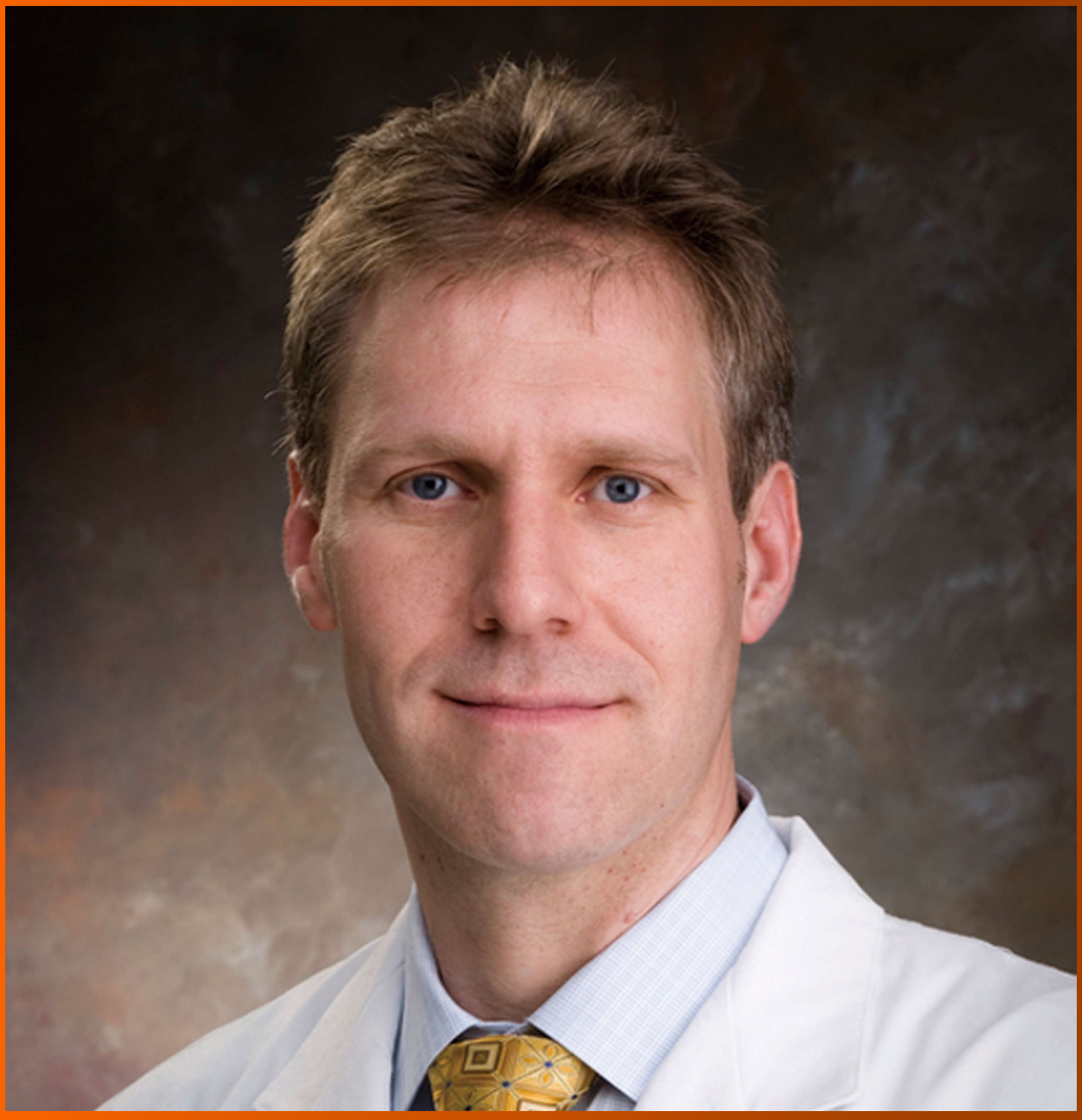

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EVIDENCE-BASED MEDICINE

Validation of the VitalPAC Early Warning Score at the Intermediate Care Unit

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Abstract

AIM

To assess the performance and clinical relevance of the Early Warning Scoring (EWS) system at the Intermediate Care Unit (IMCU).

METHODS

This cohort study used all the VitalPAC EWS (ViEWS) scores collected during each nursing shift from 2014 through 2016 at the mixed surgical IMCU of an academic teaching hospital. Clinical deterioration defined as transfer to the Intensive Care Unit (ICU) or mortality within 24 h was the primary outcome of interest.

RESULTS

A total of 9113 aggregated ViEWS scores were obtained from 2113 admissions. The incidence of the combined outcome was 272 (3.0%). The area under the curve of the ViEWS was 0.72 (CI: 0.69-0.75). Using a threshold value of six, the sensitivity was 68% with a positive predictive value of 5% and a number needed to trigger (*e.g.*, false alarms) of 19%.

CONCLUSION

The ViEWS at the IMCU has a discriminative performance that is considerably lower than at the hospital ward. The number of false alarms is high, which may result in alarm fatigue. Therefore, use of the ViEWS in its current form at the IMCU should be reconsidered.

Key words: Intermediate Care Unit; High-dependency unit; Clinical deterioration; Vital signs; Early Warning

Scoring

Core tip: This study used all the routinely collected Early Warning Scores (EWS) in every nursing shift from 2014 to 2016 (n = 9113) at the standalone Intermediate Care Unit to assess the performance and clinical relevance of the EWS to detect clinical deterioration amongst patients admitted in this critical care facility. It follows that although the discriminative performance was acceptable (AUC 0.72), the clinical relevance is limited as 19 false alarms were needed to detect one event. As this may result in alarm fatigue, its use in this setting should be reconsidered.

Plate JDJ, Peelen LM, Leenen LPH, Hietbrink F. Validation of the VitalPAC Early Warning Score at the Intermediate Care Unit. *World J Crit Care Med* 2018; 7(3): 39-45 Available from: URL: http://www.wjgnet.com/2220-3141/full/v7/i3/39.htm DOI: http://dx.doi.org/10.5492/wjccm.v7.i3.39

INTRODUCTION

In the past decade, increasing attention has been raised for the concept of Early Warning Scoring (EWS) systems, in order to timely detect the clinically deteriorating patient in need of intervention[1]. Frequently the EWS is used, combined with structured communication systems to allow adequate information transfer[2]. EWS systems were initially developed and validated at general hospital wards, but are currently also integrated in other settings, such as the emergency department and the prehospital setting[1,3-6]. It is however unclear if the performance of the EWS obtained in the general ward is representative for such settings, as differences in case-mix between settings are likely present[7].

One setting where EWS is used, but to our knowledge not validated, is the Intermediate Care Unit (IMCU). Although the exact extent to which EWS systems are applied at IMCUs has not been investigated, EWS systems are widely applied in the hospital setting, for example within a broad national safety program in The Netherlands[8], and the National Health Service in the United Kingdom[9]. As within the continuum of care the IMCU is positioned between the hospital ward and the intensive care unit[10,11], it has a remarkably different case-mix, which is likely to influence the performance of the EWS. Also, the haemodynamic and respiratory support provided at IMCUs directly influences the vital parameters used in (most) EWSs, and may affect its performance[10].

This validation study aims to assess the performance and clinical relevance of the EWS at the IMCU. Additionally, it investigates the potential of several IMCU-specific clinical parameters to improve the performance of EWS within this setting.

MATERIALS AND METHODS

Data sources and participants

This cohort study used prospectively collected data of all admissions at the surgical IMCU of the University Medical Centre in Utrecht, a tertiary referral hospital in the Netherlands from the period of January 1st, 2014 through December 31st, 2016. This stand-alone, mixed surgical IMCU admits patients from all surgical disciplines (except cardiothoracic surgery and neurosurgery), providing haemodynamic monitoring and cardiovascular- and respiratory-support, including inotropic use and supplementary (high flow) oxygen administration. Multiple vasoactive medications, haemodialysis, and mechanical ventilation are not performed at this IMCU. According to the Institutional Review Board the study was not subject to the Medical Research Involving Human Subjects Act and therefore the necessity of informed consent was waived (protocol No. 17-326/C).

Clinical parameters

Because the VitalPAC-Early Warning Score (ViEWS) has the highest discriminative ability compared to 34 other EWS[1], we chose to validate this EWS. The ViEWS is based on the heart frequency, respiratory rate, temperature, systolic blood pressure, oxygen saturation, inspired oxygen (yes/no) and consciousness (supplementary material). As a threshold, it often uses an aggregated score of 5[4]. In our hospital, a slightly modified score was used in routine care, to which we will refer to as the University Medical Center Utrecht-EWS (UMC-EWS). This UMC-EWS used almost similar parameters as the ViEWS. Therefore, the performance of this score (with the currently used threshold of 3) was also assessed. Additionally, possible clinically important IMCU-specific predictors were added to the ViEWS.

Data collection

The parameters required for the UMC-EWS were collected in the Electronic Health Record in every nursing shift (every 8 h), as required by the Dutch authorities. The blood pressure and saturation were additionally required to calculate the ViEWS. These were collected from nursing measurements within 2 h before the UMC-EWS measurements.

Additional clinical predictors collected were noradrenalin (norepinephrine) use (μg/kg per minute), oxygen use (L/min), nurse worry (yes/no), urine output (⩽ 75 mL over the last 4 h) and the change in ViEWS, which was the ViEWS minus the previous ViEWS at the IMCU (within two nursing shifts, defined as within 18 h). Noradrenalin (μg/kg per minute) and oxygen (L/min) were collected from nursing measurements within 2

h before the UMC-EWS measurements. Nurse worry (yes/no) and urine output (⩽ 75 mL over the last 4 h) were part of the UMC-EWS and hence, did not require additional data collection.

Outcome

The primary outcome was clinically relevant deterioration, defined as transfer to the Intensive Care Unit (ICU) or death within 24 h of the EWS measurement. Secondary outcome was transfer to the ICU or death within 12 h.

Statistical analysis

Descriptive statistics presented are the mean and 95% CI for normally distributed continuous variables, and the median and interquartile range (IQR) for non-normally distributed continuous variables[12]. Categorical variables are described as proportions. The aggregated ViEWS was calculated from the separately collected parameters from the UMC-EWS and the nursing measurements. To assess the discriminative performance of the ViEWS score, *i.e.*, the extent to which deteriorating patients can be distinguished from patients who are not deteriorating, we calculated the area under the receiver operating characteristics curve (AUROC) with its 95% CI. Subsequently, the optimal threshold value was deducted from the ROC curve by the Q-point method (*i.e.*, the threshold value with the minimum distance to the upper left corner). For this threshold value, the parameters sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and number needed to trigger (NNT) were calculated. The latter was of interest to assess the possibility of alarm fatigue[13]. Furthermore, to analyse if the discriminative performance could be improved, other possible clinical predictors were, first separately and then jointly, added to the ViEWS in logistic regression analyses. To this end, the ViEWS was included as an offset term. For these models, again discriminative performance measures using the optimal threshold were calculated. As the amount of missing data was small, complete case analyses were performed. To determine whether the occurrence of multiple measurements per admission affected the discriminative performance, an additional analysis was performed using only the first observation per IMCU admission. As the UMC-EWS was not always performed at 8 h intervals, another additional analysis was performed to determine the effect of the measurements at irregular time intervals. To this end, only regular time interval measurements (within 6-10 h after the previous measurements, thus in the consecutive nursing shift) were taken into account for this analysis. All statistical analyses were performed using R software for statistical computing version 3.3.2[14]. Where applicable, the reporting of this article follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement[15].

RESULTS

Participants

During the study period, there were 2113 admissions (1782 different patients) at the IMCU with a total of 9113 aggregated EWS. The mean age of the patients was 61.2 (SD 17.0) years. In total, 1150 (64.5%) patients were male.

The median ViEWS was 5 (IQR 3-6). Most common were ViEWS of 3 (*n* = 1754, 19.3%), 4 (*n* = 1500, 16.5%), 5 (*n* = 1398, 15.4%) and 6 (*n* = 1324, 14.5%). The median interval between subsequent EWS was 8.6 h (IQR 6.8-13.4). This was 8.1 h (IQR 6.4-11.5) for observations followed by ICU transfer within 24 h, as compared to 8.6 h (IQR 6.8-13.5) for observations that were not followed by ICU transfer within 24 h.

Figure 1 shows the percentages of observations for the separate ViEWS parameters. It should be noted that during almost all of the observations (*n* = 7530, 82.63%) patients received oxygen, hence nearly always three points were received for this item. There were 6602 (72.4%) observations during which patients received oxygen through a nasal cannula, 748 (8.2%) observations during which patients received oxygen through a non-rebreathing mask and 180 (2.0%) observations during which patients received oxygen through a high-flow nasal cannula.

There were 687 (7.5%) observations during which patients received noradrenalin (251 admissions). Nurses indicated to be worried in 895 (9.8%) of observations, and reported a decreased urine output (⩽ 75 mL over the last 4 h) in 304 (3.3%) observations. The mean change in ViEWS was -0.15 (SD 2.29) per subsequent measurement, using 6115 (67.10%) measurements.

The number of observations that were followed by clinical deterioration (ICU transfer or mortality within 24 h) was 272 (3.0%). Of these, 248 (90.1%) were ICU transfers within 24 h and 27 (8.8%) were deaths within 24 h. In three (1.1%) observations, both outcomes occurred within 24 h after the observation.

Figure 2 shows the percentage and number of observations per ViEWS and the event rate within 24 h. Two observations with a ViEWS of 16 were not followed by an event. During these observations, one admission was a patient who had sepsis due to pneumonia who stabilized, until secondary deterioration (respiratory insufficiency) and ICU transfer 3 d later. The other admission was a patient who suffered from respiratory insufficiency due to cardiac failure and pneumonia with a restricted policy of no ICU admission.

Discriminative performance

The AUROC of the ViEWS for the prediction of clinical deterioration within 24 h was 0.72 (0.69-0.75). For a threshold of five (as is recommended for hospital wards[9]), the sensitivity was 79%, PPV 4%, NPV 99%, and NNT 23. For the optimal threshold value at the IMCU of 6, the sensitivity was 68%, with a PPV

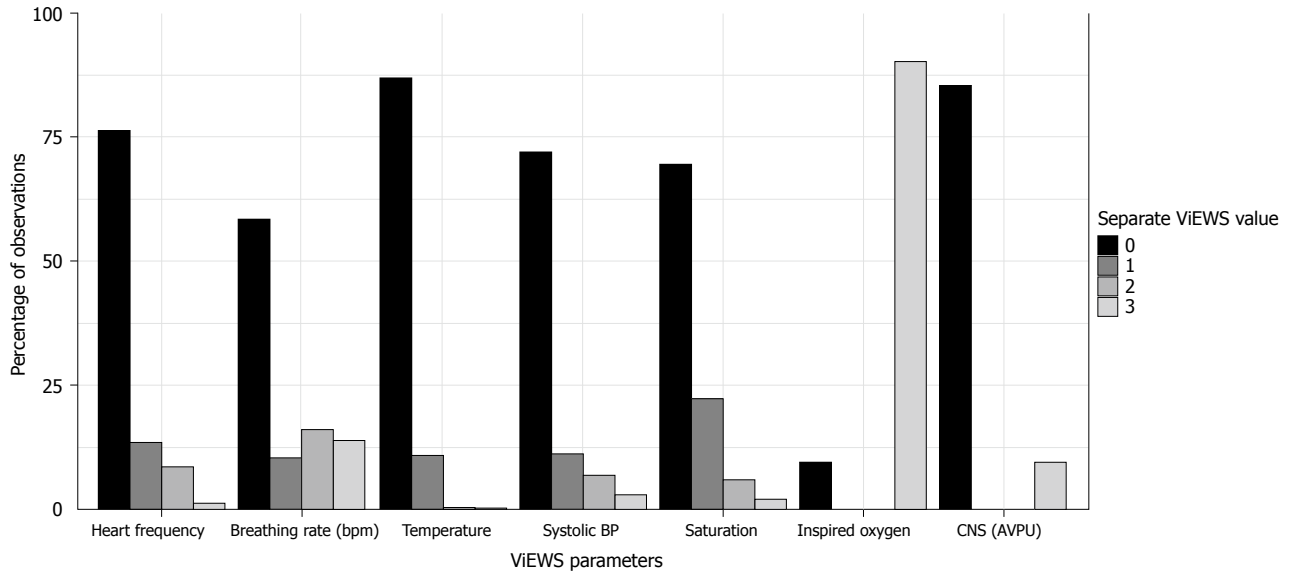

Figure 1 Frequency of Scores for Separate VitalPAC Early Warning Score Parameters. This figure shows the relative contribution of separate VitalPAC Early Warning Score (ViEWS) Parameters towards the aggregated scores at the Intermediate Care Unit. bpm: Breaths per minute; BP: Blood pressure; CNS: Central nervous system; AVPU: Alert, verbal, pain, unresponsiveness scale.

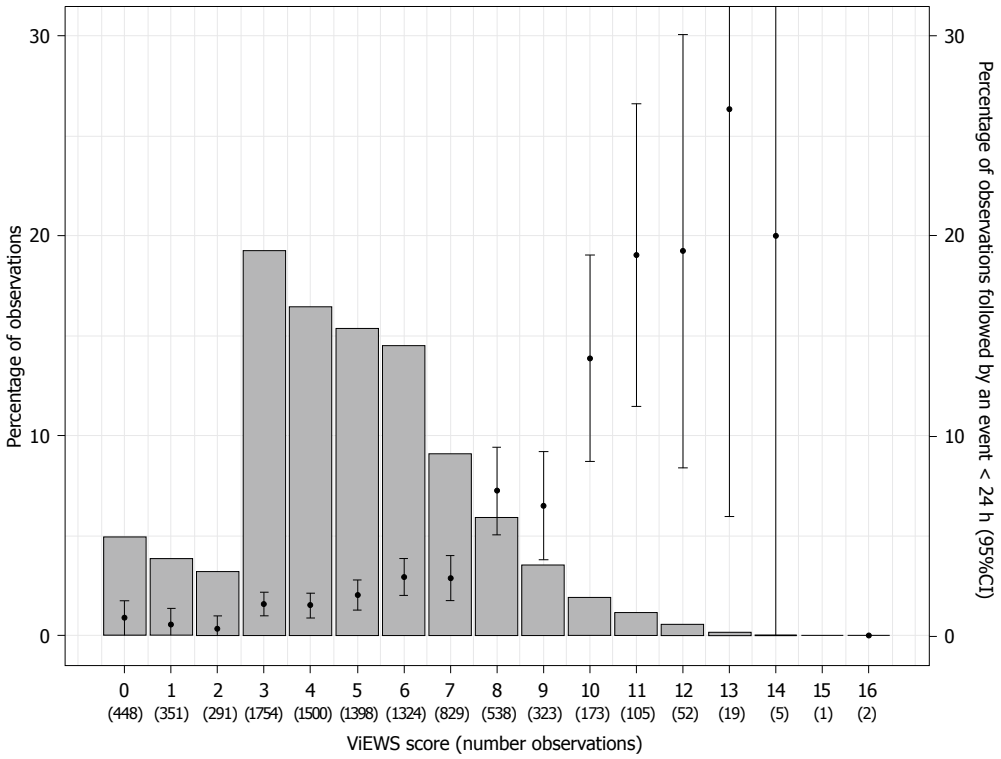

Figure 2 Distribution of VitalPAC Early Warning Score and transfer to the Intensive Care Unit rates. This figure shows distribution of the VitalPAC Early Warning Score aggregated values (bar chart) in relation with the occurrence of the event (ICU transfer or mortality within 24 h), with 95%CIs. ICU: Intensive Care Unit.

of 5%, NPV 98% and the NNT 19. For the outcome 'clinical deterioration within 12 h' the AUROC was 0.74 (0.70-0.79).

The AUROC of the hospital-adjusted EWS (UMC-EWS) was 0.71 (0.67-0.74). With the currently used threshold value of 3, the sensitivity of UMC-EWS was 58%, specificity was 73%, PPV 6%, NPV 98% and NNT 17.

Addition of all the variables noradrenalin use, oxygen (L/min), nurse's worry, urine output (≤ 75 mL over the last 4 h) and the change in ViEWS, increased the AUROC to 0.78 (0.74-0.81), with a NNT of 11 at the optimal cut-off value (Table 1).

When analysing only the first observation of the

Table 1 Predictive Performance of the regular VitalPAC Early Warning Score and updated models at the Intermediate Care Unit

Predictors	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	NNT
ViEWS, with regular threshold (5)	0.72 (0.69-0.75)	79	49	4	99	23
ViEWS, with optimal threshold (6)	0.72 (0.69-0.75)	68	64	5	98	19
ViEWS and noradrenalin	0.72 (0.69–0.75)	68	64	5	98	19
ViEWS and oxygen (continuous)	0.74 (0.71-0.77)	61	76	7	98	14
ViEWS and nurse worry score	0.73 (0.70-0.76)	70	63	5	99	21
ViEWS and change in ViEWS	0.74 (0.70-0.78)	65	70	7	99	16
ViEWS and noradrenalin, nurse worry score, oxygen (continuous) and change in ViEWS	0.78 (0.74-0.81)	62	78	10	99	11

The numbers presented indicate the area under the curve (AUROC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and number needed to trigger (NNT). This is shown for the original VitalPAC early warning score model (ViEWS) with both the regularly used and optimal threshold, and for the updated models containing additional parameters, all with their optimal thresholds as determined by the Q-point method. ViEWS: VitalPac Early Warning Score; NNT: Number needed to trigger.

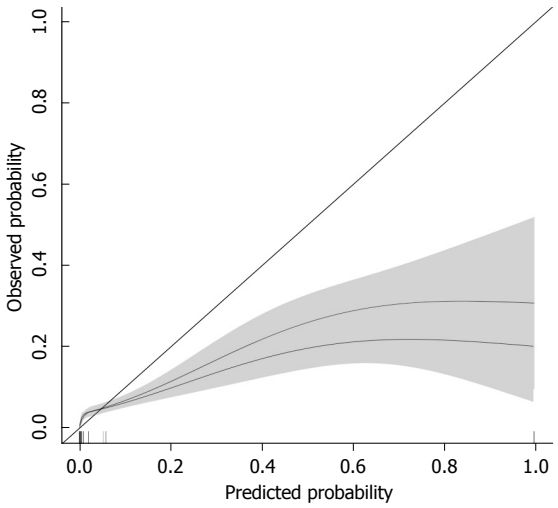

Figure 3 Calibration plots of the VitalPac Early Warning Score and the VitalPac Early Warning Score with additional parameters at the Intermediate Care Unit. This figure shows the calibration plot of the ViEWS (lower plot) and the ViEWS with the additional parameters noradrenalin, nurse worry score, oxygen (continuous) and change in ViEWS (upper plot). ViEWS: VitalPac Early Warning Score.

ViEWS per IMCU admission (n = 2113), the AUROC was 0.72 (0.65-0.79) using the optimal threshold. When including only the observations that were part of a regular measurement interval (n = 5255), the AUROC was 0.70 (0.66-0.74) for the optimal threshold.

Calibration

The calibration of the ViEWS and the ViEWS with additional parameters (noradrenalin, nurse worry score, oxygen (continuous) and change in ViEWS) is shown in Figure 3. From this, it follows that the ViEWS underpredicts clinical deterioration for Probability < 0.05, while it overpredicts clinical deterioration for Probability > 0.05.

DISCUSSION

This study shows that the discriminative performance of the (Vi)EWS at the IMCU is moderate. However, its clinical relevance is debatable as its use carries the risk of alarm fatigue (NNT = 19).

In comparison, considerably higher AUROCS have been described for the ViEWS at the hospital ward. One study using the same composite outcome found an AUROC of 0.87 (0.87-0.87)[4]. At external validation studies AUROCs of 0.87 (no confidence interval) and 0.89 (0.83-0.95) for 24 h mortality were observed in, respectively, first world and lower-income countries[3,16]. In the pre-hospital setting an AUROC of 0.815 (0.730-0.990) was reported in external validation for the composite outcome of ICU transfer or mortality within 48 h[5]. A possible explanation for the lower discriminative performance of the (Vi)EWS at the IMCU is the considerably different case-mix when compared to the hospital ward: IMCU patients are already closely monitored and often receive haemodynamic and respiratory support. Hence, many patients achieve a relatively high ViEWS score, which diminishes the discriminative potential of the score. Furthermore, the supervising clinicians at the IMCU are trained and experienced in supporting the deteriorating patient, and thus deterioration (as measured by the EWS) may not directly lead to ICU transfer and mortality, as a large part of the resuscitation can be provided at the IMCU.

Subsequently, this study shows that the addition of IMCU-specific clinical parameters increases the discriminative performance (AUROC 0.78, CI: 0.74-0.81) and decreases the false alarm rate (NNT = 11). We did however not intend to develop and present a revised IMCU-specific EWS. First further external validation

would be necessary, and second, it would require collection of extra parameters, which would make the EWS less easy to use. It should be noted that the moderate performance of the EWS was not specific for the ViEWS, as the observed performance of the UMC-EWS was lower than the ViEWS (AUROC of 0.71, CI: 0.67-0.74) in the IMCU.

Clinically, we do not consider a prediction model with a NNT of 19, *i.e.* only 1 out of 19 triggers, does indeed indicate clinical deterioration, to be feasible. This carries a high risk of alarm fatigue and therefore has the potential to compromise patient safety while increasing the (administrative) burden at the IMCU. In its current design, we therefore believe that it should not be used. We would regard a NNT of 4 or less as ideal (with a sensitivity of $\geqslant$ 50%), as this would indicate that at least 25% of the alarms are justified. It should be noted that the addition of the other IMCU-specific clinical parameters increased the amount of data to be collected, still resulting in a higher NNT; therefore, more detailed modelling, likely connected with automated data collection to reduce administrative burden, would be necessary to achieve this goal. Furthermore, as these additional IMCU-specific clinical parameters are used to fit a model in our own cohort, there is a risk of overfitting and thus the real performance of this updated model is likely even less.

We recognize that this clinical relevance highly depends on the organisation of the IMCU and, in particular, on the extent to which the IMCU is independent. IMCUs that are an extension of the hospital ward perhaps do benefit from the ViEWS, whereas independent (stand-alone) IMCUs with extensive monitoring and supportive options probably do not. The clinical relevance of the ViEWS at the IMCU also depends on the hospital organization, as "transfer to the ICU" is a process measure which is potentially susceptible to logistical factors (the occupancy rates at both units). Although the in-hospital mortality rate is preferably an outcome measure[1], its use as single outcome parameter was not considered feasible due to its rare occurrence (0.30%) and susceptibility to treatment restrictions. Additionally, as necessity for ICU transfer often is due to mechanical ventilation[10], its use as an outcome measure for deterioration at IMCUs can likely be generalized.

This study has multiple strengths. First, it is the first to investigate the validity and clinical relevance of the ViEWS at the IMCU. Second, it analyses a large dataset, using a standardized data collection protocol in which the EWS is consistently collected on a regular basis.

Its limitations are that physicians have likely acted upon EWS values to prevent further deterioration. Although we have partly taken this into account by using ICU transfer as an outcome, we did not include other treatment changes, such as increasing the amount of noradrenalin. Therefore, we were unable to assess the relevance of the ViEWS for the prediction of these treatment changes. Another limitation is, as indicated before, that we cannot generalize our findings to IMCUs with a case-mix which is more comparable to the hospital ward, in particular as our IMCU may be unique in its possibility to administer vasopressors.

Further research to detect the deteriorating patient at the IMCU should probably not solely focus on cross-sectional measurements of vital signs (as is done in the EWS). Rather, focus should shift towards using (automated) repeated measurements of these vital signs to adequately and timely detect the deteriorating patient at the IMCU. By optimal support through ICT and electronic medical record systems, this preferably results in a real-time trend analysis and score visualization with an easy read-out of clinical deterioration and adjustable thresholds per patient. Especially in an environment with constant monitoring, this could possibly lead to earlier interventions and improved patient outcomes.

The ViEWS at the IMCU has a discriminative performance that is considerably lower than at the hospital ward. As the number of false alarms is high, it carries the risk of alarm fatigue. Therefore, its application in this setting should be reconsidered. As the addition of IMCU-specific clinical predictors does not sufficiently improve the performance, further research should focus on more complex models incorporating repeated measurements of vital functions.

ARTICLE HIGHLIGHTS

Research background

Early Warning Scoring (EWS) systems to recognize the clinically deteriorating patient are widely used in the clinical setting, including in Intermediate Care Units (IMCUs). However, they have been developed and validated for the general hospital ward population and hence their applicability within the IMCU population is unclear.

Research motivation

The application of prediction models (EWS) at a different setting than the setting at which they were developed (IMCU instead of hospital ward), could lead to an inefficient use of scarce resources and may compromise patient safety. To justly consider the (ongoing) use of the EWS at the IMCU, its discriminative performance and applicability need to be investigated.

Research objectives

This validation study aims to assess the performance and clinical relevance of the VitalPAC-EWS (ViEWS) at the IMCU. Further, it aims to improve the EWS for its use at the IMCU.

Research methods

Electronically collected data from 2014 to 2016 at the IMCU were used to obtain the area under the receiver operating curve (AUC) and the number needed to trigger (false alarm rate) at the current and the optimal threshold.

Research results

The AUC of the ViEWS was 0.72 (CI: 0.69-0.75). The number needed to trigger was 19 per one event. Although the discriminative performance is acceptable, the clinical relevance is limited as 19 false alarms are needed per one event. This carries the risk of alarm fatigue. Therefore, this study contributes to this research field that the use of the EWS at the stand-alone IMCU should be reconsidered. The main problem that remains to be solved are that an

alternative system needs to be developed to timely detect clinical deterioration at the IMCU.

Research conclusions

The new findings of this study are that the use of the ViEWS at the IMCU should be reconsidered. It proposes that this is due to remarkable case-mix differences between the hospital ward and the IMCU. This study proposes to use new methods to detect clinical deterioration at the IMCU, using automated data collection and perhaps more sophisticated statistical methods. The implication for clinical practice is that the EWS in its current form at the IMCU should perhaps not be used.

Research perspectives

General experiences and lessons that can be learned from this study are that prediction models should not be used in different settings without prior validation. Further research should focus on alternative methods to detect the clinically deteriorating patient at the IMCU, through the modelling of repeated measurements in prediction models. Also, further research should focus on the use of the EWS in differently formatted IMCUs, such as the IMCU that is integrated into the ICU.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics and outcomes associated with nasal intermittent mandatory ventilation in acute pediatric respiratory failure

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Abstract

AIM

To characterize the clinical course and outcomes of nasal intermittent mandatory ventilation (NIMV) use in acute pediatric respiratory failure.

METHODS

We identified all patients treated with NIMV in the pediatric intensive care unit (PICU) or inpatient general pediatrics between January 2013 and December 2015 at two academic centers. Patients who utilized NIMV with other modes of noninvasive ventilation during the same admission were included. Data included demographics, vital signs on admission and prior to initiation of NIMV, pediatric risk of mortality Ⅲ (PRISM-Ⅲ) scores,

complications, respiratory support characteristics, PICU and hospital length of stays, duration of respiratory support, and complications. Patients who did not require escalation to mechanical ventilation were defined as NIMV responders; those who required escalation to mechanical ventilation (MV) were defined as NIMV non-responders. NIMV responders were compared to NIMV non-responders.

RESULTS

Forty-two patients met study criteria. Six (14%) failed treatment and required MV. The majority of the patients (74%) had a primary diagnosis of bronchiolitis. The median age of these 42 patients was 4 mo (range 0.5-28.1 mo, IQR 7, $P = 0.69$). No significant difference was measured in other baseline demographics and vitals on initiation of NIMV; these included age, temperature, respiratory rate, O2 saturation, heart rate, systolic blood pressure, diastolic blood pressure, and PRISM-Ⅲ scores. The duration of NIMV was shorter in the NIMV non-responder *vs* NIMV responder group (6.5 h *vs* 65 h, $P < 0.0005$). Otherwise, NIMV failure was not associated with significant differences in PICU length of stay (LOS), hospital LOS, or total duration of respiratory support. No patients had aspiration pneumonia, pneumothorax, or skin breakdown.

CONCLUSION

Most of our patients responded to NIMV. NIMV failure is not associated with differences in hospital LOS, PICU LOS, or duration of respiratory support.

Key words: Continuous positive airway pressure; Pediatric; Noninvasive positive pressure ventilation; Nasal intermittent mandatory ventilation; High flow nasal cannula; Acute respiratory failure; Bilevel positive airway pressure

Core tip: In our cohort of patients between 0.5 and 28.1 mo of age with acute respiratory failure, the majority of patients were successfully supported with nasal intermittent mandatory ventilation (NIMV) alone or NIMV in conjunction with other modes of noninvasive ventilation (NIV). Use of NIMV with or without NIV was not associated with significant differences in hospital length of stay (LOS), pediatric intensive care unit LOS, or duration of respiratory support. Failure of NIMV with or without NIV was recognized in a median of 6.5 h.

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INTRODUCTION

Acute respiratory failure accounts for 46% to 59% of unplanned admissions to the pediatric intensive care unit (PICU) with 68% of these patients requiring advanced respiratory support[1-3]. While endotracheal intubation with mechanical ventilation (MV) is the classic management of respiratory failure, noninvasive ventilation (NIV) is rapidly gaining acceptance as a first line intervention. Continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP), high flow nasal cannula (HFNC), and nasal intermittent mandatory ventilation (NIMV) are examples of NIV.

NIMV is a time-cycled, time-triggered pressure control mode of non-invasive ventilation typically administered through nasal prongs or nasal mask via mechanical ventilator. Unlike BIPAP or endotracheal mechanical ventilation, mandatory breaths on NIMV are often not synchronized to patient breaths, though newer ventilators may synchronize to diaphragmatic stimulation (*e.g.*, Noninvasive neurally adjusted ventilatory assist) or when a negative inspiratory pressure threshold is reached.

NIV modalities have been shown to prevent intubation and reintubation in the adult and neonatal population[4,5]. Relatively few studies have assessed its efficacy in the pediatric critical care setting[6-10]. NIMV in particular is infrequently used outside of the neonatal intensive care unit (NICU) and, to our knowledge, has not been studied in the setting of acute respiratory failure in the PICU. In the absence of data from robust studies, we reviewed our experience with NIMV in critically ill pediatric patients and describe the clinical characteristics and outcomes of pediatric patients with acute respiratory failure who were treated with NIMV.

MATERIALS AND METHODS

Inclusion and exclusion criteria

We performed a retrospective chart review of children between 1 d to 28 mo of age in acute respiratory failure admitted to the PICU or intermediate-level pediatric unit of two academic medical centers between January 2013 and December 2015. Institutional review board approval was obtained at each site.

Patients were identified through ICD codes associated with acute respiratory failure and CPT codes for endotracheal intubation or NIV. NIV modalities reviewed include NIMV, HFNC, CPAP, and BIPAP. All patients treated with NIMV were individually reviewed. Due to the paucity of patients utilizing NIMV alone, patients treated with other modes of NIV in series with NIMV during a single admission were included. Exclusion criteria were patients who did not utilize NIMV during hospitalization, managed in the NICU, chronic CPAP or BIPAP dependence, tracheostomy dependence, and post-extubation NIV.

Materials

NIV and NIMV settings were initiated and titrated at clinician discretion based on the patient's clinical response. NIMV was administered *via* RAM cannula (Neotech Products, Valencia, CA) nasal prongs sized according to the child's age and weight and connected to a humidified

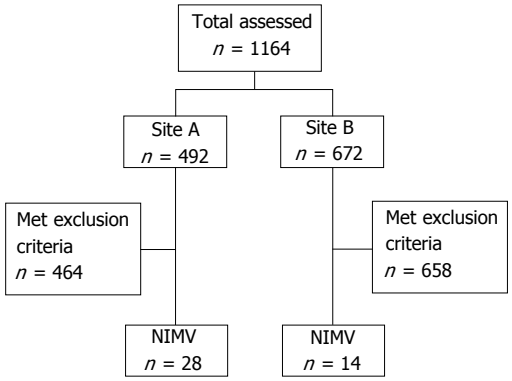

Figure 1 Patient selection by institution. NIMV: Nasal intermittent mandatory ventilation.

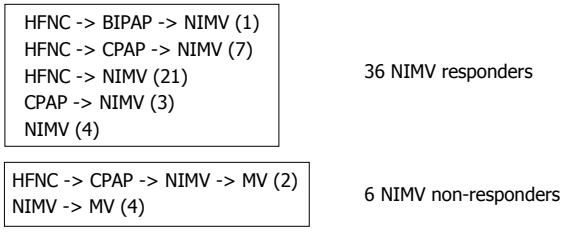

Figure 2 Escalation of respiratory support modalities[1]. [1]Progression of respiratory support indicated by arrows and number of patients (in parentheses) following each pathway. HFNC: High flow nasal cannula; BIPAP: Bilevel positive airway pressure; NIMV: Nasal intermittent mandatory ventilation; CPAP: Continuous positive airway pressure; MV: Mechanical ventilation.

Avea ventilator (CareFusion, Franklin Lakes, NJ) in NIMV mode. This mode of ventilation was asynchronous to patient breaths at both our institutions. The decision to escalate to invasive mechanical ventilation was made at the discretion of the physician.

Data

Data included (1) demographics--age in days, gender, admission, discharge weight and discharge diagnosis; (2) vital signs on initiation of and with any changes in NIV; (3) characteristics of respiratory support--modality, length of time on each modality, maximum settings (delta P, FIO2, PEEP, and mandatory rate); (4) complications--aspiration pneumonia, pneumothorax, skin breakdown; and (5) outcome data-MV, mortality, pediatric risk of mortality Ⅲ (PRISM-Ⅲ) scores, and hospital and PICU length of stay. Respiratory support characteristics were recorded hourly in PICU site A and every 4 h in the pediatric units of site A and PICU site B.

Statistical analysis

Successful NIMV treatment was defined as use of NIMV without the use of invasive mechanical ventilation. Patients successfully treated with NIMV (NIMV responders) were compared to those unsuccessfully treated with NIMV, which we defined as escalation to MV (NIMV non-responders).

Standard descriptive statistics were reported. Medians (min-max, IQR) were analyzed for numerical variables and frequency count (%) for categorical variables. Fisher's Exact tests were used for the comparison of categorical characteristics and Wilcoxon rank sum tests were used for the comparison of numerical characteristics. *P* values less than 0.05 were considered statistically significant. All statistical analysis was performed by a biomedical statistician who utilized SAS v9.4 (SAS Institute Inc., Cary, NC).

RESULTS

During our study period, 1164 charts were initially reviewed and 1122 were removed based on exclusion criteria. Forty-two patients used NIMV during their hospital admission. Figures 1 and 2 illustrate the selection process and the sequence of escalation of respiratory support, respectively.

Comparison of NIMV responders and NIMV non-responders

In our 42 patients who received NIMV, 36 (86%) were successfully supported without further escalation, while 6 (14%) subsequently required endotracheal intubation and MV after trial of NIMV with or without other modes of NIV. Eight (19%) of the 42 patients used NIMV exclusively; of these 8 patients, 4 (50%) failed and required mechanical ventilation. Except for the patients requiring MV, NIMV was used as the final mode of noninvasive respiratory support in patients treated with more than one NIV modality (Figure 2).

The median age of these 42 patients was 4 mo (range 0.5-28.1 mo, IQR 7). Half of the patients were males. The leading discharge diagnosis was bronchiolitis (n = 31, 74%). Demographics (weight, age, gender), PRISM-III scores on admission, and vitals prior to initiation of NIMV (heart rate, respiratory rate, blood pressure, oxygen saturation, temperature) between these two subgroups were similar (Table 1). The distribution of diagnoses was similar between NIMV responders and NIMV non-responders (Table 2).

We observed no significant difference in maximum NIMV settings (delta P, FIO2, PEEP, and rate), time to escalation to maximum settings, hospital and PICU length of stay, or in total duration of all respiratory support between NIMV responders and non-responders, or those that required MV (Table 3). However, NIMV responders remained on this mode of support for a greater length of time than those who failed (65 h *vs* 6.5 h, $P < 0.0005$).

DISCUSSION

In our cohort of pediatric patients with acute respiratory failure treated with NIMV with or without other NIV modalities, 86% did not require MV. This rate is similar to data on heterogenous modes of NIV modalities in the PICU described in separate studies conducted by Yaman *et al*[7], Milési *et al*[8], and Wolfler *et al*[11] in the PICU. To our knowledge this is the first study that characterizes the patients, pathologies, and clinical outcomes of NIMV for

Table 1 Comparison of nasal intermittent mandatory ventilation responders to nasal intermittent mandatory ventilation non-responders - baseline characteristics[1]

Baseline characteristic	NIMV responders (*n* = 36)	NIMV non-responders (*n* = 6)	Total (*n* = 42)	*P* value
Age (mo)	4 (0.5-20, IQR = 6.4)	5.2 (0.5-28.1, IQR = 12.6)	4 (0.5-28.1, IQR = 7)	0.69
Admission weight (kg)	4.9 (2.3-12, IQR = 4.3)	7.1 (2.6-10.9, IQR = 4.8)	5.1 (2.3-12, IQR = 4.4)	0.39
T Max in Celsius (range)	38 (36.6-40, IQR = 1.6)	38.9 (37.4-39.7, IQR = 1.7)	38.1 (36.6-40, IQR = 1.6)	0.2
Respiratory rate (in breaths per minute)	60 (24-97, IQR = 19)	56 (42-77, IQR = 32)	60 (24-97, IQR = 22)	0.76
O2 saturation (%)	98 (68-100, IQR = 5.5)	99 (98-100, IQR = 2)	98.5 (68-100, IQR = 5)	0.31
Heart rate (beats per minute)	152.5 (95-205, IQR = 34.5)	158.5 (127-210, IQR = 24)	153.5 (95-210, IQR = 33)	0.99
Systolic blood pressure (mmHg)	100 (71-129, IQR = 21)	112 (81-120, IQR = 25)	103 (71-129, IQR = 20)	0.3
Diastolic blood pressure (mmHg)	51 (37-84, IQR = 20)	59.5 (43-81, IQR = 25)	51 (37-84, IQR = 22)	0.41
PRISM-Ⅲ score	0 (0-11, IQR = 0)	1 (0-7, IQR = 3)	0 (0-11, IQR = 0)	0.08

[1]Vital signs were the last recorded values before initiation of NIMV. Values are presented as median (range, IQR). NIMV: Nasal intermittent mandatory ventilation; PRISM-Ⅲ: Pediatric risk of mortality Ⅲ.

Table 2 Diagnoses causing acute respiratory failure in nasal intermittent mandatory ventilation responders *vs* nasal intermittent mandatory ventilation non-responders[1]

Diagnosis	NIMV responders *n* (%)	NIMV non-responders *n* (%)	Total (%)	*P* value
Asthma exacerbation	1 (3)	2 (33)	3 (7)	0.11
Bronchiolitis	28 (78)	3 (50)	31 (74)	
Heart failure	1 (3)	0 (0)	1 (2)	
Pneumonia	3 (8)	1 (17)	4 (10)	
Viral syndrome	3 (8)	0 (0)	3 (7)	

[1]Values expressed as number (percent). NIMV: Nasal intermittent mandatory ventilation.

Table 3 Comparison of nasal intermittent mandatory ventilation responders to nasal intermittent mandatory ventilation non-responders - maximum support and clinical outcomes[1]

Support or outcome variable	NIMV responders (*n* = 36)	NIMV non-responders (*n* = 6)	Total (*n* = 42)	*P* value
Max delta P of NIMV (cmH_2O)	16 (6-26, IQR = 6.5)	17.5 (10-30, IQR = 6)	16.5 (6-30, IQR = 6)	0.68
Max FIO2 of NIMV (%)	40 (25-100, IQR = 22.5)	42.5 (30-70, IQR = 10)	40 (25-100, IQR = 15)	0.84
Max PEEP of NIMV (cmH_2O)	6 (5-8, IQR = 2)	5 (5-8, IQR = 2)	6 (5-8, IQR = 2)	0.37
Max rate of NIMV (breaths per minute)	30 (20-70, IQR = 3.5)	30 (20-60, IQR = 5)	30 (20-70, IQR = 2)	0.32
Time to max FIO2 (h)	0 (0-119, IQR = 1.5)	0 (0-29.5, IQR = 6)	0 (0-119, IQR = 2)	0.75
Time to max setting (h)	1 (0-48, IQR = 9)	3 (0-29.5, IQR = 20)	1 (0-48, IQR = 10)	0.8
Hospital length of stay (d)	7 (3-30, IQR = 3.5)	9 (4-14, IQR = 7)	7.5 (3-30, IQR = 4)	0.73
PICU length of stay (d)	6 (3-30, IQR = 3)	6.5 (3-14, IQR = 5)	6 (3-30, IQR = 3)	0.64
Total duration of NIMV (h)	65 (5-240, IQR = 47.5)	6.5 (0.5-30, IQR = 24)	59.5 (0.5-240, IQR = 53)	0.001
Total duration of all respiratory support (h)	94.5 (28-254, IQR = 60)	115 (65-230, IQR = 31.5)	95.8 (28-254, IQR = 57)	0.3

[1]Values are presented as median (range, IQR). NIMV: Nasal intermittent mandatory ventilation; PICU: Pediatric intensive care unit.

acute respiratory failure in pediatric patients outside of the NICU. The strongest evidence for NIMV in the pediatric population to date are limited to pathologies encountered in the NICU; for example, it shows significant clinical benefit over other modes of NIV in neonatal respiratory distress syndrome, apnea of prematurity, and the prevention of post-extubation failure[4,12,13]. In discordance with the NICU literature, a recent prospective study of NIV for post-extubation support in the PICU showed no difference in respiratory effort when compared between NIMV, HFNC, and CPAP, though NIMV in this study was synchronized to approximately 50%[14].

An ongoing concern of NIV is delay in endotracheal intubation and MV that may lead to worsening physiologic status at time of intubation and thus worse clinical outcomes[15]. Our data do not support this hypothesis. We revealed substantially less time on NIMV in the cohort that proceeded to MV compared to those that responded successfully to NIMV. Our observed median time to intubation of 6.5 h in NIMV nonresponders was similar to treatment failure observed by another study utilizing mask BIPAP in adults[11]. Additionally, similarities in clinical outcomes of hospital length of stay, PICU length of stay, and complications suggest that recovery time may be independent of the mode of respiratory support. There was a single mortality due to an uncorrectable congenital lung pathology.

MV is associated with a number of challenges and complications such as sedation, paralysis, polyneuropathies, iatrogenic pneumonia, chemical pneumonitis,

soft tissue trauma, pneumothorax, and other lung injuries[16]. Unlike MV, NIV modalities have three to fivefold fewer rates of these complications, particularly ventilator associated pneumonia and barotrauma[17,18]. Non-invasive ventilation also reduces complications such as mortality and nosocomial infections[7,17,19]. None of our patients had aspiration pneumonia, pneumothorax, barotrauma, or soft tissue injury associated with NIMV use. Additionally, only one patient required mild sedation with an oral benzodiazepine during NIMV support.

The clinical application of NIMV or any NIV is in the hope of avoiding MV. The general practice in our two divisions is to apply NIMV as a last-resort modality prior to MV in young infants. We confirmed this practice pattern in our observation that NIMV, when applied, was used as the final means of noninvasive respiratory support (Figure 2).

Our study is limited in that this was a non-randomized, non-protocolized, retrospective review of chart data with a limited sample size, thus rendering the power of our study low. Limitations in NIMV experience in our PICUs precluded protocols for its application. There is no head-to-head randomization and comparison between other NIV modalities. Treatment with several non-invasive modalities limits the ability to extrapolate the contribution of each mode to successful support or failure. This aspect also limits our data on NIMV alone. Lastly, the criteria to initiate NIV, modify mode of NIV, and decision to intubate was based on clinician judgment and not protocolized.

Despite these limitations, our study provides the first retrospective analysis of outcomes associated with NIMV use in pediatric acute respiratory failure at two academic institutions that are widely disparate geographically. Future goals include verification of this data with a larger cohort and protocolized escalation of respiratory support. Larger and multicenter prospective studies may identify useful clinical parameters that may assist in the identification of patients who may benefit from NIMV. Future goals may include randomization of patients to NIMV alone *vs* other modes of NIV.

NIMV successfully supported 86% of pediatric patients with acute respiratory failure. The remaining patients who failed NIMV did not have a longer PICU, hospital LOS, or total duration of respiratory support when compared to those successfully supported with NIMV. NIMV failure was recognized within a median of 6.5 h, therefore the use of NIMV did not delay escalation to endotracheal intubation

ARTICLE HIGHLIGHTS

Research background

Nasal intermittent mandatory ventilation (NIMV) is a mode of noninvasive ventilation (NIV) seldomly utilized outside of the neonatal intensive care unit (NICU). To our knowledge NIMV has not been studied in the pediatric intensive care unit (PICU) population.

Research motivation

Acute respiratory failure requiring advanced respiratory support accounts for a large proportion of PICU admissions. NIV is rapidly gaining acceptance as the first mode of oxygenation and ventilatory support for many of these patients. The potential use of NIMV adds to the arsenal of respiratory support strategies. Its success could obviate the need for mechanical ventilation in some patients.

Research objective

Our primary objectives were to review our experience with NIMV-both alone and in conjunction with other modes of NIV-and describe our patient outcome data and compare with existing literature. In particular our interests were intubation rate, PICU length of stay, hospital length of stay, duration of respiratory support, and complications.

Research methods

During our study period, we identified all patients who utilized NIMV with or without other modes of NIV at two academic institutions. We excluded patients in the NICU, those dependent on chronic continuous positive airway pressure (CPAP) or bilevel positive airway pressure or tracheostomy, and post-extubation NIV. Data included demographics, vitals, characteristics of respiratory support, diagnoses, complications, and outcome data. Patients who did not require escalation to mechanical ventilation (MV) were defined as NIMV responders; those who required escalation to MV were defined as NIMV non-responders. NIMV responders were compared to NIMV non-responders. Standard descriptive statistics are used. All statistical analyses were run by a certified biostatistician using SAS v9.4.

Research results

We identified 42 patients during our three-year study period. Median age of these patients was 4 mo. The majority of patients had a primary diagnosis of bronchiolitis. Six failed NIMV. Baseline demographics, vitals, diagnoses, and pediatric risk of mortality III scores were similar between NIMV responders and NIMV non-responders. However, NIMV non-responders were on this mode of ventilation for a significantly shorter period of time. Outcome data including hospital length of stay, PICU length of stay, and duration of respiratory support were similar between the two groups. No patients had aspiration pneumonia, pneumothorax, or skin breakdown associated with NIMV. There was a single mortality due to an uncorrectable and fatal lung pathology.

Research conclusions

NIMV was utilized in pediatric patients with acute respiratory failure and successfully supported the majority of our patients. Failure of NIMV was quickly identified in a median of 6.5 h. Patients who required intubation did not have a longer PICU length of stay, hospital length of stay, or total duration of respiratory support when compared to those successfully supported with NIMV.

Research perspectives

Based on our data, NIMV appears to be a promising mode of noninvasive respiratory support. Future goals include prospective, and randomized studies to describe and evaluate the efficacy of NIMV.

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REVIEW

Vitamin C in the critically ill - indications and controversies

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Abstract

Ascorbic acid (vitamin C) elicits pleiotropic effects in the body. Among its functions, it serves as a potent anti-oxidant, a co-factor in collagen and catecholamine synthesis, and a modulator of immune cell biology. Furthermore, an increasing body of evidence suggests that high-dose vitamin C administration improves hemodynamics, end-organ function, and may improve survival in critically ill patients. This article reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with respect to its therapeutic potential.

Key words: Ascorbic acid; vitamin C; Sepsis; Shock; Critical care medicine; Vasopressors; Cardiovascular

Core tip: An increasing body of evidence suggests that high-dose vitamin C administration improves hemodynamics, end-organ function, and may improve survival in critically ill patients. This article reviews studies that evaluate vitamin C in pre-clinical models and clinical trials with respect to its therapeutic potential.

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INTRODUCTION

Vitamin C is one of the most well-known essential nutrients and is believed by many to confer a litany of health benefits (Figure 1). The Nobel Prize Winner Linus Pauling may have been the foremost ambassador to date who suggested that vitamin C would enhance cardiovascular health, improve the body's immune function to overcome infections, and even help abate cancer[1-4]. These health claims created significant controversies that lasted for decades. While many of Pauling's "more is better" claims have not been supported by rigorous scientific

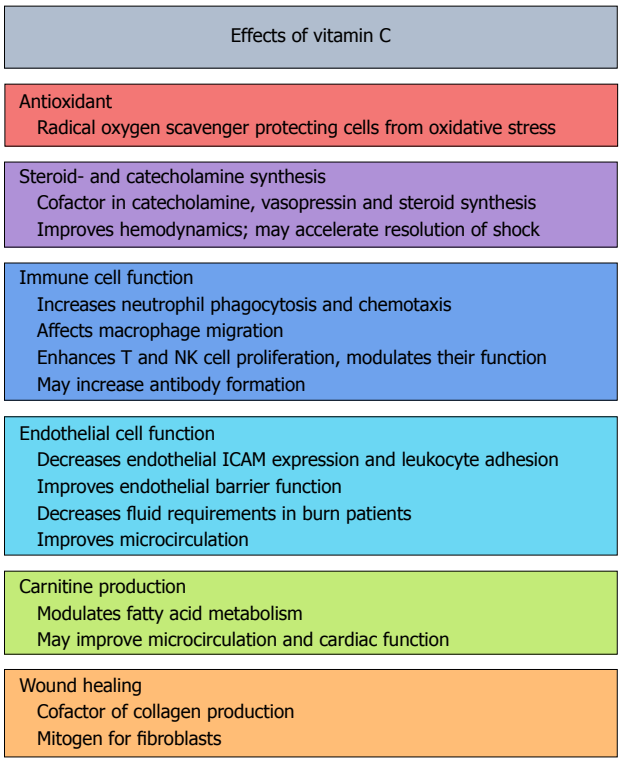

Figure 1 Biological functions of vitamin C. NK: Natural killer cells; ICAM: Intercellular adhesion molecule.

investigation, a growing number of benefits of vitamin C administration have been identified for medical treatment, including in the field of critical care. This mini-review will examine the evidence in support of vitamin C administration for critically ill patients and provide general recommendations for use by intensive care unit practitioners.

VITAMIN C LEVELS IN THE CRITICALLY ILL

Vitamin C is water-soluble and circulates in the plasma. It is freely filtered by the glomerulus and reabsorbed in the proximal tubule *via* the first sodium-dependent vitamin C transporter (SVCT1). In the setting of hypovitaminosis C, its urinary excretion is minimal[5]. While SVCT1 regulates whole-body homeostasis of vitamin C, a high-affinity, low-capacity sodium-dependent vitamin C transporter SVCT2 protects metabolically-active cells against oxidative stress, which facilitates vitamin C accumulation where it is needed[6]. The recommended daily oral dose of vitamin C is 75 mg (adult female)/90 mg (adult male), and only ten mg of daily oral vitamin C is necessary to prevent scurvy (plasma level < 0.1 mg/dL; normal range 0.8-1.6 mg/dL). Despite meeting these recommended daily intakes, many critically ill patients exhibit decreased vitamin C plasma levels. Carr *et al*[7] reported hypovitaminosis C in 44 critically ill patients receiving standard intensive care unit nutrition, of which one-third had vitamin C deficiency. The degree of vitamin C deficiency was more pronounced in the septic population as compared to the non-septic critically ill. Continuous renal replacement is commonly utilized in critically ill patients and is believed to lead to a depletion of water-soluble vitamins[8-10]. A retrospective study of critically ill patients receiving continuous renal replacement revealed that 87% (13 out of 15) had vitamin C deficiencies[9].

BIOLOGICAL EFFECTS OF VITAMIN C

Among vitamin C's pleiotropic functions that are of relevance to critical illness are its immune-enhancing effects, anti-oxidant properties, and potential anti-mutagenic effects[11,12]. Vitamin C has been shown to enhance neutrophil chemotaxis, phagocytosis, and thus microbial clearance[13,14]. In addition, vitamin C promotes T cell and natural killer cell proliferation and modulates their functions[13,15]. Studies on vitamin C's effects on B cells have revealed conflicting data with regard to proliferation and differentiation[13,15]. Vitamin C appears to induce antibody production in human lymphocytes and those of guinea pigs[16,17]. In a mouse model of abdominal sepsis induced by cecal-puncture ligation, parenteral vitamin C administration improved sepsis outcomes through reversal of regulatory T cell inhibitory function[18]. Hypovitaminosis C in a sepsis model using guinea pigs was also associated with fewer macrophages in the peritoneal cavity and impaired macrophage migration[19,20]. Interestingly, the adverse effects of vitamin C deficiency were more pronounced in elderly guinea pigs[19].

In cell culture and rodent experiments, vitamin C has been shown to decrease lipid peroxidation, prevent occludin dephosphorylation, and thus diminish the loosening of tight junctions[5,21-23]. Vitamin C also improves microcirculatory flow impairment by inhibiting tumor-necrosis-factor (TNF)-induced intercellular adhesion molecule 1 expression, thereby decreasing leukocyte adhesiveness[5,24,25]. In smokers, a single bolus administration of vitamin C (3 g Ⅳ) was found to increase coronary flow reserve, which is an integrated parameter of endothelial function and vascular smooth muscle relaxation. This effect was not seen in healthy control patients[26].

Vitamin C is a cofactor in collagen synthesis, a mitogen for fibroblasts, and is believed to positively modulate proinflammatory signaling and inflammation resolution that occur in wound beds[27,28]. Vitamin C supplementation in deficient mice promotes wound healing through enhanced matrix deposition and fibroblast proliferation[27]. In addition, topical vitamin C increases dermal collagen biosynthesis in healthy volunteers[29,30]. However, vitamin C supplementation does not consistently improve pressure ulcer healing in nursing homes and hospitalized patients, and recent systematic reviews have concluded that vitamin C (often administered in conjunction with zinc and other nutrients) is ineffective in treatment for this condition[31-35].

Vitamin C is a cofactor in carnitine synthesis, a molecule that facilitates fatty acid shuttling into mitochondria,

reduces oxidative stress, and promotes endothelial sprouting[36,37]. Its deficiency has been linked to cardiomyopathy and neurometabolic disease[38,39]. Despite carnitine's essential metabolic roles, clinical data to date have not yielded convincing evidence that supplementation in critically ill patients will improve outcomes[40-42].

Vitamin C is also a cofactor in catecholamine synthesis and adrenal steroidogenesis[43,44]. Vitamin C contributes to the conversion of dopamine to norepinephrine by dopamine beta-hydroxylase[45]. Vitamin C enhances norepinephrine synthesis both by recycling tetrahydrobiopterin, a critical cofactor in catecholamine synthesis, and increasing tyrosine hydroxylase expression[46]. Furthermore, vitamin C is a cofactor for the peptidylglycine α-amidating monooxygenase that is required for the endogenous synthesis of vasopressin[47]. One study in cardiac surgical patients has suggested that pre-operative administration of vitamin C mitigates etomidate-induced adrenal suppression[48]. Thus, there has been significant interest in utilizing vitamin C for the management of hemodynamically-unstable patients[49].

VITAMIN C IN CARDIOVASCULAR PATIENTS

While a recent review concluded that there is insufficient evidence to support the use of vitamin C to reduce cardiovascular disease risk or mortality in the general population, increasing evidence suggests that it may have a beneficial role in patients with acute coronary syndromes or undergoing cardiac surgical procedures[50]. Cardiac surgery, extracorporeal membrane oxygenation and hemodialysis produce oxidative stress, which negatively impacts morbidity and mortality[51]. Vitamin C's ability to scavenge reactive oxygen species and increase nitric oxide production through induction of endothelial nitric oxide synthase have made it a focus of interest as a cardiovascular therapy adjunct[52]. In one study of cardiac surgical patients undergoing cardiopulmonary bypass, statistically significant reductions in plasma levels of vitamin C were found intraoperatively compared to preoperative levels, even prior to initiation of cardiopulmonary bypass (Δ16.3% compared to baseline). This decrease in vitamin C plasma levels continued after cardiopulmonary bypass and lasted for at least six days[53].

Perioperative vitamin C administration has also been shown to prevent post-operative atrial fibrillation in the majority of the studies[54-59]. Its effects appear to result in reductions in the duration of hospital and intensive care unit patient stay following cardiac surgery[54-57].

Other studies examining the effects of vitamin C administration on patients with acute myocardial infarction and undergoing coronary revascularization procedures have reported improved left ventricular ejection fraction, microcirculation, and limited infarct size in patients with acute myocardial infarction[60-62]. One recent randomized multicenter clinical trial on patients with myocardial infarction undergoing percutaneous coronary angioplasty did not show a significant improvement in infarct size or ejection fraction at the time of the intervention with vitamin C administration. However, a decline in the LVEF between 7-15 d and 2-3 mo noted in the control group was not seen in the vitamin C group[63]. The authors of this study suggested that vitamin C may have ameliorated myocardial reperfusion injury[63].

In addition to potential beneficial effects on microperfusion and myocardial protection, a growing body of evidence suggests that vitamin C administration may positively affect hemodynamic parameters and hasten freedom from vasopressors in critically ill patients[64-67]. Interestingly, some evidence suggests that vitamin C's effects on hemodynamics may have a ceiling effect. A recently reported pharmacokinetic study by de Grooth *et al*[68] only found a minimal reduction in heart rate among critically ill patients randomized to receive 2 g/d *vs* 10 g/d of vitamin C. However, only the treatment group that received the 2 g/d of vitamin C, but not the 10 g/d treatment regimen, had a clinically-relevant decrease in norepinephrine requirements over 48 h[68].

VITAMIN C IN BURN-INJURED PATIENTS

Increased capillary leakage is a clinical hallmark of burn injury. It is associated with significant fluid and protein extravasation. The term "fluid creep" was coined to describe the phenomenon that burn patients often receive significantly more resuscitation fluid than anticipated based on Parkland formula calculations[69]. This excess fluid resuscitation can be associated with edema-related complications[70]. Endothelial damage leading to increased permeability in patients with burn injury may partly be mediated by reactive oxygen species-induced lipid peroxidation. As an antioxidant, vitamin C has been evaluated as a therapy to decrease fluid resuscitation requirements[71,72]. In a rodent model of burn injury, high-dose vitamin C appeared to improve microvascular barrier dysfunction, without affecting leukocyte activation[73]. In a study of guinea pigs with 70% third-degree burns given high dose vitamin C (170, 340 and 680 mg/kg per day), fluid requirements were significantly reduced while stable cardiac outputs were maintained[74]. In a study of dogs with burn injuries, vitamin C administration (14 mg/kg per hour) decreased lipid peroxidation and microvascular protein and fluid leakage[75]. A burn study in sheep provided additional evidence that high-dose vitamin C (250 mg/kg bolus plus 15 mg/kg per hour) could reduce fluid requirements and lipid peroxidation, as well as improve antioxidant status[76]. Preliminary studies in humans have also been promising. In a study of 37 patients with > 30% total body surface area burns, vitamin C administration (66 mg/kg per hour) reduced fluid requirements, wound edema, and increased the ratio of PaO2 to a fraction of inspired oxygen[66]. In a retrospective review of 40 patients with > 20% total body surface area, vitamin C (66 mg/kg per hour) was associated with increased urine output and decreased fluid requirements, but no change in outcomes or incidence of acute kidney injury[77]. In another small

study (n = 30) of patients with second degree burns, topical vitamin C accelerated formation of granulation tissue[78].

VITAMIN C IN SEPTIC PATIENTS

There has recently been a surge of interest in the use of vitamin C as an adjuvant treatment for sepsis. This interest was stimulated by the findings of a cohort study by Marik *et al*[64] that administered a cocktail of vitamin C (1.5 g Ⅳ every 6 h), hydrocortisone (50 mg Ⅳ every 6 h) and thiamine (200 mg Ⅳ every 12 h) to 47 septic patients and found a significant reduction in SOFA scores, dependence on vasopressors, and most importantly in hospital mortality to 8.5% in the treatment arm *vs* 40.4% in a historic control group. These findings were consistent with small phase Ⅰ double-blinded placebo-controlled trials suggesting the beneficial effects of vitamin C in patients with sepsis[67]. This trial, which randomized 24 septic patients with documented hypovitaminosis C to receive placebo, low-dose (50 mg/kg per day) or high-dose (200 mg/kg per day) parental vitamin C for four days, found significant reductions in SOFA scores and CRP plasma levels in the vitamin C-treated groups[67]. In another small trial of critically ill surgical patients, Zabet *et al*[65] reported a significant reduction in 28 d mortality in 14 patients with septic shock who were randomized to receive 25 mg/kg per day of ascorbic acid every 6 h for 72 h, when compared to 14 patients with septic shock who received placebo. Despite these promising findings, there are potential safety concerns worthy of consideration with vitamin C administration in the critically ill population. A recent study by De Grooth *et al*[68] evaluated four parenteral vitamin C repletion regimens (2 g/d *vs* 10 g/d; bolus *vs* continuous infusion) administered for 48 h to critically ill patients with multiple organ dysfunction. The patients receiving 10 g vitamin C per day had supraphysiologic vitamin C levels and hyperoxaluria, oxalate being a metabolite of vitamin C. These findings raise concern for an increased risk of oxalate nephropathy, as has been reported with high-dose vitamin C administration and more prolonged administration in the noncritically ill population[68,79,80]. This theoretical risk of oxalate nephropathy stands in contrast with the mostly reassuring data about the safety of short-term high-dose vitamin C administration[64,65,67].

At present, multiple ongoing randomized controlled trials, including the VICTAS, ACTS, and HYVCTTSSS trials, are aimed at confirming the beneficial effects of vitamin C and adjuncts in critically ill patients with sepsis[81-83].

VITAMIN C IN HEMORRHAGIC SHOCK

Trauma and hemorrhagic shock can lead to significant coagulopathy and inflammation, and both are associated with increased mortality and morbidity. Given its antioxidant effects, vitamin C has long been evaluated as a protective agent to mitigate effects on proinflammatory and procoagulant pathways caused by trauma and hemorrhagic shock[84-88].

In a swine model of acute hemorrhagic shock, animals were randomized to receive either intravenous normal saline, low-dose Vitamin C (50 mg/kg), or high-dose Vitamin C (200 mg/kg). The group of animals receiving normal saline (control) showed significantly greater histological end-organ damage, including elevated acute lung injury scores and increased mRNA levels of interleukin (IL)-1β, IL-8, TNF-α, plasminogen activation inhibitor-1 and tissue factor compared with the groups receiving vitamin C. Furthermore, only a modest correction of coagulopathy was observed in the vitamin C group when compared to the normal saline group[88]. Similarly, in a rat model of hemorrhagic shock, vitamin C administration (low 100 mg/kg or high 500 mg/kg) was shown to attenuate renal injury, possibly *via* a SIRT1-mediated mechanism. Levels of serum creatinine, BUN, TNF-α, and IL-1β were lower in the vitamin C group when compared to a sham group. Conversely, levels of hemeoxygenase-1 (HO-1), a stress-response protein believed to play key roles in mediating protection against oxidant-mediated lung injury, were higher in kidneys treated with vitamin C. This effect appeared to occur irrespective of the vitamin C dose administered[89]. Another study of the effects of vitamin C administration (100 mg/kg) on renal function found a decrease in expression of the induced dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin protein in the tubular epithelial cells of rat kidneys. Levels of this protein are believed to correlate with the occurrence of kidney injury. Vitamin C administration prior to resuscitation was also found to decrease proinflammatory cytokine production, which mitigated renal injury[90]. Another rat model of hemorrhagic shock found that vitamin C treatment induced HO-1 expression in a variety of tissues, including kidney, lung and liver, with decreased organ injury and proinflammatory responses[91]. Likewise, vitamin C pretreatment in the setting of hemorrhagic shock appears to protect the intestinal epithelium by decreased proinflammatory cytokine expression and neutrophil infiltration. This effect was also believed to be mediated by HO-1 and was abrogated by pharmacological HO-1 inhibition[92]. Prior studies have suggested that pretreatment of rats with vitamin C (1 mg/100 g or 5 mg/100 g) decreases gastric mucosal bleeding after induction of hemorrhagic shock and retransfusion[93]. Lastly, the combination of vitamin C administration (50 mg/kg per day for 3 d) prior to inducing hemorrhage together with intravenous infusion vitamin C (50 mg/kg) following hemorrhage improved cardiovascular parameters, such as blood pressure and LV dp/dt, and decreased free radical production in a rat model of hemorrhagic hypotension[94].

These beneficial effects of vitamin C stand in contrast with those obtained in a rat model of liver injury and hemorrhagic shock, in which vitamin C preconditioning (10 mg/kg) did not improve the recovery of animals after resuscitation[95]. Likewise, a survival study in rats with hemorrhagic shock did not show a difference when lactated Ringer's solution plus vitamin C (50 mg/kg) was administered for resuscitation, compared with lactated

Ringer's solution alone[96].

These preclinical studies point out multiple mechanisms by which vitamin C may serve as an antioxidant in hemorrhagic shock and thus could provide organ protection. However, evidence suggesting a vitamin C-mediated survival benefit is missing. To our knowledge, there is thus far no human trial data available that demonstrate a clinical benefit of vitamin C administration as an adjunct for the treatment of trauma and hemorrhagic shock.

VITAMIN C AND PAIN

Pain is a common problem in critically ill patients, either due to injuries secondary to infection, inflammation, trauma, surgery, cancer, or in the setting of the reactivation of herpes zoster. Evidence suggests that vitamin C acts as a cofactor for the biosynthesis of opioid peptides and as a potent anti-inflammatory agent[97,98].

Several case reports and a cohort study have reported clinical improvement in relief for patients with acute herpes zoster exacerbation who were administered vitamin C [99-101]. While a recent randomized controlled trial of high dose intravenous vitamin C (5 g *iv* bolus per day on day 1, 3 and 5) failed to find a reduction in acute herpes zoster pain, there was a decrease in the incidence of post-herpetic neuropathy[102]. A similarly designed study found lower plasma concentrations of vitamin C in patients with post-herpetic neuropathy than in healthy volunteers, and a reduction in spontaneous post-herpetic neuropathy pain after high-dose vitamin C treatment[103].

Several trials have found reductions in the development of complex regional pain syndrome after wrist and ankle surgery with vitamin C[104-107]. A study of patients with osteoarthritis-related hip or knee joint pain found that vitamin C that was administered enterally for 14 d provided modest pain relief, equivalent to approximately half the effect of nonsteroidal anti-inflammatory drugs[108]. In a randomized controlled trial of vitamin C in patients undergoing single-level posterior lumbar interbody fusion, there was no difference in postoperative pain intensity between the two groups, but vitamin C administration was associated with improved functional status[109].

A majority of the prospective and case studies of vitamin C administration for cancer-related pain have reported improvements in quality-of-life indicators such as pain, fatigue, insomnia, nausea and vomiting[110-115]. However, clinical trial data regarding vitamin C-related opioid-sparing effects in cancer patients have yielded mixed results[116-119].

VITAMIN C IN CANCER PATIENTS

Perhaps more widely investigated than any other vitamin C-related claim is the assertion of benefit for patients with cancer. In fact, a quick PubMed search of "ascorbic acid + cancer" yielded 4,376 items, 247 of which were clinical trials (as of May 2018).

Cancer patients have been recognized to have low vitamin C levels compared with healthy controls[120]. In a large randomized, placebo-controlled trial, daily intake of antioxidants, vitamins and minerals, a combination of vitamin C (120 mg/d), vitamin E, zinc, beta carotene and selenium lowered total cancer incidence and all-cause mortality in men but not women at 7.5 years[121]. A similar regimen of vitamin C and E supplementation with beta carotene did not, however, prevent the formation of colon adenomas in a randomized trial of 864 patients[122]. Another study of vitamin C and E supplementation for cancer prevention did not identify immediate or long-term effects on the risk of total cancers, prostate cancer, or other site-specific cancers[123].

A randomized clinical trial examining different doses of vitamin C (1, 2 or 4 g/d) failed to find a dose-response relationship or an association between serum ascorbic acid levels and mutagen sensitivity, which has been described as a risk factor for tobacco-related epithelial cancers[124]. Despite these clinical findings, basic science data suggest that vitamin C may have a beneficial role in cancer progression through several different mechanisms. Vitamin C was recently found to restore Tet methylcytosine dioxygenase 2 function, one of the most frequently mutated genes in hematopoietic malignancies. Through this mechanism, vitamin C may block aberrant self-renewal and leukemia progression[125]. Vitamin C also facilitates DNA oxidation in leukemia cells, rendering them more sensitive to poly ADP ribose polymerase inhibitors[125].

In cholangiocarcinoma, SVCT2 expression levels have been shown to correlate with susceptibility to vitamin C-induced cancer cell death *in vitro* and *in vivo*[126]. In separate experiments, Vitamin C has been shown to increase methotrexate-mediated hepatocellular carcinoma cell death[127]. Furthermore, vitamin C enhances the effectiveness of radiation therapy for glioblastoma and gemcitabine/epigallocatechin-3-gallate treatment for mesothelioma[128,129]. These findings are in contrast to data showing that vitamin C interferes with chemotherapy drugs such as doxorubicin, methotrexate, and cisplatin[128-131]. Moreover, vitamin C may enhance the growth of some cancers. For example, plasmocytoma cell growth is dependent on the presence of vitamin C[132]. Vitamin C exposure showed differential effects in an *in vitro* model of colony-forming bone marrow cell growth in patients with myelodysplastic syndrome. In this model, vitamin C responsiveness (both growth enhancement or inhibition) was associated with shorter survival when compared to patients with no response to vitamin C[133]. Adding to this complex picture is data derived from *in vitro* work that examined the response of HL-60 cells from an acute myeloid leukemia cell line to vitamin C. Vitamin C administration decreased oxidative stress and thus protected HL-60 cells from H_2O_2-induced cell death[134].

Curiously, high-dose vitamin C (0.5-5 mmol/L) has also been shown to increase the procoagulant properties of freshly isolated red blood cells *via* externalization of phophatidylserine, a mechanism known to lead to throm-

bus formation. Interestingly, this effect was more pronounced in red blood cells from cancer patients and could be confirmed in a rat model of thrombus formation[135].

In one study in terminal cancer patients, vitamin C was associated with increased quality-of-life and survival[116]. In contrast, in two double-blinded randomized controlled trials that included patients with advanced cancers (stomach, colon, pancreas, lung, breast and others), vitamin C (10 g/d) did not improve survival[136,137].

Given the complexities of cancer biology and vitamin C, the risks and benefits of initiating high-dose vitamin C therapy in critically ill oncology patients should be carefully weighed and discussed with the oncology consultant.

CONCLUSION

Vitamin C is once again a focus of intense interest with respect to its role in the treatment of critically ill patients. Evidence suggests that vitamin C administration may have a variety of beneficial effects in patients undergoing cardiac surgical procedures, during resuscitation with acute burn injury, for the treatment of sepsis, in reducing pain, and in the treatment of cancer. While many questions have yet to be answered, there is little data to suggest that short-term high-dose vitamin C would elicit major harm, except for the risk of oxalate nephropathy. In fact, evidence suggests that short-term high-dose vitamin C in selected patients may improve hemodynamic parameters, decrease fluid resuscitation requirements, reduce the incidence of perioperative atrial fibrillation, improve pain and potentially reduce sepsis-associated mortality. We eagerly await additions to the growing body of evidence that examine the role of vitamin C administration for improving outcomes for our sickest patients.

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REVIEW

Respiratory failure in the hematopoietic stem cell transplant recipient

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Abstract

The number of patients receiving hematopoietic stem cell transplantation (HSCT) is rapidly rising worldwide. Despite substantial improvements in peri-transplant care, pulmonary complications resulting in respiratory failure remain a major contributor to morbidity and mortality in the post-transplant period, and represent a major barrier to the overall success of HSCT. Infectious complications include pneumonia due to bacteria, viruses, and fungi, and most commonly occur during neutropenia in the early post-transplant period. Non-infectious complications include idiopathic pneumonia syndrome, peri-engraftment respiratory distress syndrome, diffuse alveolar hemorrhage, pulmonary veno-occlusive disease, delayed pulmonary toxicity syndrome, cryptogenic organizing pneumonia, bronchiolitis obliterans syndrome, and post-transplant lymphoproliferative disorder. These complications have distinct clinical features and risk factors, occur at differing times following transplant, and contribute to morbidity and mortality.

Key words: Respiratory failure; Pulmonary complications; Hematopoietic stem cell transplantation; Stem cell transplant; Immunocompromised host

Core tip: Respiratory failure in the hematopoietic stem cell transplant recipient is common and is a major contributor of morbidity, mortality, and healthcare utilization. Etiology may be infectious or non-infectious in nature, and in some cases these may coexist. While identification remains challenging, infectious and non-infectious syndromes have distinct clinical features and risks.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is increasingly utilized worldwide for definitive treatment of hematologic malignancy and other conditions, with over 50000 transplants performed annually[1]. During HSCT, patients undergo high dose conditioning chemotherapy and/or radiation therapy with a view to eradicate their immune system along with any residual malignant cells. Stem cells are collected beforehand and are administered after conditioning is complete to reconstitute the immune system. HSCT may be autologous (where the donor stem cells are the patient's own) or allogeneic (where the donor stem cells are from an appropriately matched donor).

The post-transplantation period is temporally separated into three phases and represents a dynamic, individualized spectrum of risk (Figure 1). The first phase is the pancytopenic phase immediately following transplantation, typically lasting 10-21 d following HSCT. Autologous transplant recipients typically engraft before allogeneic, and several peri-transplant factors such as peripheral stem cell harvest and the use of granulocyte stimulating factors in the post-transplant period promote earlier marrow recovery. The second phase occurs after neutrophil engraftment, once the absolute neutrophil count consistently exceeds 500 cells per mm^3. The second phase typically lasts for the first 100 or so days following transplantation. The third phase can be considered "late" complications of transplantation, occurring more often in allogeneic transplantation where graft-versus-host effects have pulmonary manifestations. Pulmonary complications and respiratory failure are common, occurring in up to two-thirds of HSCT recipients, and are associated with significant morbidity and mortality[2-4]. These pulmonary complications can be characterized by the phase of the post-transplant period when they are most likely to occur (Figure 1). The purpose of this mini-review is to highlight the infectious and non-infectious sources of respiratory failure in the HSCT recipient.

INITIAL APPROACH IN THE ACUTELY ILL PATIENT

Respiratory failure following HSCT presents on a spectrum of severity. Several aspects of the clinical presentation provide clues about possible etiologies: acute versus subacute, early post-HSCT or late post-HSCT, diffuse versus focal. A substantial number of patients on the more severe end of this spectrum present with acute hypoxemic respiratory failure and diffuse pulmonary infiltrates, meeting criteria for the acute respiratory distress syndrome (ARDS)[2]. While the underlying etiology is often not known at the time of presentation, the principles of ARDS management and prevention are equally valid in this population. Specifically, this includes lung-protective mechanical ventilation with low tidal volume strategies, appropriate recruitment, and use of neuromuscular blockade where appropriate[5-7]. In addition, there should be a focus on preventing iatrogenic "second-hits" through judicious fluid and blood product administration, aspiration precautions, and early focus on mobilization and ventilator liberation[7-10]. These lung injury prevention guidelines have been conceptualized into the Checklist for Lung Injury Prevention, which was recently implemented as part of an ARDS prevention clinical trial[7,11]. Patients with pre-existing pulmonary disease are more susceptible to pulmonary complications, particularly those receiving high dose radiation to the lungs as part of their conditioning program[12,13]. Concurrently, patients should be evaluated for possible etiologies for their presentation. These can be divided broadly into infectious and non-infectious causes.

INFECTIOUS RESPIRATORY FAILURE

Infectious pulmonary complications are most common in the immediate post-transplant period during neutropenia. Recipients of allogeneic HSCT are typically more prone to infectious pulmonary complications due to a longer period of neutropenia and the need for immunosuppressant medication administration to prevent graft-versus-host disease[14]. Routine infectious prophylaxis during neutropenia has dramatically reduced the burden of infectious complications. However, breakthrough infections can occur from a variety of causative organisms and vary dependent on patient and transplant characteristics, and time elapsed following transplant (Figure 1)[3].

Bacterial

Bacterial pneumonias most commonly occur in the early transplant period[15]. Risk for bacterial pneumonias in allotransplants is greater if myeloablative (as opposed to non-myeloablative or reduced intensity) conditioning is used, the patient has graft-versus-host disease, there is delayed engraftment and a prolonged period of neutropenia, or if there are indwelling devices[16-18]. In the early post-transplant period, gram-negative organisms such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* should be suspected, whereas encapsulated organisms are a concern late after HSCT[19]. When patients develop hypoxemic respiratory failure and new pulmonary infiltrates following HSCT, infection is typically presumed. This approach is reasonable given the substantial mortality associated with delayed antimicrobial therapy in immunocompromised patients. Ideally, microbiological sampling from bronchoalveolar lavage (BAL) is preferred,

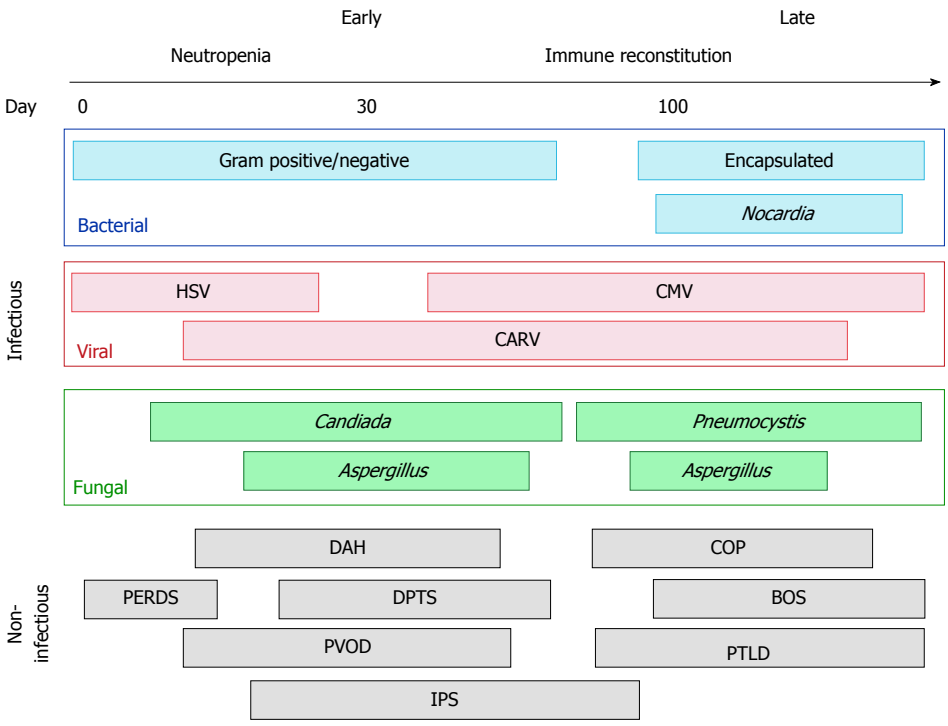

Figure 1 Time-course of pulmonary complications following hematopoietic stem cell transplantation. BOS: Bronchiolitis obliterans syndrome; CARV: Community-acquired respiratory viruses; CMV: Cytomegalovirus; COP: Cryptogenic organizing pneumonia; DAH: Diffuse alveolar hemorrhage; DPTS: Delayed pulmonary toxicity syndrome; HSV: Herpes simplex virus; IPS: Idiopathic pneumonia syndrome; PERDS: Peri-engraftment respiratory distress syndrome; PTLD: Post-transplant lymphoproliferative disorder; PVOD: Pulmonary veno-occlusive disease.

although the risk and benefits of invasive sampling need to be individually assessed. If patients are on antibacterial infectious prophylaxis when pneumonia is suspected, antibacterial agents should be broadened to cover nosocomial pathogens[20,21].

Certain infectious syndromes are worthy of additional discussion. Encapsulated bacteria, particularly *Streptococcus pneumoniae*, should be suspected later following HSCT, most commonly after 6 mo[22]. Invasive pneumococcal disease has been reported to be 30 times more prevalent in HSCT recipients compared to the general population[15], and up to 88% of cases have bacteremia[23]. Nocardia pneumonia can occur in the late post-transplant period, usually after 6 mo[24]. While nocardial infection is uncommon after HSCT, it should be suspected in non-responders to initial antimicrobial therapy. Sulfamethoxazole-trimethoprim is the treatment of choice and response to therapy is typically robust[24,25]. Routine use of sulfamethoxazole-trimethoprim for *Pneumocystis* prophylaxis does not adequately protect against nocardiosis. Mycobacterial pneumonia is rare, but can occur in the late post-transplant period, and typically presents one year after HSCT[26,27]. Incidence of *Mycobacteria tuberculosis* among HSCT recipients is higher in endemic areas and those receiving allogeneic grafts[27]. Presentation and management of these infections and non-tuberculous *Mycobacteria* are similar to that of the general population[27,28].

Viral

Herpes simplex virus (HSV) infection is relatively uncommon following HSCT due to routine infectious prophylaxis with acyclovir[29]. HSV pneumonia typically occurs in the early post-transplant period and is a result of latent reactivation (Figure 1). Allotransplants receiving grafts from seropositive donors and those with graft-versus-host disease are at increased risk of HSV[29,30]. Diagnosis of HSV pneumonia can be challenging since low-grade HSV reactivation and viral shedding is not uncommon in critical illness, and qualitative polymerase chain reaction (PCR) on BAL samples is exquisitely sensitive.

Cytomegalovirus (CMV) pneumonia occurs in up to 30% of allotransplants and typically presents after engraftment until around 4 mo (Figure 1)[31,32]. It occurs most commonly when a seropositive allograft recipient receives a seronegative transplant. Pulmonary imaging findings are nonspecific, typically bilateral and diffuse, with both alveolar and nodular opacities[33]. BAL fluid should be analyzed to confirm the presence of CMV by PCR (most common), shell assay, or viral culture. Again, low grade CMV shedding is not uncommon in critical illness and doesn't necessarily indicate pneumonitis. Definitive diagnosis requires demonstration of tissue involvement on lung biopsy[34], but this is rarely performed. In the presence of CMV in BAL and a compatible clinical/radiographic picture, supportive evidence of widespread CMV reactivation is usually needed before initiation of treatment. Elevated and escalating quantitative serum PCR, or evidence of CMV involvement in other organs (*e.g.* gut, CNS) all support systemic CMV infection. Ganciclovir is the treatment of choice for invasive CMV disease, though treatment can be limited by leukopenia,

particularly problematic among the HSCT population[35]. The epidemiology of post-HSCT CMV pneumonitis may change if novel CMV prophylactic agents are routinely administered[36].

The community-acquired respiratory viruses (CARV) including influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, rhinovirus, enterovirus, and coronavirus, can occur during the entire post-transplant period (Figure 1)[37]. Diagnosis occurs most commonly by nasal PCR-amplification assays, or with BAL. RSV is the most commonly isolated CARV, and is estimated to be recovered in up to a third of patients undergoing HSCT in the first three years[37-39]. In addition to hypoxia, patients typically present with fever, productive cough, and dyspnea[37,40]. Chest imaging findings include diffuse patchy alveolar opacities[40]. RSV in the HSCT population is highly morbid and has mortality rates reported up to 80%. Beyond supportive care no specific therapy has shown consistent benefit. Given the high mortality rates in HSCT recipients, high RSV titer immune globulin or aerosolized ribavirin may be considered[41].

Fungal

Pulmonary aspergillosis effects up to two-thirds of HSCT recipients, although incidence is declining with routine anti-*Aspergillus* prophylaxis during neutropenia and more effective treatment of graft-versus-host disease[42-44]. Pulmonary aspergillosis has been reported in upwards of 30% of HSCT recipients[3,42]. Risk factors include allogeneic transplant, unrelated donors, prolonged neutropenia, immunosuppressant use for graft-versus-host disease, and CMV infection[45-47]. Most common findings radiologically include pulmonary nodules with or without halo sign, ground glass opacities, and an air crescent sign from necrotic tissue in advanced cases[47-49]. Hemoptysis can be present and is typically associated with poor prognosis[50-52]. Diagnosis is confirmed by *Aspergillus*-specific PCR or *Aspergillus* sp. antigen in BAL[53,54]. Monotherapy with isavuconazole or voriconazole is the preferred first-line treatment and therapeutic drug monitoring should be utilized to ensure adequacy of dosing[55]. Severe cases refractory to medical therapy or recurrent hemoptysis may be considered for surgical evaluation, though lung resection is highly morbid and associated with significant mortality in this population[56].

Incidence of *Pneumocystis jirovecii* pneumonia (PCP) has marginally declined in recent years as the use of prophylaxis has increased[57,58]. However, there is limited guidance and no consensus on which patients outside of HIV-positive individuals should receive prophylaxis, and therefore PCP remains highly relevant in HSCT recipients. Our institution routinely implements prophylaxis from engraftment until the first 100 d (or longer if patients are immunosuppressed for graft-versus host disease). PCP occurs late after HSCT and presents with acute onset severe respiratory failure[58-60]. Diagnosis is confirmed by the identification of *Pneumocystis* organisms in respiratory samples by PCR or fungal smear[58,61]. Sulfamethoxazole-trimethoprim is the treatment of choice and is highly effective in killing *Pneumocystis* sp[58]. Patients with PCP typically die due to refractory hypoxemia from severe respiratory failure, and corticosteroids have failed to demonstrate benefit outside of the HIV population[62,63]. Nonetheless, adjunctive corticosteroids are typically administered in individuals with HSCT who develop PCP.

NON-INFECTIOUS RESPIRATORY FAILURE

Noninfectious respiratory failure syndromes are common throughout the entire post-HSCT period, and our understanding of them remains incomplete. The risks of these syndromes vary based on transplant type, and a variety of modifiable and non-modifiable transplant and patient characteristics. In addition to key distinguishing clinical criteria, non-infectious complications are categorized by when they occur temporally following HSCT (Figure 1). Often infection cannot be ruled out at the time of initial presentation and should be concurrently treated given the substantial mortality associated with delayed antimicrobial administration.

Peri-engraftment respiratory distress syndrome

The peri-engraftment respiratory distress syndrome (PERDS) is a pulmonary subset of the engraftment syndrome, a systemic capillary leak disorder that develops around the time of immune system reconstitution early after autologous HSCT (Figure 1)[64]. PERDS is defined as hypoxemic respiratory failure and bilateral pulmonary infiltrates that occur in the 5 d surrounding neutrophil engraftment, not fully explained by cardiac dysfunction or infection.

Focused studies of PERDS patients found an incidence of nearly 5% in autotransplants[65,66]. Case-fatality rates in excess of 20% nearly two decades ago have substantially reduced to 6% in the current era[65,66]. Risk factors include female gender, blood product administration, rapid engraftment, and HSCT for the POEMS syndrome. We recently found radiographic changes consistent with lung injury precede neutrophil engraftment and may aid in early identification of the syndrome[66]. Treatment consists of short courses of high dose corticosteroids, most commonly 1 to 2 mg/kg methylprednisolone twice daily for 3 d, followed by a rapid taper[65,67]. Response is typically prompt with improvements in oxygenation in most within 24 h of steroid initiation.

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is a syndrome characterized by diffuse, bilateral pulmonary infiltrates, progressively bloody return during BAL, and presence of > 20% hemosiderin-laden macrophages in alveolar lavage fluid[64]. While hemoptysis can be seen, it is often absent[68]. DAH mainly occurs during the early post-transplant period (Figure 1).

DAH occurs in 5%-12% of HSCT recipients and is highly morbid with reported mortality rates as high as

60% to 100%[68-72]. Risk factors include age over 40 years, higher intensity conditioning therapies, total body irradiation, and HSCT for acute leukemia and myelodysplastic syndrome[69,70,73]. Our understanding of DAH following HSCT is limited. While some cases of alveolar hemorrhage occur during the thrombocytopenic period following transplant, many cases occur after platelet counts are adequate. Also, while DAH may occur in the setting of ARDS or pneumonia, some DAH cases occur in the absence of both.

Treatment of DAH consists of high-dose corticosteroids, most commonly 500 to 1000 mg methylprednisolone per day for 5 d[70,72,74-76]. While one study showed improved survival in 8 patients treated with anti-fibrinolytic aminocaproic acid[70], a subsequent larger study failed to show benefit[75]. Further, even in the presence of thrombocytopenia, platelet transfusion did not affect morbidity or mortality in DAH[68].

Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) is an umbrella term for widespread alveolar injury occurring in the absence of cardiac or renal dysfunction, iatrogenic-induced circulatory overload, and infection[64]. Symptoms are consistent with ARDS and pulmonary imaging typically reveals diffuse, bilateral pulmonary infiltrates. There are many similarities and overlap in the clinical presentation of IPS and other non-infectious complications discussed in this review. Those conditions have key distinguishing features and are therefore discussed separately.

IPS effects up to 10% of HSCT recipients, more so allotransplants, and typically occurs during the early post-transplant period (Figure 1)[64]. Mortality is as high as 80% and even greater in those requiring respiratory support with the mechanical ventilator[45,64]. Risk factors include higher intensity conditioning therapies, radiation administration, allogeneic transplant, age, and the presence of graft-versus-host disease.

Treatment of IPS is controversial, and no therapy has shown favorable outcome. Corticosteroids may be administered, though while some studies have shown benefit[45,77], others have not[78,79]. When given, higher doses (4 mg/kg per day, prednisolone equivalent) have been shown to be no better than lower doses (2 mg/kg per day or less, prednisolone equivalent), but have the potential to carry greater risk of adverse effects[45]. There has been an ongoing interest in tumor necrosis factor (TNF)-α inhibition due to the observation that patients with IPS have cytokine-rich BAL fluid[64]. Preliminary retrospective studies have shown promise with increased response rates and improved overall survival when TNF-α inhibitor, etanercept, was added to corticosteroid therapy[80,81], though these findings were not replicated when a randomized controlled trial design as applied[82]. Further studies are needed to better phenotype what IPS truly represents, and whether any therapies can be effective.

Pulmonary veno-occlusive disease

Pulmonary veno-occlusive disease (PVOD) is a rare complication of HSCT with high associated mortality, typically occurring late after HSCT (Figure 1)[83-85]. PVOD should be suspected in those who are progressively dyspneic, have evidence of pulmonary hypertension in the absence of left heart failure, and imaging suggestive of pulmonary edema[64,83,85]. PVOD may occur in the absence of these and therefore, diagnosis must be confirmed by the presence of fibrous intimal proliferation of the pulmonary venules on open surgical lung biopsy[64,86].

Due to the low incidence of PVOD following HSCT and inability to study large numbers of cases, risk factors are extrapolated from the non-HSCT population. These include viral infections, genetic predisposition, autoimmune disorders, and toxic insult to endothelia[86]. In the context of HSCT, these insults include conditioning chemotherapies bleomycin, mitomycin, and carmustine, and irradiation[86-89]. Despite their use in primary pulmonary hypertension, pulmonary vasodilators may be detrimental in PVOD and should be avoided. Dilating the pulmonary arterial vasculature in the setting of fixed venous resistance may precipitate pulmonary edema and worsen respiratory status[86]. Corticosteroids may be administered, though data is sparse[83,86]. Overall, prognosis is poor and patients may consider evaluation for lung transplantation if eligible.

Delayed pulmonary toxicity syndrome

The delayed pulmonary toxicity syndrome (DPTS) is a constellation of interstitial pneumonitis and fibrosis occurring in the late transplant period, and can present years after HSCT[64]. Characteristically, DPTS appears to be confined to patients receiving high-dose chemotherapy followed by autologous stem cell rescue for breast cancer[90-93]. Accordingly, the incidence of DPTS in this specific population is reported to be as high as 72%[91]. Symptoms are non-specific and include dyspnea, fevers, and non-productive cough[64]. Similarly, chest imaging reveals bilateral interstitial infiltrates and ground glass opacities. DPTS occurs late following HSCT and can present several years following transplant (Figure 1)[90-93]. The syndrome is highly responsive to corticosteroids and typically associated with favorable outcomes[91,92].

Cryptogenic organizing pneumonia

Cryptogenic organizing pneumonia (COP) is an interstitial and airspace disease with symptoms mimicking classic pneumonia. Imaging findings include nodular lesions, ground glass attenuation, and patchy peribronchovascular, peripheral, band-like consolidative distributions[64,94]. Biopsy reveals chronic alveolar inflammation and extensive granulation of the alveolar ducts and small airways[94]. Bronchoscopy is useful to distinguish COP from infectious pneumonia, and analysis of lavage fluid reveals a predominant lymphocytosis[95]. Previously referred to as bronchiolitis obliterans-organizing pneumonia, COP is a distinct entity from the bronchiolitis obliterans syndrome (BOS), which is discussed separately and should not be confused.

COP occurs in up to 10% of HSCT recipients and typically presents late following transplant (Figure 1)[94,96].

Risk factors include cyclophosphamide conditioning, total body irradiation, male allotransplants with a female cell donor, presence of graft-versus-host disease, and HSCT for leukemia[94,95,97]. Generally, COP is responsive to corticosteroid therapy and typical regimens include 1 mg/kg prednisone daily with an extended taper up to 6 mo[94]. Case fatality rates are reported up to 20%, and are usually due to respiratory failure in the setting of relapsed, steroid-refractory disease[97,98].

BOS

BOS is a slow progression of small airway obstruction believed to be a consequence of graft-versus-host disease[99]. While BOS classically manifests over months to years, abrupt decompensation and severe respiratory failure is not uncommon[100-102]. Histology will reveal intraluminal fibrosis, however yield on transbronchial biopsy is highly dependent on disease presence in the area sampled and open surgical biopsy is very high risk in this population[64,103]. Therefore in the acute setting, diagnosis is established on the basis of reduced expiratory flow with obstructive airflow and radiologic findings include hyperinflation, air trapping, and a mosaic pattern of attenuation[64,95,103].

The incidence of BOS is estimated to be up to 20% and more likely associated with the presence of chronic graft-versus-host disease[99,104,105]. Other risk factors include elder age, reduced expiratory capacity pre-transplantation, unrelated graft donor, irradiation, and viral infection post-HSCT[99,105,106]. High-dose corticosteroids administered for weeks to months are the mainstay of treatment, though response rates are poor as BOS is irreversible, and mortality rates can be as high as 40%[4,95,99,103]. Despite extensive extrapolated use from solid organ transplant patients, macrolides have shown to worsen airflow decline-free survival in HSCT recipients[107]. Other therapies with inconclusive utility include inhaled corticosteroids, intravenous immune globulin, TNF-α inhibitors, cyclosporine, and tacrolimus[4]. Extracorporeal photophoresis is a promising therapy with increasing evidence suggesting its potential benefit[108,109]. Lung transplantation for advanced BOS has been reported[110-113].

Post-transplant lymphoproliferative disorder

Post-transplant lymphoproliferative disorder (PTLD) is a rare form of malignancy secondary to Epstein Barr virus (EBV)-infected B lymphocytes occurring in the first six months following allotransplant (Figure 1)[64,114,115]. Risk factors include T-cell depleted donors, HLA donor mismatch, T-cell depleting therapies including antithymocyte globulin and anti-CD3 antibodies, and CMV antigens[114,115]. In addition to hypoxia, symptoms are consistent with viral illness, and chest imaging reveals diffuse basal and subpleural infiltrates[64,114]. Definitive diagnosis is established when EBV-associated lymphoid proliferation is demonstrated on biopsy[64,116]. Treatment includes modulation of T-cell depleting immunosuppression and administration of rituximab, an anti-B cell antibody[117,118]. Preliminary reports demonstrate promise of infusion of EBV-specific T-cells as a therapeutic for PTLD, though others have demonstrated resistance to such therapy[119].

CONCLUSION

Respiratory failure due to infectious and non-infectious complications is common following HSCT and is associated with significant mortality, especially in those necessitating mechanical ventilation. Pulmonary complications are differentiated by key distinguishing features and their time-course following transplantation. In acutely ill patients meeting ARDS criteria, routine use of best-practice lung-protective strategies is recommended even once the underlying explanation for the respiratory failure is identified.

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ORIGINAL ARTICLE

Retrospective Study

Intensive care unit complications and outcomes of adult patients with hemophagocytic lymphohistiocytosis: A retrospective study of 16 cases

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Abstract

AIM

To study the management, complications and outcomes of adult patients admitted with hemophagocytic lymphohistiocytosis (HLH) in the intensive care unit (ICU).

METHODS

We performed a retrospective observational study of adult patients with the diagnosis of "HLH" admitted to the two academic medical ICUs of Baylor College of Medicine between 01/01/2013 to 06/30/2017. HLH was diagnosed using the HLH-2004 criteria proposed by the Histiocyte Society.

RESULTS

Sixteen adult cases of HLH were admitted to the medical ICUs over 4 years. Median age of presentation was 49 years and 10 (63%) were males. Median Sequential Organ Failure Assessment (SOFA) score at the time of ICU admission was 10. Median ICU length of stay (LOS) was 11.5 d and median hospital LOS was 29 d. Septic shock and acute respiratory failure accounted for majority of diagnoses necessitating ICU admission. Septic shock was the most common ICU complication seen in (88%) patients, followed by acute kidney injury (81%) and acute respiratory failure requiring mechanical ventilation (75%). Nine patients (56%) developed disseminated intravascular coagulation and eight (50%) had acute liver failure. 10 episodes of clinically significant bleeding were observed. Multi system organ failure was the most common cause of death seen in 12 (75%) patients. The 30 d mortality was 37% (6 cases) and 90 d mortality was 81% (13 cases). There was no difference in mortality based on age (above or less than 50 years), SOFA score on ICU admission (more than or less than 10), immunosuppression, time to diagnose HLH or direct ICU admission versus floor transfer.

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CONCLUSION
HLH is a devastating disease associated with poor outcomes in ICU. Intensivists need to have a high degree of clinical suspicion for HLH in patients with septic shock/multi system organ failure and progressive bi/pancytopenia who are not responding to standard management in ICU.

Key words: Lymphohistiocytosis; Cytopenia; Hypercytokinemia; Hemophagocytosis; Shock

Core tip: Hemophagocytic lymphohistiocytosis is a serious disorder in intensive care unit (ICU) with high morbidity and mortality. Septic shock, acute kidney injury and respiratory failure are the most common manifestations in ICU. We observed high incidence of bleeding complications and bloodstream infections. High index of suspicion is necessary for ICU patients with severe septic shock and multi organ failure who do not respond to standard treatment.

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INTRODUCTION

"Hemophagocytic lymphohistiocytosis" or HLH, first described in 1952 by Farquhar and Claireux, is a rare fatal disorder of dysregulated immune activation of natural killer cells and cytotoxic T cells, leading to hypercytokinemia, hemophagocytosis, multiple organ dysfunction and failure[1]. Clinically, the syndrome presents as a constellation of fever, cytopenias (anemia, leukopenia, thrombocytopenia), hepatosplenomegaly, high ferritin and triglyceride levels, low fibrinogen levels and histologic evidence of hemophagocytosis in various organs[2-6]. HLH is classified into two types, primary (familial) and secondary (reactive). Primary or familial HLH is a genetic disorder seen in pediatric population, usually fatal within 2 mo if left untreated. Secondary or reactive HLH is more often diagnosed in adults and usually due to underlying immunosuppression from lymphoid malignancy, infection, connective tissue disorder or idiopathic causes[2-6].

There has been an improved awareness in recent years amongst physicians with regard to HLH presentation, diagnosis and management. Due to the nature of disease to cause multiple organ dysfunctions, the number of intensive care unit (ICU) admissions and management by Intensivists in collaboration with hematologists and immunologists has increased over the last few years[7]. Management of HLH in ICU is very challenging for an intensivist for a variety of reasons. First, the patients are critically ill with multiple organ involvement and failure, putting them at highest risk of mortality. Previous studies have investigated predictors of poor outcomes and reported hospital mortality in the range of 20%-75% and ICU mortality between 50%-80%[7-27]. The most common causes of death include multiple system organ failure (MSOF), bleeding and sepsis[23]. Second, the disease is rare in occurrence and the true incidence, course, complications and risk factors for poor outcomes in ICU are still not clear. Third, the disease is often under recognized in ICU as suggested by the autopsy studies[28]. The reasons include non-specific presentation of disease, lack of specific biomarker and absence of a validated HLH diagnostic criteria in ICU. HLH has many clinical and laboratory features in common with septic shock which inevitably leads to delayed diagnosis and treatment[25,29]. A recent paper by Halacli *et al*[30] emphasized to keep HLH in the differential diagnosis of patients with severe sepsis/septic shock who develop bicytopenia and are resistant to treatment. Hemophagocytosis and macrophage activation, a histologic feature of HLH, is also seen in septic shock, with the incidence of 0.8% and 4% respectively, making it sensitive but less specific for the diagnosis of HLH[29,31-33]. HLH-2004 criteria proposed by Histiocyte Society and H-

score have been used to diagnose HLH in ICU but are not well validated in ICU setting[7,8,10,34-37]. Also, there is no specific biomarker for this disease. Ferritin, an acute phase reactant, can be elevated in other infections and acute and chronic inflammatory conditions in ICU and is not specific for HLH[38-43].

Although much research in recent years has focused on hospital complications and outcomes of HLH patients, few researchers have addressed the problem in ICU[1,6-10,25-27]. Buyse *et al*[8] published the first retrospective review on HLH patients in ICU in 2010. Since then, only two other studies (with sample sizes of more than 10 patients) have described ICU course and outcomes of HLH patients in the critical care setting[7,10]. More evidence to guide Intensivists manage these complex patients with rare, fatal and under diagnosed syndrome in ICU is warranted. The present paper examines the ICU course, complications, management and outcomes of HLH patients admitted to the academic medical ICUs of a tertiary medical center over the last 4 years.

MATERIALS AND METHODS

The present study is a retrospective observational study of patients with the diagnosis of "HLH" admitted to the two academic medical ICUs of Baylor College of Medicine between 01/01/2013 to 06/30/2017. The research project was approved by the Institutional Review Board of the Baylor College of Medicine and need for written informed consent was waived. All adult patients above 18 years of age admitted to the two medical ICUs with the diagnosis of HLH were included in the study. HLH was diagnosed using the HLH-2004 criteria proposed by the Histiocyte society. Patients were identified using ICD-9 and ICD-10 codes for HLH and data was extracted from EPIC electronic health record with the help of clinical analytics team at Baylor College of Medicine. Data regarding patient demographics [age, sex, Sequential Organ Failure Assessment (SOFA) score on ICU admission, underlying immunodeficiency, precipitating factors *etc*.], most extreme pertinent laboratory values and ICU complications [30 d and 90 d mortality, septic shock, need for mechanical ventilation, acute kidney injury (AKI) *etc*.] was collected. Data analysis was performed using STATA 15 software and descriptive statistics were expressed as median and interquartile range except where mentioned otherwise. For the subgroup analysis in table 4, Fisher's exact test was used to compare categorical variables and calculate "*P*" value since the sample size was less than 20.

RESULTS

Demographics

Sixteen adult patients were admitted to our medical ICUs over the study period with the diagnosis of HLH, 3 of them had a prior history of HLH. Four patients had established diagnosis of HLH before ICU admission and rest were diagnosed during ICU stay. The baseline characteristics of patients are presented in Table 1. The median age of presentation was 49 years and ten (63%) were males. Median SOFA score on ICU admission was ten. Median time from hospital to ICU admission was half day with interquartile range of zero to seven days. Eleven patients (69%) had a known immunodeficiency in the form of underlying malignancy, autoimmune disease or human immunodeficiency virus (HIV) infection. Precipitating factors for HLH included infectious causes in five (31%), malignancy related in two (13%), both infection and malignancy related in five (31%) and idiopathic in four (25%) cases.

Clinical presentation

Severe sepsis/shock and acute respiratory failure accounted for up to 80% diagnoses for ICU admission. Median ICU length of stay (LOS) was 11.5 d and median hospital LOS was 29 d. Table 2 lists relevant laboratory parameters observed at the time of ICU admission and most extreme values. Thirteen bone marrow biopsies were performed of which, ten (77%) showed evidence of hemophagocytosis. Septic shock was the most common ICU complication seen in fourteen (88%) patients, followed by AKI (81%) and acute respiratory failure requiring mechanical ventilation (75%). Majority of the patients with acute renal failure required continuous renal replacement therapy (CRRT). Nine patients (56%) developed features of disseminated intravascular coagulation (DIC) and eight (50%) had acute liver failure. Of note, ten episodes of clinically significant bleeding requiring intervention were observed in our series. Because most of our patients (94%) were initiated on eight week regimen of standard chemotherapy with dexamethasone and etoposide per HLH-94 protocol they were

Table 1 Descriptive statistics of 16 intensive care unit patients with hemophagocytic Lymphohistiocytosis [expressed as median (IQR)] *n* (%)

Parameter	Value
Age (yr)	49 (26-61)
Sex	
Male	10 (63)
Female	6 (37)
SOFA score on ICU admission	10 (7-15)
Time from hospital to ICU admission	0.5 (0-7)
Time to diagnose HLH (d)	3 (1-7)
Immunodeficiency	11 (69)
HIV infection	2
Malignancy	7
Autoimmune (SLE, autoimmune hemolytic anemia)	2
Precipitating factors	
Infection only	5 (31)
Pneumonia	2
EBV	2
Typhoid fever	1
Malignancy only	2 (13)
Diffuse large B cell lymphoma	1
T cell lymphoma	1
Infection and malignancy combined	5 (31)
EBV and plasmablastic lymphoma	1
EBV and Hodgkin lymphoma	1
EBV and diffuse large B cell lymphoma	1
EBV and NK cell leukemia	1
EBV associated lymphoproliferative disorder	1
Idiopathic	4 (25)
Number of HLH criteria met	5 (5-6)
Principal reason for ICU admission	
Severe sepsis/septic shock	9 (56)
Acute respiratory failure	4 (25)
GI Bleed	2 (13)
Acute encephalopathy	1 (6)
ICU length of stay (d)	11.5 (5-29)
Hospital length of stay (d)	29 (17-40)
Prior history of HLH	3 (19)
Biopsies performed	23
Bone marrow	13
Liver	4
Lymph node	3
Skin	2
Lung	1
Bi/pancytopenia on ICU admission	10 (63)
Hemophagocytosis seen on bone marrow biopsy (out of total)	10 (77)
Chemotherapy received	15 (94)

HLH: Hemophagocytic lymphohistiocytosis; ICU: Intensive care unit; SOFA: Sequential organ failure assessment; HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematosus; EBV: Epstein-Barr virus; NK: Natural killer.

prone to infectious complications. Six cases of pneumonia (including 3 fungal) and ten cases of blood stream infections (bacteremia in nine and fungemia in one) were observed. One patient developed intra-abdominal abscess and required interventional radiology guided drainage procedure. Of note, the ICU complications occurred both

before and after starting chemotherapy. Table 3 lists the ICU complications.

Outcomes

Multi system organ failure was the most common cause of death seen in twelve (75%) patients. The 30 d mortality was 37% (six cases) and 90 d mortality was 81% (thirteen cases).

We also performed subgroup analysis comparing categorical variables listed in Table 4 and found no difference in mortality based on age of presentation (above or less than 50 years), SOFA score on ICU admission (above or less than 10), presence of underlying immunosuppression at the time of HLH diagnosis, time to diagnose HLH (more than or less than 3 d) and whether patients were directly admitted to the ICU versus from the floor.

DISCUSSION

HLH is a rare disease, annual incidence being one per 800000 people and one to ten per 1 million children in Italy, Sweden, and the United States[2]. Secondary or reactive HLH usually affects adults who may have underlying immunosuppression from malignancy, HIV infection or autoimmune disorders[2-6]. Usually, the disease is precipitated by factors like infection, malignancy or idiopathic causes. Malignancy associated HLH usually has a poorer prognosis compared to infectious or idiopathic causes[44].

Multiple studies have investigated morbidity, mortality and predictors of poor outcomes in patients with HLH but very few have been conducted in an ICU setting[7-27]. Since HLH is a rare and under diagnosed syndrome in ICU, there are only three retrospective studies reported in literature on ICU patients with sample sizes of 10 or more (ranging from 10 to 71 patients)[7,8,10]. HLH in ICU affects all age groups including young adults, median age varying from 25 to 57 years[7,8,10]. The disease is associated with massive systemic inflammatory response due to cytokine storm, leading to multiple organ failure and circulatory shock[45]. Shock and acute respiratory failure with need for mechanical ventilation are the major reasons for ICU admission in literature, accounting for up to 80% of principal diagnoses in our series[1,7,8,10,25,27]. Other reasons include acute encephalopathy, acute kidney failure, acute liver failure, bleeding complications or MSOF[46]. Distributive shock (septic shock) due to intense vasodilation is the most common form of shock in ICU with reported incidence in literature from 50%-80%[1,7,8,10,25,27]. In our case series, 88% patients developed septic shock and one had concomitant cardiogenic shock requiring mechanical circulatory support with intra-aortic balloon pump.

Patients can develop acute hypoxemic respiratory failure requiring mechanical ventilatory support, incidence of which varies from 58% to 100%[1,7,8,10,25,27]. Various etiologies include pneumonia (infectious/aspiration), acute respiratory distress syndrome, sepsis related respiratory failure, cardiogenic pulmonary edema, atelectasis *etc*[47].

A retrospective study by Aulagnon *et al*[48] reported a high incidence of AKI in HLH patients (62%) and majority of them (59%) needed renal replacement therapy. Main etiologies of AKI in their study included acute tubular necrosis, hypo perfusion, tumor lysis syndrome and HLH related glomerulopathies[48]. Many patients in ICU with AKI require CRRT due to hemodynamic instability with incidence from 30% to 54%.

Patients with HLH in ICU are prone to develop infectious/nosocomial complications like pneumonias, blood stream infections as they are usually immunocompromised. The largest retrospective study in ICU by Barba *et al*[7] with 71 confirmed cases of HLH found out that the incidence of invasive aspergillosis was 25%, another study reported 10% incidence of invasive mucormycosis[10]. We saw 3 cases of invasive fungal infections with 2 due to aspergillosis and 1 from mucormycosis. All three patients died from invasive Pneumonia. There was a high incidence of bacteremias in our patients with incidence of 62%, none with Catheter related bloodstream infections (CRBSI). Only one previous ICU study reported 10% incidence of CRBSI[10].

Severe coagulopathy and DIC add to the morbidity in HLH patients. None of the previous ICU studies have reported any clinically significant bleeding complications in ICU. We observed 10 serious bleeding complications in our case series. In a report by Valade *et al*[49], thrombocytopenia was seen in all patients, coagulation abnormalities in 68% and DIC in 50% patients. 22% of their patients developed severe bleeding complications and 5 of them died from hemorrhagic shock. Low fibrinogen < 2 g/L and elevated PT value were associated with higher mortality[49].

Multi system organ failure was the most common cause of death in our patients,

Table 2 Laboratory tests in patients with hemophagocytic lymphohistiocytosis [expressed as median (IQR)]

Laboratory test	Value
Hemoglobin on ICU Admission (gm/dL)	9.3 (8.4-11.35)
Lowest Hemoglobin during ICU stay (gm/dL)	6 (4.4-6.7)
Platelet count on ICU admission (K/cubic mm)	89 (37-159)
Lowest platelet count (K/cubic mm)	7.5 (4-22)
White blood cell count on ICU admission (K/microL)	3.75 (1.75-5.4)
Lowest White blood cell count (K/microL)	0.1 (0.1-0.7)
Fibrinogen on ICU admission (mg/dL)	263 (86-312)
Lowest Fibrinogen (mg/dL)	70 (50-176)
First Ferritin level in ICU on clinical suspicion of HLH (microgram/L)	17728 (7689-37981)
Highest ferritin (microgram/L)	40000 (16500-55000)
Triglycerides (mg/dL)	350 (269-556)

ICU: Intensive care unit.

incidence being 75% which is similar to previous ICU studies (56% to 70%)[7,8,10].

None of the diagnostic criteria including HLH-2004 (proposed by Histiocyte society), H-score proposed by Fardet *et al*[36] or Delphi study criteria have been validated in an ICU setting[34-37]. Of the three major retrospective studies in ICU, two used HLH-2004 criterion and one used H score ≥ 169 to diagnose HLH in ICU[7,8,10]. H-score might have higher specificity compared to HLH-2004 criteria and HLH-2004 criteria suffer from some intrinsic problems[40]. Serum ferritin, an acute phase reactant, has been utilized as a diagnostic and prognostic marker for HLH[38-43]. Higher cutoff value of ferritin level above > 10000 μg/L may increase sensitivity to 90% and specificity to 96% in ICU but still can be positive in many conditions other than HLH, thereby lowering specificity[38-43,50]. The incidence of hypertriglyceridemia in HLH is estimated to be between 60%-70%[51]. Improvement of triglyceride level with chemotherapy might be an important predictor of response to treatment[51]. Intensivists should have a high index of suspicion for HLH in patients with septic shock/multi system organ failure and progressive bi/pancytopenia[52]. There should be a low threshold to obtain simple tests like serum ferritin, triglyceride and fibrinogen in patients with suspected HLH. Hemophagocytosis, a pathologic marker for HLH, is a fairly sensitive but not specific criterion for diagnosis. It can be observed in other conditions like sepsis, hemolytic anemias and malignancy[29,31-33]. Its incidence in ICU varies between 70%-80% in pathologic specimens with our case series showing incidence of 77%[32,33]. The results can be false negative based on the experience of the pathologist and is usually seen in the advanced stage of the disease.

In addition to the treatment of the underlying trigger, early diagnosis and treatment with chemotherapy per HLH-94 protocol with 8 wk course of etoposide and dexamethasone is associated with good outcomes[53-57]. Optimal duration of treatment in ICU is unclear and not being studied as patients become prone to infectious complications due to immunosuppression by prolonged chemotherapy. ICU mortality for HLH patients varies between 38% to 70%[1,7,8,10,25,27]. Buyse *et al*[8] reported ICU mortality of 39% and hospital mortality of 52%. Factors associated with higher mortality included shock on ICU admission and presence of thrombocytopenia (platelet count less than 30 gm/L). The largest retrospective study by Barba *et al*[7] reported 28 d ICU mortality of 38% and hospital mortality of 68%. SOFA score on admission, advanced age and lymphoma related HLH were factors associated with higher mortality. Our case series had 30 d ICU mortality of 37% and 81% 90 d mortality. We did not see any mortality difference based on SOFA scores (above or less than 10), age (above or less than 50 years), presence or absence of immunosuppression at the time of HLH diagnosis, time to diagnose HLH (more than or less than 3 d) and direct ICU admission versus transfer from floors. This might be attributable to the overall sickness of our population and the aggressive nature of the disease per se. The median SOFA score at the time of ICU admission in our series was 10 while previous ICU studies reported median SOFA score in the range of 6-8. Larger multi center studies targeting HLH population in ICU and need to create HLH registry are essential in future to improve our understanding of this syndrome.

The major limitations of our study are single center population, retrospective design and relatively small sample size. Our retrospective study reported data over 4

Table 3 Intensive care unit complications in patients with hemophagocytic lymphohistiocytosis (Total number of patients = 16)

ICU complications	*n* (%)
Mechanical ventilation	12 (75)
Septic shock	14 (88)
AKI	13 (81)
With renal replacement therapy	10
Without renal replacement therapy	3
Acute liver failure	8 (50)
Clinically significant bleeding	10 (62)
GI bleed	4
Intracerebral bleed	2
Hemoptysis	1
Retroperitoneal bleed	1
Epistaxis	1
Hematoma-neck	1
DIC	9 (56)
ARDS	4 (25)
With ECMO	2
Without ECMO	2
Pneumonia	6 (37)
Bacterial	3
Fungal	3
Viral/others	0
Acute encephalopathy	5 (31)
Stress cardiomyopathy	2 (12)
Arrythmias (Atrial, ventricular)	4 (25)
Bloodstream infections	10 (62)
Bacteremia	9
Gram positive organisms	2
Gram negative organisms	7
Fungemia	1
MSOF	12 (75)
Tracheostomy	3 (19)
Mortality	
30 d	6 (37)
90 d	13 (81)
Miscellaneous (Seizures, perforated viscus, cardiogenic shock requiring IABP, intra-abdominal abscess)	5 (31)

ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; AKI: Acute kidney injury; DIC: Disseminated intravascular coagulation; ECMO: Extracorporeal support; MSOF: Multi system organ failure.

years whereas previous ICU studies reported data over 10-12 years, thereby explaining our small sample size. The major strength of our study is that the HLH population comes from medical ICUs of general medical-surgical hospital and not specialized hematology/oncologic centers, thereby mimicking setup of most of the adult North American ICUs.

In conclusion, HLH is a devastating disease with dismal outcomes. Septic shock, AKI and acute respiratory failure with need for mechanical ventilation were the most common ICU complications in our study. We observed high incidence of clinically significant bleeding and bloodstream infections in our series. Most patients died of MSOF with 80% 90 d mortality.

Table 4 Differences in mortality based on various categorical variables

Categorical variable	Categorical variable	*P* value
Age above 50 yr (8 patients)	Age less than or equal to 50 yr (8 patients)	0.5
SOFA score on ICU admission above 10 (7 patients)	SOFA score on ICU admission less than or equal to 10 (9 patients)	0.6
Underlying immunosuppression (11 patients)	No underlying immunosuppression (5 patients)	0.7
Direct admission to ICU (8 patients)	Transfer from floor to ICU (8 patients)	0.5
Time to diagnose HLH more than 3 d (7 patients)	Time to diagnose HLH less than or equal to 3 d (9 patients)	0.4

HLH: Hemophagocytic lymphohistiocytosis; ICU: Intensive care unit; SOFA: Sequential organ failure assessment.

ARTICLE HIGHLIGHTS

Research background

Hemophagocytic lymphohistiocytosis (HLH) is a rare, fatal syndrome increasingly being recognized in intensive care unit (ICU) now. Not many studies have been conducted in an ICU setting to study the complications and outcomes of this patient population.

Research motivation

There is an urgent need for more evidence in literature to help guide Intensivists identify and manage these sick and complicated patients in ICU. This will help to improve their outcomes and decrease complications.

Research objectives

The objective of our research is to study the ICU course, complications and outcomes of adult patients admitted with HLH over the period of 4 years.

Research methods

It is a retrospective observational study of adult patients with HLH admitted to the two academic medical ICUs from 1/1/2013 to 6/30/2017. The diagnosis of HLH was established using HLH-2004 criteria. Data was collected using ICD 9 and 10 codes. Statistical analysis was performed using STATA 15 software.

Research results

Sixteen adult patients were admitted to ICUs over 4 years with HLH with median age of 49 years. Median ICU LOS was 11.5 d and median hospital LOS was 29 d. Septic shock, acute kidney injury (AKI) and acute respiratory failure were the most common ICU complications. Multi system organ failure was the most common cause of death with high mortality of 80% over 90 d. Age (above or below 50 years), Sequential Organ Failure Assessment score on ICU admission, time to diagnose HLH and immune status of patient did not predict mortality.

Research conclusions

Our study showed that HLH in ICU is associated with mortality of 80% over 90 d periods. Most common complications include septic shock, respiratory failure and AKI. Multi system organ failure is the most common cause of death. Clinically significant bleeding and bloodstream infections were also observed in our case series.

Research perspectives

Presentation of HLH in ICU mimics severe sepsis/septic shock. High index of suspicion for HLH is warranted in patients with septic shock and bi/pan cytopenia, not responding to standard treatment. Tests like serum ferritin, fibrinogen, triglycerides, bone marrow/lymph node biopsies help in diagnosis of HLH. Early diagnosis and treatment with chemotherapy is crucial for improved outcomes.

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