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ABOUT COVER

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MINIREVIEWS

Enhancing the awakening to family engagement bundle with music therapy

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Abstract

Survivors of prolonged intensive care unit (ICU) admissions may present undesirable long-term outcomes. In particular, physical impairment and cognitive dysfunction have both been described in patients surviving episodes requiring mechanical ventilation and sedation. One of the strategies to prevent the aforementioned outcomes involves the implementation of a bundle composed by: (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement (ABCDEF bundle). The components of this bundle contribute in shortening length of stay on mechanical ventilation and reducing incidence of delirium. Since the first description of the ABCDEF bundle, other relevant therapeutic factors have been proposed, such as introducing music therapy. This mini-review describes the current evidence supporting the use of the ABCDEF bundle, as well as current knowledge on the implementation of music therapy.

Key Words: Bundle; Delirium; Mechanical ventilation; Mobility; Music therapy

Core Tip: Data support the implementation of the (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement bundle for mechanically ventilated patients. The role of music therapy is evolving.

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INTRODUCTION

Innovation of clinical practices and introduction of new technologies have improved survival of critically ill patients[1]. Furthermore, the implementation of specific strategies for mechanical ventilation [2], pharmacotherapy[3], fluid therapy[4] and bundles of care[5] brought about improvement in other relevant outcomes, such as shorter mechanical ventilation or intensive care unit (ICU) lengths of stay (LOS). Despite those aforementioned achievements, a variety of other long-term outcomes directly affected by ICU admissions still remain problematic for patients, families, and the entire society. Over the last two decades, multiple publications have described significant long-term post-ICU impairments. In particular, the presence of muscle waist with its consequent alteration of physical function, and high rates of cognitive dysfunction have been repeatedly reported. A landmark article, which described 1-year outcomes in 109 survivors of acute respiratory distress syndrome (ARDS) revealed that those patients had persistent functional disability[6]. The physical role domain score in the Medical Outcomes Study 36-item Short-Form (SF-36) questionnaire was only 25 points, while the score in normal population was 84. Strikingly, at 12 months from hospital discharge, only 49% of those individuals had returned to work. Among those, only 78% had returned to their original job. Reported reasons for not returning to work included chronic fatigue and weakness, stressing the relevance of general muscular debility as a cause of their inactivity. A follow-up study published by the same group, which addressed functional disability 5 years post-ICU discharge, showed that the mean score of the physical component of the SF-36 remained approximately 1 standard deviation below the mean score of an age and gender-matched control population[7]. Also, the distance walked in 6 min was significantly correlated with the physical-component score of this survey. Interestingly, the mental component domains of the SF-36 questionnaire remained within normal limits over the 5 years of follow up. These long-term quality of life alterations were not only limited to patients with ARDS. A study that followed a large cohort of patients for more than 6 years after admission to surgical ICUs (SICUs) showed significant impact in their response to the EuroQol-6D tool (another quality-of-life questionnaire)[8]. Specifically, 52% of patients reported impairment in mobility, 29% had anxiety and/or depression, and 43% disclosed cognitive impairment. Alterations in physiology during ICU admissions have been linked with the development of neurocognitive impairments[9]. A prospective cohort study that included 126 mechanically ventilated patients admitted in ICU, mostly due to sepsis and/or ARDS, showed that at 12 months post-discharge, 71% presented cognitive impairment[10]. Interestingly, increasing delirium duration was deemed as an independent predictor of poor cognitive performance among this population. Based on the aforementioned data, individual strategies have been studied in order to avoid the previously described outcomes. Specifically, reduction and/or possible avoidance in the use of sedatives, protocolized liberation from mechanical ventilation, selection of drugs with lower deliriogenic effect, detection and management of delirium, early mobilization, and family participation in care have all been investigated. The positive outcomes brought about by these individual strategies concluded with the development of a bundle of care, known as the ABCDEF bundle (Figure 1). Each element of the bundle corresponded to a demonstrated beneficial intervention, such as: (1) Awakening trial (SAT) ; (2) Spontaneous breathing trial (SBT) and mechanical ventilation liberation; (3) Selective choice of drugs, particularly sedatives; (4) Detection, management, and prevention of delirium; (5) Early patient mobilization; and (6) Family and/or caregiver involvement in care. While the ABCDEF bundle has been widely accepted and implemented, other interventions have been found potentially beneficial, and could enhance the bundle. Particularly, the utilization of music therapy may have promising outcomes. The next sections of the manuscript will describe: (1) Evidence supporting individual components of the ABCDEF bundle; (2) Evidence supporting the ABCDEF bundle implementation; and (3) Supporting data for the use of music therapy.

EVIDENCE SUPPORTING INDIVIDUAL COMPONENTS OF THE ABCDEF BUNDLE

Spontaneous awakening trials

Over the last few decades, the strategies for providing sedation to critically ill mechanically ventilated patients have followed a pendular fashion. In a thoughtful editorial written by Dr. Thomas L. Petty in 1998, he stated: "When we first started our unit in 1964, patients who required mechanical ventilation were awake and alert and often sitting in a chair by being awake and alert, these individuals could interact with their family, friends, and the environment". In another paragraph, referring to practices

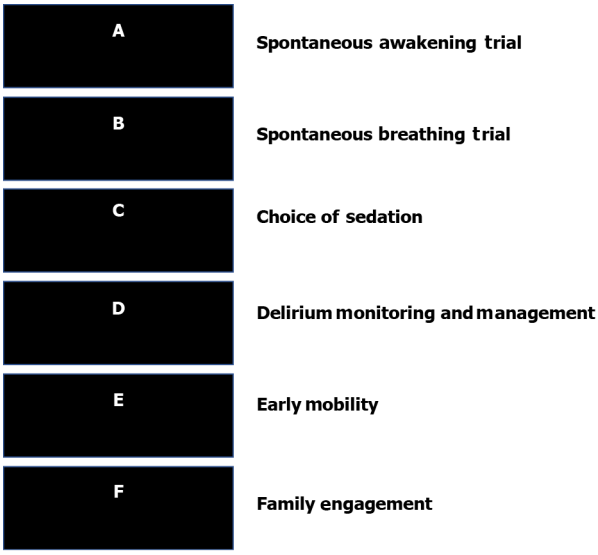

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Figure 1 Bundle components.

held in 1998, he mentioned: "What I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise"[11]. Evidence published by the end of the '90s and during the 2000s has caused a movement back towards patient awakening. A prospective observational cohort study that followed 93 mechanically ventilated patients receiving intravenous (IV) continuous sedations *vs* 149 patients receiving sedation boluses or no-sedation showed significant longer duration on mechanical ventilation within the group receiving continuous IV sedation (185+/-190 h *vs* 56+/-75.6 h; $P < 0.001$)[12]. Furthermore, the ICU and hospital LOS were also longer within the continuous IV sedation group (13.5+/-34 d *vs* 4.8+/-4; and 21 +/-25 d *vs* 13+/-14, $P < 0.001$, respectively). A year later, a randomized, control trial studied whether a nurse-implemented protocol-directed sedation strategy *vs*. no protocol resulted in improved outcomes in mechanically ventilated patients[13]. Notably, duration of mechanical ventilation was shorter in the protocol-directed group (89 h ± 134 h *vs* 124 h ± 154, $P = 0.003$). ICU and hospital stays were also shorter within this group (5.7 d ± 6 *vs* 7.5 d ± 7, $P = 0.013$; and 14 d ± 17 *vs* 20 d ± 24, $P < 0.001$, respectively). Based on the aforementioned data, it became apparent that intermittent (rather than continuous) and protocol-directed sedation strategies were beneficial compared with prior usual practices. A landmark randomized control study (RCT), which included 128 mechanically ventilated patients sedated by a continuous IV strategy, allocated patients to an intervention of daily sedation vacation to awakening trials *vs* sedation management at the discretion of clinicians[14]. This study confirmed the previously described findings. In more detail, patients assigned to the intervention group had a ventilator duration of 4.9 d, compared with 7.3 d in the control group ($P = 0.004$). The median LOS in the ICU was 6.4 d *vs* 9.9 d, respectively ($P = 0.02$). Contrary to the sufficient evidence that exists regarding daily awakening trials and using protocol-directed strategies, the depth of initial sedation implemented immediately after intubation has been an area of uncertainty. However, a multicenter, longitudinal cohort study evaluated whether initial sedation depth (assessed by Richmond Agitation-Sedation Scale – RASS) within 24-48 h post-intubation was associated with time-to-extubation and/or survival[15]. Notably, initial depth of sedation resulted an independent predictor of time to ventilator liberation [hazard ratio (HR): 0.90; $P < 0.01$], hospital mortality (HR: 1.1; $P = 0.01$), and 180-d mortality (HR: 1.08; $P = 0.02$). Based on these findings, a strategy of 'light' initial sedation upon institution of mechanical ventilation became justified. Finally, a randomized study evaluated 140 critically ill, mechanically ventilated patients to a strategy of no-sedation *vs* a control group, which involved initial sedation with propofol and subsequent midazolam [16]. This group underwent daily awakening trials. Of note, patients receiving no sedation had significantly more ventilator-free d (13.8 d *vs* 9.6 d; $P = 0.0191$) than those receiving interrupted sedation. No sedation was also associated with a shorter ICU LOS. As a summary, based on the previously described data, current sedation standard of care involves light or no sedation over deep sedation, daily awakening trials over continued sedation, and protocol-directed strategy over individual clinician decisions. Despite evidence supporting light sedation strategies, certain areas of concern still remained, regarding whether these strategies would affect patient mental health by causing post-traumatic stress disorder (PTSD), anxiety or depression post-hospital discharge. In order to answer that question, a randomized, open-label, control study included 137 patients who had undergone light *vs* deep sedation. Patients self-reported measures correlated with PTSD, anxiety or depression upon hospital discharge and 4 weeks later. Interestingly, at the 4 week follow-up, patients in the deep sedation arm had a tendency toward more PTSD symptoms ($P = 0.07$), more difficulty remembering the

ICU event (37% *vs* 14%; *P* = 0.02) and more disturbing recollection of the ICU (18% *vs* 4%; *P* = 0.05)[17]. These findings may be explained by prior evidence, which suggested that memory recall (more commonly seen after light sedation) could have a protective effect against subsequent mental health disorders post-discharge. Conversely, the presence of delusional memories after deep sedation could have an association with development of PTSD.

Spontaneous breathing trials

Observational studies attempting to identify the best methods for discontinuing mechanical ventilation have been reported for many decades[18]. However, a landmark study published in 1996 provided the framework that would be accepted as current standard of care in ICU. In this study, 149 patients were enrolled to a strategy involving 3 phases: (1) Daily screening of respiratory function; (2) A trial of spontaneous breathing; and (3) Notifying the physician of successful results. 150 other patients were the control group, with physician guided weaning. The results of this study revealed that the median duration of mechanical ventilation was 4.5 d in the intervention group and 6 d in the control group (*P* = 0.003)[19]. Furthermore, the weaning time was shortened by 2 d by using the intervention strategy (*P* < 0.001). This study incorporated the notion of protocol-directed weaning. It also confirmed the benefits of SBTs, rather than the gradual reduction of ventilator support. Years later, building on the prior knowledge regarding the benefits of awakening trials, an RCT including 336 mechanically ventilated patients was published. The study allocated half of these patients to an intervention strategy involving the performance of SAT followed by an SBT. The control group involved sedation *per* usual care plus SBT, without coordination[20]. The study showed that patients in the intervention group spent more days breathing without assistance during the 28-day trial period than those in the control arm (14.7 d *vs* 11.6 d; *P* = 0.02). They were also discharged earlier from the ICU (median time in intensive care 9 d *vs* 13 d; *P* = 0.01). Strikingly, at any point during the 12-month follow up, patients included in the intervention arm had less chances to expire compared with subjects in the control one (HR 0.68; *P* = 0.01). The positive outcomes of this study enhanced the rational of linking SAT with subsequent SBT in clinical practice. In fact, a multicenter quality improvement (QI) collaborative, coordinated by the Center for Disease Control and Prevention Wake Up and Breath, studied whether the implementation of the SAT/SBT bundle was associated with a reduction of ventilator-associated events (VAEs)[21]. The QI showed that the VAE rate went from around 10 events *per* 100 episodes of mechanical ventilation in 2011 to 5 events *per* 100 episodes in 2013 [adjusted odds ratio (OR): 0.63; 95% confidence interval (CI): 0.42 to 0.97]. Furthermore, the mean duration of mechanical ventilation decreased by 2.4 d (95%CI: 1.7 to 3.1), and the ICU LOS by 3.0 d (95%CI: 1.6 to 4.3) after implementing the SAT/SBT bundle.

Choice of sedatives

As described above, a strategy of daily awakening trials on sedated mechanically ventilated patients has shown reduction on ventilation duration and ICU stay. In addition, several studies revealed that certain sedatives may be associated with intrinsic complications. A Canadian multicenter randomized open label study allocated patients to be sedated with midazolam *vs* propofol[22]. Patients were subsequently divided for analysis accordingly to length of sedation in: (1) Short time, < 24 h on sedation; (2) Intermediate time, 24 h - 72 h on sedation; and (3) Long time, > 72 h on sedation. Overall, pooled results demonstrated that patients treated with propofol were extubated earlier than those treated with midazolam (6.7 h *vs* 24.7 h, respectively; *P* < 0.05) following discontinuation of sedation. A meta-analysis of 16 studies compared outcomes of midazolam *vs* propofol within groups of post-acute surgery and critically ill patients. The analysis showed that propofol was generally associated with reduced ventilation time of 4.46 h (*P* = 0.004, 6 studies). In critically-ill patients, sedation with propofol was associated with reduced extubation time of 32.68 h (*P* = 0.0001, 9 studies). For post-surgical patients, propofol was associated with a reduction of ICU LOS of 5.07 h (*P* = 0.006, 5 studies), ventilator time of 4.28 h (*P* < 0.0001, 3 studies), and extubation time of 1.92 h (*P* = 0.00001, 9 studies)[23]. Recently, the introduction of dexmedetomidine in clinical practice brought about new data. A prospective, double-blind, randomized trial conducted in 5 countries compared dexmedetomidine *vs* midazolam in their ability to maintain patients within a predefined level of sedation (RASS range). Secondary outcomes included prevalence of delirium, duration of mechanical ventilation, and ICU LOS. Even though there was no difference between groups in percentage of time within sedation range, there were significant differences in secondary outcomes. In particular, the prevalence of delirium was 54% in the dexmedetomidine-treated patients *vs* 76.6% in the midazolam group (*P* < 0.001). Median time to extubation was about 2 d shorter in the dexmedetomidine group (*P* = 0.01). The ICU LOS was similar in both groups (5.9 d *vs* 7.6 d; *P* = 0.24)[24]. Another double-blind RCT, which included 106 mechanically ventilated in medical and surgical ICU at 2 tertiary care centers, compared dexmedetomidine *vs* lorazepam for the outcome of days alive without delirium or coma. The study also aimed at comparing both drugs in terms of the percentage of days spent within 1 RASS point of an established goal. The trial showed that patients sedated with dexmedetomidine had more days alive without delirium or coma (median days, 7.0 *vs* 3.0; *P*= 0.01). Patients assigned to this group also spent more time within 1 RASS point of their sedation goal compared with patients sedated with lorazepam (median percentage of days, 80% *vs* 67%; *P* = 0.04)[25]. Finally, two RCTs, which were published simultaneously, compared dexmedetomidine *vs* midazolam and dexmedetomidine *vs* propofol, respectively. In both studies,

outcomes included non-inferiority of dexmedetomidine (compared with control groups) in regards to proportion of time at target sedation level, and its superiority (compared with controls) in regard to mechanical ventilation duration. The secondary outcome included subjects' capability to disclose pain [by utilizing the visual analogue scale (VAS)]. Both studies reveal that dexmedetomidine was not inferior compared with midazolam or propofol in maintaining light to moderate sedation ranges. Nevertheless, median duration of mechanical ventilation was shorter with dexmedetomidine (123 h) *vs* midazolam (164 h; $P = 0.03$). There were no differences on ventilation duration between dexmedetomidine *vs* propofol. Patients' interaction (measured using VAS) was superior with dexmedetomidine compared to both midazolam and propofol ($P < 0.001$, for both studies)[26]. In summary, based on the higher deliriogenic effect and prolonged stay on mechanical ventilation, benzodiazepines should not be selected as medications of choice for mechanically ventilated patients. Dexmedetomidine or propofol are currently deemed as preferred medications, the choice between them depending on other anticipated side-effects (*i.e.*, bradycardia, hypotension, *etc.*).

Delirium detection, management and prevention

The presence of delirium in mechanically ventilated patients is common, with some studies describing a prevalence up to 48%[27]. Due to difficulties in assessing this complication in non-communicative patients, a number of tools have been developed to allow its detection. In more detail, the original description of the Confusion Assessment Method for the ICU (CAM-ICU) tool reported sensitivities of 100% and 93% and specificities of 98% and 100% (when performed by two different nurses). The interrater reliability was very high, as well (kappa = 0.96; 95%CI: 0.92 to 0.99)[28]. Another tool, the Intensive Care Delirium Screening Checklist (ICDSC) was also proved to be very accurate. Its ability to predict delirium was assessed by a receiving operating characteristic (ROC) curve, which showed an area under the curve (AUC) of 0.9. Sensitivity and specificity, when using 4 points as a cut-off, were 99% and 64%, respectively[29]. A comparison between the two was performed by a meta-analysis that included 13 studies. Its results showed that the pooled sensitivity of the CAM-ICU was 80.0% (95%CI: 77.1 to 82.6), and the pooled specificity was 95.9% (95%CI: 94.8 to 96.8). The pooled sensitivity of the ICDSC was 74% (95%CI: 65.3 to 81.5), and the pooled specificity was 81.9% (95%CI: 76.7 to 86.4). The AUCs in the CAM-ICU and ICDSC ROCs for their ability in diagnosing delirium were 0.97 and 0.89, respectively[30]. These data revealed that CAM-ICU may have higher accuracy for the detection of delirium in mechanically ventilated patients. Over the years, focus has been placed on describing delirium severity. A recent instrument, the CAM-ICU-7 delirium severity scale has been introduced. In more detail, a 7-point scale (0-7) was derived from responses to the CAM-ICU and Richmond Agitation-Sedation Scale items. The CAM-ICU-7 scores showed correlation with higher odds of in-hospital mortality (OR = 1.47; 95%CI = 1.30 to 1.66) and lower odds of being discharged home (OR = 0.8; 95%CI: 0.72 to 0.9) after adjusting for age, race, gender, severity of illness, and chronic comorbidities. Furthermore, higher CAM-ICU-7 scores were also associated with increased ICU stay ($P = 0.001$)[31]. Pharmacologic management of delirium has been studied over many years. Nevertheless, up to this day, no medication has shown clear benefits for its management in mechanically ventilated patients. A randomized, double-blind, placebo-controlled trial allocated 101 mechanically ventilated patients to receive haloperidol or ziprasidone or placebo every 6 h for up to 14 d. During the 21-d study period, patients in the haloperidol group had similar number of days alive without delirium or coma, as did patients in the ziprasidone and placebo groups (14 d *vs* 15 d *vs* 12.5 d, respectively; $P = 0.66$). There were no differences in other outcomes, such as hospital LOS, ventilator-free days, and mortality[32]. A subsequent RTC allocated ventilated and/or patients with shock to receive intravenous boluses of haloperidol, ziprasidone, or placebo. In this trial, dose of drug or placebo were halved or doubled every 12 h intervals, based on the presence or absence of delirium. This study confirmed prior data. In more detail, the median number of days alive without delirium or coma (primary outcome) were 7.9 d, 8.7 d, and 8.5 d for the haloperidol, ziprasidone, and placebo groups, respectively ($P = 0.26$)[27]. Another double-blind, placebo-controlled, parallel-group RCT included 74 mechanically ventilated patients with delirium and agitation. Patients were allocated to dexmedetomidine at a rate of 0.5 μg/kg/h (or placebo) and increased up to 1.5 μg/kg/h to reach provider-directed sedation goals. The trial showed an increase in ventilator-free hours within 7 d post-randomization in the dexmedetomidine group (144.8 h) *vs* placebo (127.5 h), ($P = 0.01$)[33]. Finally, a recently published multicenter, blinded, placebo-controlled trial randomized 1000 ICU patients with delirium to receive intravenous haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a maximum daily dose of 20 mg) *vs* placebo[34]. The medications were administered for as long as delirium continued. At 90 d, the mean number of days alive and out of the hospital (primary outcome) was 35.8 (95%CI: 33 to 39) in the haloperidol group and 32.9% (95%CI: 30 to 36) in the placebo group ($P = 0.22$). This study re-affirmed the lack of effective pharmacological treatment for delirium management. Of note, some publications reported possible effectiveness of non-pharmacological interventions for the reduction of incidence and duration of delirium. Nevertheless, these multi-component strategies are still under investigation[35]. The recognition of cognitive impairment after development of delirium motivated several researchers at investigating its prevention. An RCT included 142 mechanically ventilated patients within 72 h post-admission. The study allocated patients to receive haloperidol 2.5 mg or 0.9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. As a result, patients in the haloperidol

arm spent about the same number of days alive, without delirium, and without coma as did patients in the placebo one (median 5 d *vs* 6 d; $P = 0.53$)[36]. A subsequent study performed at 21 ICUs included 1,789 critically ill patients to receive either haloperidol at 1 mg or 2 mg, or placebo. Haloperidol doses (or placebo) were ad-ministered 3 times *per* day intravenously. Whereas the 1-mg haloperidol group was prematurely stopped because of futility, the haloperidol 2 mg and placebo groups showed no difference in 28-d survival ($P = 0.93$)[37]. Finally, a two-center, double-blind, placebo-controlled trial randomized 100 delirium-free critically ill adults, already receiving sedatives, to receive nocturnal (9:30 pm to 6:15 am) intravenous dexmedetomidine or placebo. The result of the study revealed that nocturnal dexmedetomidine was associated with a greater proportion of patients remaining delirium-free (80%) *vs* placebo (54%) ($P = 0.006$)[38]. In summary, despite high accuracy for delirium detection in ICU patients by using the CAM-ICU and ICDSC tools, the ability to provide pharmacologic management or prevention remains disputable. In addition, underutilization of those tools may result in low delirium detection, as well[39]. Studies using dexmedetomidine showed promising results. However, further investigations are needed to extrapolate these findings in to clinical practice.

Early mobility

The recognition of physical impairment as one of the most important factors affecting Quality of Life post-ICU admission has triggered a number of investigations to explore the benefits of early mobilization in the ICU setting. In 2007, a pilot study aimed at showing the feasibility and safety of patient mobilization in the ICU[40]. The study reported a total of 1,449 activity events in 103 ventilated patients. The activities involved sitting on the bed, sitting in a chair, and ambulation. Of note, there were less than 1% activity-related adverse effects, as pre-specified by the investigators. Since this experience, other investigators have explored early mobility in ICU, reaching positive results. A prospective cohort study in a university medical ICU included 230 ventilated patients to receive early mobility within 72-hours of intubation *vs* usual care. Patients in the intervention group had at least one physical therapy session compared with those included in the usual care group (80% *vs* 47%, $P < 0.001$). Furthermore, patients in the early mobility group were out of bed earlier (5 d *vs* 11 d, $P < 0.001$). Notably, patients in the intervention group had shorter ICU (5.5 d *vs* 6.9 d; $P = 0.025$) and hospital LOS (11.2 d *vs* 14.5 d; $P = 0.006$)[41]. Two years later, a seven-month prospective before-and-after quality improvement project involving the implementation of full-time physical and occupational therapists who followed specific ICU guidelines, showed an increase in the number of rehabilitation events *per* subject (1 pre- *vs* 7 post-implementation, $P < 0.001$), and a higher level of functional mobility (56% *vs* 78%, $P = 0.03$). Furthermore, there was a reduction of ICU and hospital LOS post-implementation (7 d *vs* 4.9 d, $P = 0.020$; and 17.2 d *vs* 14.1 d, $P = 0.030$, respectively)[42]. In addition to the aforementioned data, the highest level of evidence was presented by an RCT. This study allocated 104 patients to early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation *vs* daily sedation vacation episodes with therapy as ordered by the primary care team. The primary outcome was defined as the percentage of individuals able to regain functional independence at hospital dismissal. Functional independence entailed the capability to perform 6 activities of daily living, and walk with independence. The primary outcome was seen in twenty-nine (59%) subjects in the intervention arm, whereas it was achieved in nineteen (35%) subjects in the control one ($P = 0.02$). Furthermore, patients in the intervention arm had shorter duration of delirium (median 2.0 d *vs* 4.0 d, $P = 0.02$), and more ventilator-free days (23.5 d *vs* 21.1 d; $P = 0.05$) during the 28-d follow-up period[43]. This study provided the framework for the implementation of early mobility in ICU as standard practice. Further publications with mixed results have been published ever since. A multicenter, international, parallel-group, assessor-blinded RCT in SICUs was published in 2016[44]. Two hundred mechanically ventilated patients were allocated to receive early mobility *vs* usual care. Three outcomes were assessed: The mean SICU optimal mobilization score (SOMS) level; length of stay in SICU; and functional independence, measured by the mini-modified functional independence measure score (mmFIM) at hospital discharge. The study showed a mean SOMS of 2.2 in intervention group *vs* 1.5 in control group ($P < 0.0001$). There was a decrease in the SICU length of stay of 3 d, favoring the intervention group ($P = 0.0054$). Lastly, functional independence measured by mmFIM score was also improved ($P = 0.0002$). Few years later, a systematic reviewed and meta-analysis, which included twenty-three RCTs comprising 2308 critically ill patients, assessed the impact of early mobility[45]. The results showed that early mobilization decreased the incidence of ICU-acquired weakness at hospital discharge [three studies, relative risk (RR): 0.60; 95%CI: 0.40 to 0.90; $P = 0.013$], increased the number of ventilator-free days [six studies, standardized mean difference (SMD): 0.17; 95%CI: 0.02 to 0.31; $P = 0.023$], and increased the discharged-to-home rate (seven studies, RR: 1.16, 95%CI: 1.00 to 1.34; $P = 0.046$). Despite the aforementioned positive studies, a number of articles showing lack of impact with the implementation of an early mobility program were also published. Particularly, a meta-analysis that included fourteen studies with a total of 1753 patients showed that early mobilization had no significant impact on short- or long-term mortality, quality of life, or mechanical ventilation duration ($P > 0.05$) [46]. Nevertheless, the program led to greater muscle strength as measured by the Medical Research Council Sum Score, and greater probability of walking without assistance. Both outcomes were measured at hospital discharge. An RCT that included mechanically ventilated patients to receive an intervention of intensive physical therapy *vs* usual care showed that the intensive physical therapy

program did not improve long-term physical performance at 1, 3- or 6-months post-discharge[47]. In this study, physical performance was assessed by a Continuous Scale Physical Functional Performance Test short form. A randomized, parallel-group, assessor-blinded, controlled trial allocated patients who had received a minimum of 48 hours of invasive or non-invasive ventilation to an intervention of 90-min of physical rehabilitation *per* day *vs* a control group, which received 30-min *per* day[48]. At 6 months, there was no difference in the Physical Component Summary of the SF-36 (primary outcome). Another single-center RCT allocated mechanically ventilated patients to an intervention consisting of passive range of motion, physical therapy, and progressive resistance exercises on a daily basis (intervention group) *vs* weekday physical therapy when ordered by the clinical team (control group)[49]. Within tree-hundred randomized subjects, the median hospital stay was 10 d [interquartile range (IQR), 6 to 17] in the intervention arm *vs* 10 d (IQR, 7 to 16) in the control one (median difference, 0; 95%CI: -1.5 to 3; P = 0.41). No differences were seen in ICU or ventilation LOS. Furthermore, no effects were seen at six months in handgrip (P = 0.23), SF-36 physical health score (P = 0.05), or SF-36 mental health score (P = 0.19). Lastly, a recently published RCT that assigned 750 mechanically ventilated patients to receive early mobilization *vs* usual care showed that the median number of days that patients were alive and out of the hospital (primary outcome) was 143 d (IQR 21 to 161) in the intervention group *vs* 145 d (IQR 51 to 164) in the usual care one (P = 0.62)[50]. Of note, the difference of mobilization time between groups was only 12.0 min *per* day (95%CI: 10.4 to 13.6). Despite the previously described data, which showed mixed findings, early mobilization remains a broadly accepted treatment by bedside clinicians and patients. Furthermore, the appropriate 'physical therapy-dose', which may have explained differences in outcomes, remains unknown.

Family involvement

In recent years, a growing number of reports supported the benefits of family member or caregiver involvement in the medical care of critically ill patients. A recent before-and-after study showed that a change in the visiting hour policy from 6-hour to 24-hours resulted in a reduction in the incidence of delirium from 12.1% to 6.7% (P = 0.03)[51]. Furthermore, another study that randomized ICU patients to receiving recorded messages in a family member's voice *vs* same messages in a non-family voice *vs* no messages, resulted in an increase in delirium-free days in the group allocated to receiving familiar voice messages (P = 0.044)[52]. A recently published retrospective cohort study, which compared the effect of physical presence of family *vs* telephone phone calls *vs* no presence, showed no significant association between those events and the prevalence of delirium. However, physical presence of family and telephone encounters were both associated with a reduction on delirium duration compared with no presence (-1.87 d and -1.41 d, respectively; P < 0.001)[53]. These studies underscore the importance of family presence and interaction during critical illness. Nevertheless, research regarding this area is still in its infancy.

EVIDENCE SUPPORTING THE ABCDEF BUNDLE IMPLEMENTATION

In the section above, evidence supporting individual elements of the ABCDEF bundle was described. In this section, the focus is placed on evidence supporting the implementation of the bundle as a whole. Despite its acceptance and broad implementation, evidence supporting the ABCDEF bundle is based on quality improvement projects or observational trials. A prospective cohort quality improvement study, which involved 7 community hospitals within the state of California, assessed hospital survival and delirium- and coma-free days according to the rate of compliance (total *vs* partial) with the ABCDE bundle. Interestingly, among the 6064 patients assessed for survival, for each 10% increment in compliance with the complete bundle, subjects presented 7% higher chances of hospitalization survival (OR, 1.07; 95%CI: 1.04 to 1.11; P < 0.001). Similarly, for each 10% increment in compliance with partial components of the bundle, patients presented 15% higher chances of hospitalization survival (OR, 1.15; 95%CI: 1.09 to 1.22; P < 0.001). Among the 5581 subjects evaluated for delirium and coma-free days, they experienced more days alive and free of delirium and coma with both total and partial bundle compliance [incident rate ratio (IRR) 1.02; 95%CI: 1.01 to 1.04; P = 0.004; and IRR 1.15; 95%CI: 1.09 to 1.22; P < 0.001, respectively][54]. This study demonstrated the value of implementing bundle elements, even when compliance with the entire bundle was not feasible. A subsequent prospective, multicenter, cohort study from a national quality improvement collaborative, which included 15226 critically ill patients demonstrated the benefit of complete bundle compliance and a 'dose-effect' response. In more detail, full bundle compliance resulted in lower likelihood of hospital death within 7 d (adjusted hazard ratio: 0.32; 95%CI: 0.17 to 0.62), delirium (adjusted OR: 0.60; 95%CI: 0.49 to 0.72), coma (adjusted OR: 0.35; 95%CI: 0.22 to 0.56), ICU readmission (adjusted OR: 0.54; 95%CI: 0.37 to 0.79), physical restraint use (adjusted OR: 0.37; 95%CI: 0.30 to 0.46), and dismissal to a facility (adjusted OR: 0.64; 95%CI: 0.51 to 0.80)[55]. Furthermore, a higher proportion of bundle elements utilized in patient care was associated with a lower likelihood of those outcomes. This study demonstrated that full compliance with the bundle was better than partial. Also, within the group of patients who received partial bundle compliance, the higher the number of elements achieved resulted in better outcomes. Finally, a

prospective cohort study assessed the impact of a stepwise implementation of the complete *vs* partial ABCDE bundle on mechanical ventilation duration, ICU and hospital LOS, and costs[56]. At baseline, the ICUs were already compliant with element 'B' of the bundle. In the first phase, elements 'A' and 'D' were implemented in both groups. In the last stage, element 'C' and 'E' were implemented in the group allocated to the fully compliant bundle, whereas no further elements were incorporated in the ICUs allocated to partially compliant. The implementation of the complete (B-AD-EC) *vs* partial (B-AD) bundle was associated with a reduction of ICU LOS (-10.3%; $P = 0.028$), hospital LOS (-7.8%; $P = 0.006$), and mechanical ventilation duration (-22.3%; $P < 0.001$). This study also demonstrated the value of implementing the full ABCDE bundle, rather than partial elements. Further studies assessed the value of the ABCDE bundle in a pre- *vs* post-implementation fashion. An eighteen-month, before-and-after study, which included five ICUs, one step-down unit, and one oncology care unit, showed that patients in the post-implementation period spent three more days breathing without mechanical assistance than those in the pre-implementation group (median, 24 *vs* 21; $P = 0.04$). After adjusting for multiple covariates, patients managed with the bundle had near half odds of presenting delirium (odds ratio, 0.55; 95%CI: 0.3 to 0.9; $P = 0.03$)[57]. Another implementation study, which evaluated the effect of the ABCDE bundle in the prevalence and duration of delirium (measured by the ICDSC tool), showed that after instituting the ABCDE bundle, the prevalence of delirium was reduced (from 38% to 23%, $P = 0.01$) and the mean number of days with delirium also decreased (from 3.8 to 1.72 d, $P < 0.001$)[58]. Lastly, a recently published meta-analysis that included 20 studies assessed the effect of implementing the ABCDE bundle in ICUs. The results revealed a lower incidence of delirium, shorter time on mechanical ventilation and ICU LOS, increased early mobility, and decreased ICU and hospital mortality after bundle implementation[59]. In addition, the study identified frequent barriers for bundle implementation, which included communication and planning challenges, excessive documentation, and fear of risks to the patient. It is important to note that previously described studies addressed the implementation of an ABCDE bundle, rather than an ABCDEF one. The evidence supporting the importance of family involvement (letter F) in ICU care was recently studied. Therefore, at the time the previously described studies were published, data on the relevance of family support were lacking.

MUSIC THERAPY IN THE ICU

Over the last few years, evidence has emerged regarding the impact of music listening in the critical care setting. An RCT performed in an academic medical-surgical ICU randomized mechanically ventilated patients to receive personalized music *vs* slow-tempo music *vs* an audiobook. Each session lasted about 1-hour and they were conducted twice a day for 7 consecutive days. The study revealed equivalent delirium-free days in all 3 groups, but provided feasibility of the aforementioned interventions[60]. A systematic review that included eighteen RCTs with a total of 1173 participant showed that music interventions of 20 to 30 min each were efficacious to reduce pain in adult ICU patients, who were able to self-report[61]. Importantly, 'music listening' should be differentiated from the concept of 'music therapy'. While music listening refers to the passive act of listening to pre-recorded music administered by registered nurses or caregivers, music therapy requires specific training and expertise for its delivery. The American Music Therapy Association defines music therapy as "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program." Beyond a Bachelor's degree in music therapy, a minimum of 1200 h of clinical training, in addition to credentialing by the Music Therapy-Certification Board are required to provide this therapy[62]. A recent RCT that included 373 mechanically ventilated patients from 12 ICUs at 5 hospitals in Minnesota allocated subjects to self-initiated patient-directed music (PDM) tailored by a music therapist *vs* patient-initiated noise canceling headphones *vs* usual care. The main endpoints were daily evaluations of anxiety (by a 100-mm VAS), and measures of sedative frequency and intensity. Patients included in the music therapy arm listened to music for a mean of 79.8 min/day. The study showed that the PDM group had an anxiety score that was 19.5 points lower than patients in the usual group ($P = 0.003$). There were no differences compared with the noise canceling group. In terms of sedative intensity and frequency, PDM showed lower points on both aspects of sedation (intensity and frequency) compared with noise canceling ($P = 0.01$) and usual care groups ($P = 0.04$)[63]. A subsequent study published by the same group, reported the cost-effectiveness analysis of such music therapy implementation. Direct costs were calculated on US$ based on 2015 standards. Overall, the total mean cost of the PDM was $329.14. The mean anxiety scores -VAS were 33 for PDM and 52 for usual care. The cost savings of PDM over usual care included $2460 in ICU costs, $170 in physician costs, and $22 in sedative medication costs, totaling $2652 (a value eight times the costs of implementing PMD). Notably, the major contributing factor to the cost savings were the estimated 1.4 fewer days of mechanical ventilatory support of patients randomized to PDM[64]. Finally, a recent publication proposed an interesting algorithm for the delivery of music therapy in ICU, incorporating familiar auditory sensory training, in addition to patient-specific music listening. The aforementioned integration resulted in the positive stimulation for medically sedated protocol. Of note, the implementation of this protocol required a previous training in the use of the Music Therapy

Assessment Tool for Awareness in Disorders of Consciousness or its adaptation[65]. In summary, the implementation of music therapy as an enhancement for the ABCDEF bundle is still in its infancy. More studies are needed to assess the effect of such intervention. Nevertheless, current information (although scarce) supports its use in this patient population.

CONCLUSION

Over the last two decades, strong evidence emerged supporting each element of the ABCDEF bundle. Consequently, observational trials and quality improvement projects reported positive outcomes resulting from full bundle implementation. In the author's opinion, recently described interventions may enhance the ABCDEF bundle. The introduction of music therapy protocols in ICU demonstrated reduction in patients' anxiety and direct costs. This intervention seems to be cost-effective, balancing cost-saving *vs* cost of implementing and could be considered as a possible addition to the ABCDEF bundle.

FOOTNOTES

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MINIREVIEWS

Point-of-care ultrasound in diagnosis and management of congestive nephropathy

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Abstract

Congestive nephropathy is kidney dysfunction caused by the impact of elevated venous pressures on renal hemodynamics. As a part of cardiorenal syndrome, the diagnosis is usually made based on history and physical examination, with findings such as jugular venous distension, a third heart sound, and vital signs as supporting findings. More recently, however, these once though objective measures have come under scrutiny for their accuracy. At the same time, bedside ultrasound has increased in popularity and is routinely being used by clinicians to take some of the guess work out of making the diagnosis of volume overload and venous congestion. In this mini-review, we will discuss some of the traditional methods used to measure venous congestion, describe the role of point-of-care ultrasound and how it can ameliorate a clinician's evaluation, and offer a description of venous excess ultrasound score, a relatively novel scoring technique used to objectively quantify congestion. While there is a paucity of published large scale clinical trials evaluating the potential benefit of ultrasonography in venous congestion compared to gold standard invasive measurements, more study is underway to solidify the role of this objective measure in daily clinical practice.

Key Words: Ultrasound; Point-of-care ultrasonography; Doppler; Venous excess ultrasound score; Congestion; Hemodynamics; Heart failure; Nephrology

Core Tip: Congestive nephropathy denotes kidney dysfunction in fluid overload states as a result of venous congestion. Conventional methods to assess congestion at the bedside lack sensitivity and diagnostic accuracy. Point-of-care ultrasound is emerging as an enhancement to physical examination for objective assessment of congestion and guide therapy. Future research should focus on its impact on practical outcomes such as freedom from congestive symptoms, quality of life, and recurrent hospitalizations.

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INTRODUCTION

It is well known that unresolved congestion is associated with adverse outcomes in patients with heart failure, increasing the risk of re-hospitalization and death[1,2]. In 2017 alone, heart failure admissions occurred at a rate of approximately 5 per 1000 United States adults with about a quarter of those patients experiencing readmissions, which highlights the magnitude of this problem[3]. The deleterious effects of fluid overload are now being recognized outside of heart failure, with multiple studies showing a positive fluid balance being associated with increased mortality[4,5]. Though seemingly straightforward, evaluation and management of congestion require a thorough understanding of the pathophysiology and hemodynamic principles. Multiple bedside diagnostic methods and tools exist for clinicians to assess congestion including signs and symptoms, physical examination, laboratory data, and radiography, but these all have limitations. On the other hand, timely diagnosis is vital as faster rates of decongestion are associated with a reduced risk of mortality and hospitalization[6]. In addition, end-organ effects of fluid overload are being increasingly recognized, which brings us to the topic of congestive nephropathy. Congestive nephropathy is defined as renal dysfunction that occurs due to venous congestion leading to impaired organ perfusion[7]. While this term was recently coined[8], several studies have previously shown that elevated central venous pressure (CVP) is associated with worsening renal function despite preserved cardiac index[9]. This does have pathophysiologic basis as the renal perfusion pressure is the difference between mean arterial pressure and CVP; if the CVP is elevated, the perfusion pressure drops, impairing renal blood flow. In addition, activation of the renin angiotensin-aldosterone system and consequent sodium and water retention, interstitial edema, endothelial dysfunction, and increased intra-abdominal pressure all contribute to increased pressure within the encapsulated kidney (*renal tamponade*), ultimately leading to organ dysfunction. Further, renal dysfunction can exacerbate the existing fluid overload, resulting in a vicious cycle. In this article, we will provide a kidney-centric overview of the bedside tools available to assess congestion, focusing on advances in point-of-care ultrasonography (POCUS).

CONVENTIONAL METHODS TO ASSESS CONGESTION

The bedside assessment of a patient's intravascular volume is challenging. Traditionally, this assessment involves taking a thorough history and performing cardiopulmonary physical examination. A patient's given history can often be misleading or not reflective of their hemodynamic physiology. Physical examination, including assessment of jugular venous pressure, lower extremity edema, presence of an 'S3', and auscultation of the lungs for evidence of pulmonary edema, has traditionally been a common way for clinicians to assess intravascular volume status at the bedside. This is wrought with subjectivity and inaccuracies, and has almost no correlation with right heart catheterization, which is the invasive gold-standard assessment[10,11]. Similarly, chest X-ray remains a common modality to diagnose pulmonary congestion resulting from heart failure or other etiologies, despite having considerable diagnostic limitations including high false negative rate[12]. The degree of venous congestion beyond that of the jugular vein, specifically the alteration of blood flow in the hepatic, portal, and renal veins leading to congestive organ injury, cannot be assessed by physical examination or an X-ray. All these traditional approaches have significant limitations and cannot reliably detect hemodynamic congestion. Diagnosis of congestive nephropathy is challenging as no gold standard exists. Traditionally, the diagnosis of congestive nephropathy has been based on clinician gestalt after a trial-and-error period without any objective way to evaluate renal hemodynamics. POCUS using vascular Doppler analysis is emerging as a promising modality to assess for venous congestion along the continuum from the heart to the kidneys.

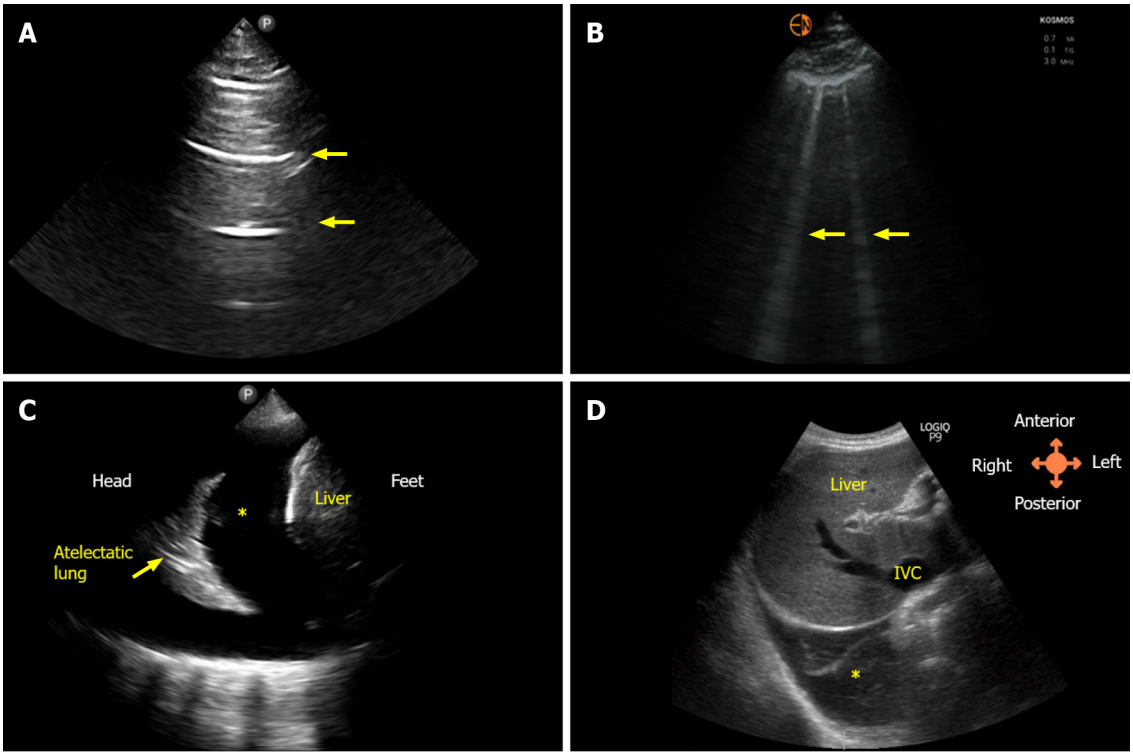

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Figure 1 Lung ultrasound images. A: Normal lung showing horizontal artifacts, *i.e.*, A-lines (arrows); B: Vertical artifacts (arrows) known as B-lines indicating interlobular septal thickening, typically seen in congestion; C: Pleural effusion (asterisk) as seen on lateral scan; D: Right pleural effusion (asterisk) as seen from subxiphoid scanning window. IVC: Inferior vena cava.

POINT-OF-CARE ULTRASOUND

POCUS is a limited ultrasound examination performed at the bedside and interpreted by the treating physician. It is used to answer focused clinical questions, and is integrated with the patient's history, physical examination, and other available data to narrow the differential diagnosis and inform management. POCUS is becoming more accessible to clinicians owing to the recent advances in ultrasound technology and availability of the low-cost, highly portable equipment. Compared to conventional examination, POCUS offers substantially higher diagnostic accuracy[13]. In the context of heart failure and congestion, POCUS not only aids in the diagnosis, but also guides decongestive therapy with potential implications for patient outcomes. In this section, we will outline the various components of sonographic evaluation of a patient with suspected fluid overload/venous congestion.

Lung ultrasound

Lung ultrasound (LUS) has shown superiority over chest X-ray for nearly all clinical indications[14] and can detect extravascular edema prior to the onset of clinical symptoms. From diagnosing pneumonia[15] to identifying pulmonary edema[16], LUS has proven to be more accurate, and in some settings, more accessible. In a meta-analysis of six studies and more than 1800 patients, LUS had better sensitivity (88% *vs* 73%) when compared to chest X-ray for the diagnosis of cardiogenic pulmonary edema[17]. LUS findings are shown to have prognostic significance in various clinical scenarios including heart failure and end-stage renal disease[18,19]. With respect to guiding therapy, in the recent LUST trial[20], LUS-guided ultrafiltration strategy was associated with a reduction in the recurrence of decompensated heart failure and other cardiovascular events in hemodialysis patients. Similarly, in heart failure patients, LUS-guided management has shown to reduce acute decompensation events and urgent care visits[21, 22]. LUS is an important diagnostic, prognostic, and management tool in the assessment of clinical or subclinical fluid overload. While it does not directly diagnose congestive nephropathy, it influences the treatment by establishing fluid tolerance *vs* intolerance. For example, in a patient with acute kidney injury, presence of extravascular lung water on LUS would sway away the clinician from administering empiric intravenous fluids, thus avoiding iatrogenic fluid overload. Figure 1 illustrates normal and abnormal LUS findings seen in fluid overload.

Focused cardiac ultrasound

Focused cardiac ultrasound (FoCUS) is a POCUS examination of the heart and inferior vena cava (IVC). Essentially, it is a limited and problem-focused evaluation performed by any clinician trained in POCUS

analogous to auscultation and not restricted to cardiologists. On the contrary, consultative echocardiography involves a comprehensive evaluation documenting a predefined set of parameters and measurements. FoCUS has a much higher diagnostic accuracy than conventional physical examination [23] and quickly provides vital information related to cardiac structure and function. Pathologies requiring immediate attention such as pericardial effusion, impaired contractility, gross chamber enlargement, and valvular anomalies can be diagnosed at the bedside and promptly addressed. In addition, IVC ultrasound allows non-invasive estimation of the CVP/right atrial pressure (RAP). As mentioned, elevated CVP is the starting point of venous congestion and is associated with impaired renal function as well as mortality[24]. In spontaneously breathing patients, current guidelines recommend stratifying RAP as follows. RAP is estimated to be 3 mmHg (0-5 mmHg) if the maximal anteroposterior diameter of the IVC is < 2.1 cm with > 50% collapse during a sniff. If the IVC is > 2.1 cm and collapses < 50%, RAP is documented as 15 mmHg (10-20 mmHg). An intermediate value of 8 mmHg (5-10 mmHg) is assigned where IVC parameters do not fit this paradigm. Elevated RAP estimated by IVC ultrasound is associated with hospital readmissions and mortality[25,26]. Despite its simplicity and apparent clinical utility, isolated IVC ultrasound has several pitfalls. First, estimation of RAP by IVC ultrasound is not accurate in mechanically ventilated patients. Even in those who are spontaneously breathing, strength of 'sniff' considerably varies among patients, leading to false impressions. Moreover, trained athletes and active young adults can have a chronically dilated IVC without elevated RAP whereas patients with elevated intra-abdominal pressure may have a collapsed IVC despite high RAP. In addition, IVC POCUS in long axis is subject to cylinder effect, which means when the ultrasound beam bisects the three-dimensional vessel (presumably a cylinder) in the periphery rather than the center, a falsely low diameter will be recorded. This leads to incorrect interpretation during follow-up studies, particularly when different operators are performing the study. Therefore, the IVC must be examined in both long and short axis views, where feasible[27,28]. Also, in conditions such as cirrhosis, IVC size/shape may be altered by the local structural changes, making it unreliable to predict RAP. Furthermore, it must be noted that isolated IVC POCUS does not provide real-time information on end-organ congestion, which in turn depends on both RAP and venous compliance. In other words, a plethoric IVC increases the probability of congestive organ injury but cannot objectively demonstrate it.

Venous excess ultrasound score: Venous excess ultrasound score (VExUS) stands for venous excess Doppler ultrasound. It involves Doppler evaluation of the abdominal veins (hepatic, portal, and intrarenal) to assess the flow pattern and thereby detect venous congestion that effects organ perfusion. While the Doppler patterns in these individual veins have been studied long before[29-32], the concept of VExUS is fairly new and first documented by Beaubien-Souligny *et al*[33] in 2020. In their study including 145 cardiac surgery patients, the investigators found that severe flow abnormalities in at least two of the three above-mentioned veins together with a dilated IVC (≥ 2 cm) predicts the risk of acute kidney injury (*i.e.*, congestive nephropathy) with a hazard ratio of 3.69, outperforming isolated CVP measurement. Therefore, adding VExUS to IVC ultrasound improves the risk prediction of organ dysfunction. Based on the degree of flow alteration in individual veins, a scoring system was proposed to quantify systemic venous congestion, which is illustrated in Figure 2. In addition to diagnosing congestion, VExUS allows objective monitoring of congestion while the patient is receiving decongestive therapy as these waveforms are dynamic[34]. For example, Argaiz *et al*[35] have demonstrated that improvement in portal vein pulsatility coincides with improvement in renal function in patients with heart failure receiving diuretic therapy. In addition, several case reports exist demonstrating this phenomenon in multiple veins[36-41]. While there have not been published randomized clinical trials to date, outcome data for VExUS is emerging in the literature. For example, a high VExUS score, indicating severe hemodynamic congestion, has been shown to be associated with development of acute kidney injury in various clinical settings[34,42]. Specifically in heart failure patients, altered renal vein flow has been shown to confer worse outcomes[32,43,44]. In isolation, all these waveforms have limitations, which we have discussed in detail previously and is beyond the scope of this manuscript[45,46]. Of particular note, VExUS cannot distinguish between volume and pressure overload. For instance, a patient with precapillary pulmonary hypertension can have the same Doppler stigmata of congestion as a patient with iatrogenic fluid overload. It is up to the clinician to interpret the findings in the appropriate clinical context and in conjunction with other sonographic parameters (*e.g.*, Doppler echocardiography). Having said that, congestion from any cause (pressure or volume) still leads to congestive nephropathy. In a large cohort of patients with pulmonary hypertension, Husain-Syed *et al* [47] showed that intrarenal venous congestion correlates with renal dysfunction as well as mortality/morbidity end point, which exemplifies this concept.

Extended VExUS

The term extended venous excess ultrasound score (E-VExUS) or extended VExUS has been proposed to include Doppler interrogation of additional veins such as the internal jugular, superior vena cava, splenic, and femoral veins in situations where the primary veins (*e.g.*, hepatic, portal in cirrhosis, and intrarenal in advanced kidney disease) suffer from limitations[28,48]. This also includes estimation of RAP by greyscale POCUS of the internal jugular vein where IVC is not accessible or unreliable. Doppler

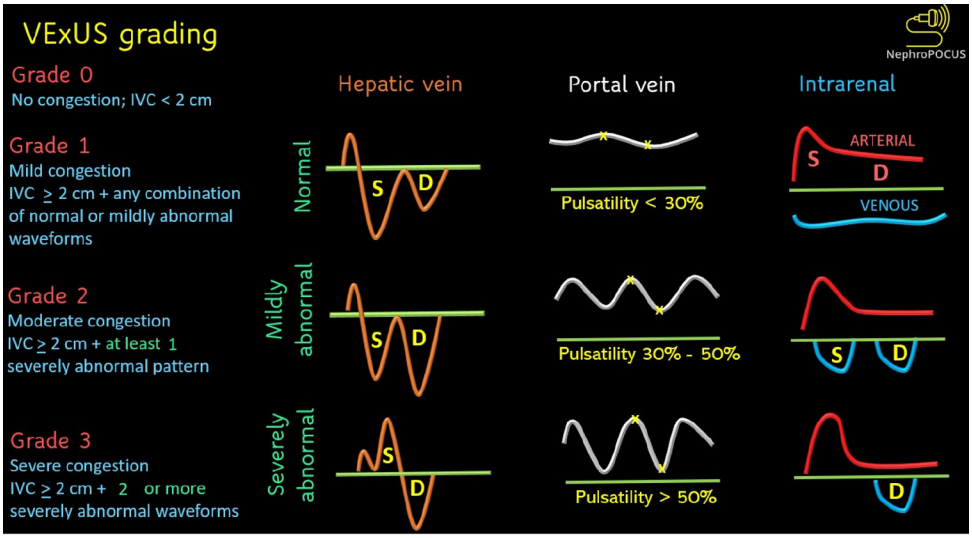

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Figure 2 Venous excess ultrasound grading. When the diameter of the inferior vena cava is > 2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (D) wave, but still below the baseline; it is considered severely abnormal when the S-wave is reversed. Portal vein Doppler is considered mildly abnormal when the pulsatility is 30% to 50%, and severely abnormal when it is ≥ 50%. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with D-only pattern. Figure adapted from NephroPOCUS.com with permission.

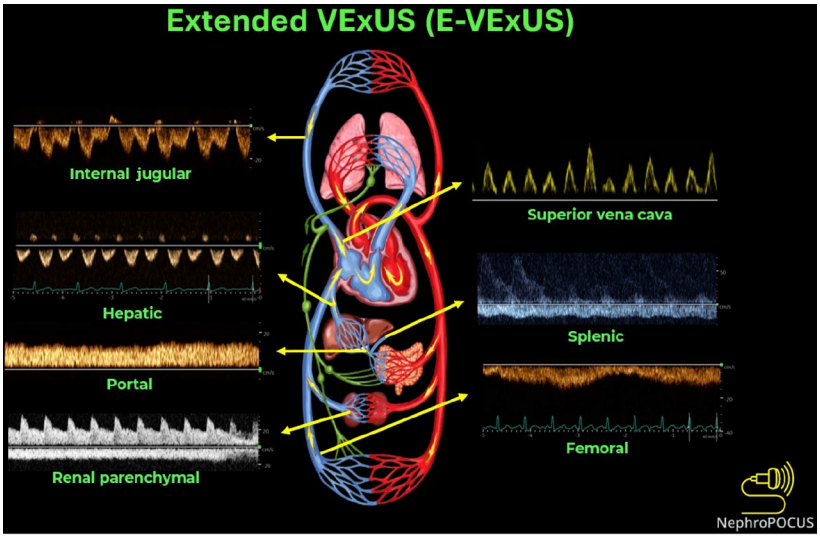

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Figure 3 Doppler components of extended venous excess ultrasound score examination. Figure adapted from NephroPOCUS.com with permission.

components of E-VExUS are illustrated in Figure 3. Similar to the components of original VExUS, these veins have also been studied individually and shown to be useful to gauge the effects of elevated RAP [49-53]. Of late, femoral vein Doppler is gaining attention due to relative ease of image acquisition. In a recent study including 57 patients undergoing right heart catheterization, femoral vein flow alteration graded by stasis index showed excellent diagnostic performance to detect elevated RAP (specificity: 92.3% [80.0-99.3]; diagnostic accuracy: 90.4 [77.4-97.3]; positive likelihood ratio: 12.5 [3.01-51.97])[54]. However, caution must be exercised in 'excluding' elevated RAP/venous congestion based on the femoral vein alone as earlier studies showed a relatively low sensitivity[55]. This VExUS expansion is still in its early stages of adoption, so there is need for more data to establish its clinical utility in routine practice. Figure 4 is the sonographic representation of chain of venous congestion from the right heart to femoral vein. Table 1 summarizes the key sonographic findings and limitations of each application in the context of congestive nephropathy.

Table 1 Key sonographic findings and limitations of each application in the evaluation of congestive nephropathy

Sonographic application	Possible findings in the context of congestive nephropathy	Limitations
Lung ultrasound	Elevated extravascular lung water (B-lines) and pleural effusion	B-lines are non-specific and can be seen in non-cardiogenic pulmonary edema, lung fibrosis, contusion, and alveolar hemorrhage
Focused cardiac ultrasound (basic)	LV systolic dysfunction (qualitative and M-mode); RV systolic dysfunction (qualitative and M-mode); Pericardial effusion; Gross chamber enlargement (*e.g.*, RV dilation leading to interventricular septal flattening); Gross valvular dysfunction (*e.g.*, tricuspid regurgitation on color Doppler); Elevated right atrial pressure (plethoric IVC)	Lack of spectral Doppler provides limited information. Qualitative assessment relies on operator experience. IVC cannot reliably estimate RAP in mechanically ventilated patients. IVC can be small in intra-abdominal hypertension despite elevated RAP. IVC can be dilated without elevated RAP in trained athletes
Focused cardiac ultrasound (advanced)	Reduced stroke volume assessed by LV outflow tract velocity time integral. Elevated LV filling pressures assessed by mitral inflow Doppler and mitral annular tissue Doppler. Elevated pulmonary artery pressures/right ventricular systolic pressure assessed by continuous wave Doppler through the RV outflow tract and tricuspid valve. Elevated right atrial pressure assessed by tricuspid inflow and tissue Doppler	Requires higher operator skill level and training than basic cardiac ultrasound. Suboptimal views/Doppler angle limit the accuracy of measurements obtained. Some of the parameters lack validation in critical illness
Hepatic vein Doppler	Reduced amplitude or reversal of the systolic wave (Normally, systolic wave is larger than the diastolic wave)	Prone to erroneous interpretation without EKG. Cannot differentiate pressure and volume overload (applies to all components of VExUS and E-VExUS). Influenced by factors other than RAP (*e.g.*, atrial fibrillation, RV systolic excursion). Diminished pulsatility in cirrhosis; may not accurately reflect the degree of congestion
Portal vein Doppler	Increased pulsatility (normal waveform is near-continuous)	Pulsatile portal vein can be seen in cirrhosis and healthy, young individuals without an elevated RAP. Can appear falsely normal despite elevated RAP in patients with portal hypertension
Intra-renal venous Doppler	Increased pulsatility, systolic wave reversal (normal waveform is near-continuous)	Most technically challenging of the three components of VExUS. Sampling a larger vessel such as the main renal vein instead of interlobar vein leads to mistaken interpretation
E-VExUS	IJ vein: Reduced amplitude or reversal of the systolic wave (normally, systolic wave is larger than the diastolic wave); Splenic vein: Increased pulsatility (normal waveform is near-continuous); SVC: Reduced amplitude or reversal of the systolic wave (normally, systolic wave is larger than the diastolic wave); Femoral: Increased pulsatility and elevated velocity of the retrograde component (normal waveform is near-continuous)	Not validated as a combination score though individual components are studied. EKG is required when there is no simultaneous arterial trace to delineate cardiac cycles. IJ vein: Susceptible to probe pressure due to its relatively superficial location. Splenic vein: Similar limitations as portal vein. SVC: Technically challenging to access *via* transthoracic windows. Femoral: Relatively less sensitive to detect elevated RAP. Severe intra-abdominal hypertension may influence the waveform

LV: Left ventricle; RV: Right ventricle; M-mode: Motion mode; IVC: Inferior vena cava; EKG: Electrocardiogram; VExUS: Venous excess ultrasound; RAP: Right atrial pressure; RV: Right ventricle; E-VExUS: Extended venous excess ultrasound; IJ: Internal jugular; SVC: Superior vena cava.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While POCUS has gained a lot of traction over the last several years, it is sometimes met with a degree of skepticism. Detractors are quick to point out that a significant mortality benefit with use of POCUS has not been shown. For example, the SHoC-ED trial randomized almost 300 patients with undifferentiated shock into a POCUS plus standard of care *vs* standard of care without ultrasonography to help diagnose the etiology of shock and help manage the condition. This showed no mortality benefit, no decrease in length of stay, decrease in intravenous fluid use, or decrease in rates of computed tomography scanning[55]. Conversely, the supporters of POCUS are quick to point out that achieving a mortality benefit in an intervention that is not therapeutic is a mountain that may prove too high to climb; in essence, unfair to expect of a diagnostic modality. In most cases, POCUS and VExUS scoring help quantify congestion in an objective manner and allow clinicians to rely much less on other unreliably recorded measures such as daily weights and intake-output documentation. Several randomized controlled trials incorporating VExUS are currently underway to determine its efficacy not only in the diagnosis but also in guiding the management such as for dosing diuretics. The use of elements of the extended VExUS examination needs to be further validated in population wide studies before becoming mainstays of the evaluation. Due to the medical community's long-standing affinity for objective scoring systems, VExUS will without a doubt become more commonplace. However, there will continue to be significant demand from clinicians for a show of mortality reduction before the practice becomes widely adopted. In the meantime, it is important to give weight to other outcomes such as time to diagnosis, readmission rates, recovery of renal function, symptom burden from heart failure and congestion, and quality of life in the judgment of this emerging technique. On the other hand, we do acknowledge that POCUS training remains an unmet need currently. Applications such as Doppler echocardiography, VExUS, and E-VExUS require solid technical skills that can only be garnered by longitudinal training. Especially in nephrology, there are a very few fellowship programs that offer

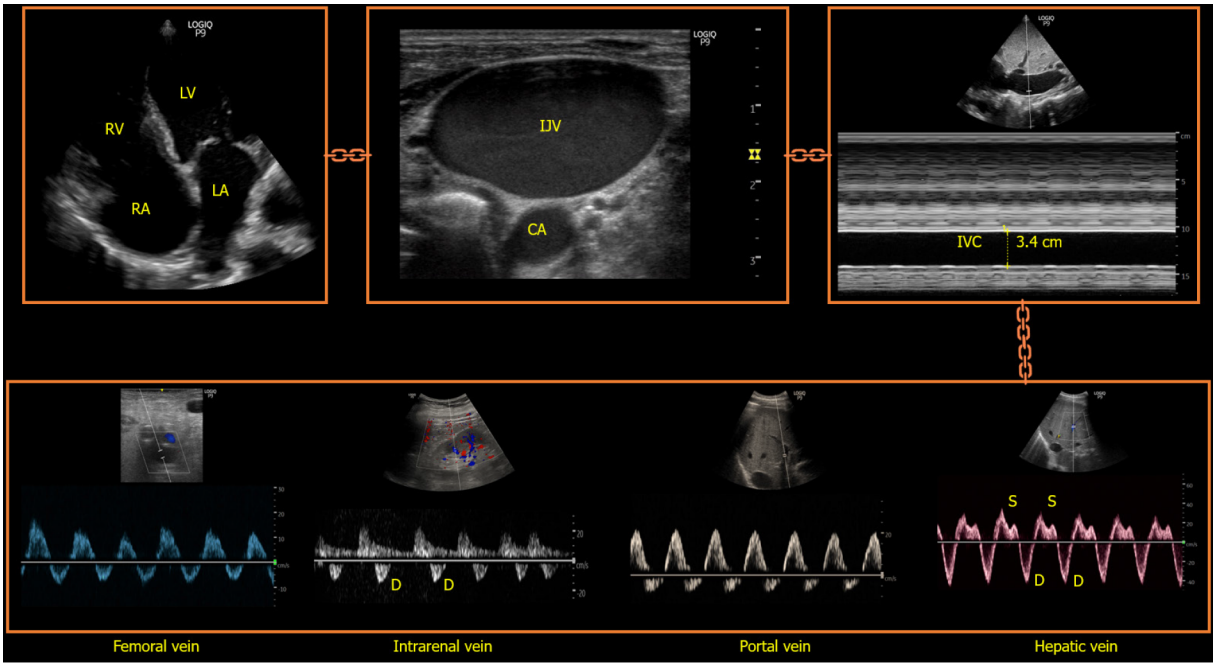

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Figure 4 The chain of venous congestion: Apical view of the heart is shown in the upper left corner where bulging of the interatrial septum into the left atrium can be noted suggestive of high right atrial pressure. Next image shows significantly dilated internal jugular vein followed by a plethoric inferior vena cava. Lower panel represents the commonly assessed Doppler parameters to assess systemic venous congestion, all of which are severely abnormal. Please see Figure 3 for the normal appearance of these waveforms and Figure 2 for venous excess ultrasound score grading. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle; CA: Carotid artery; S: Systolic wave; D: Diastolic wave.

training in comprehensive hemodynamic assessment at this time[56,57]. This is ironic given that most of the consults in a typical nephrology practice revolve around managing fluid disorders. While the situation is slightly better in critical care medicine, guideline-mandated training requirements remain vague. As such, professional organizations must step up and establish robust POCUS certification and competency assessment standards. Otherwise, performance of advanced sonographic applications by inadequately trained physicians may potentially result in patient harm.

CONCLUSION

It is well known that hemodynamic congestion has adverse effects on multi-organ function and is associated with adverse clinical outcomes. Ultrasonographic techniques have long been used to quantify venous congestion and have been validated extensively in the medical literature. The combination of Doppler findings from several organ systems into an objective evaluation is a process that has been undergoing significant study in recent years. While VExUS has its limitations, it has promise as a dependable tool in the management of congestive nephropathy and is superior to any other bedside noninvasive assessment. As with other diagnostic tools, it is critical that clinicians analyze their findings as just one part of the larger clinical puzzle in conjunction with other objective data points. In the correct clinical context, using VExUS findings to apply individualized changes to care plans may ultimately help deliver more accurate care to patients with suspected congestive nephropathy.

FOOTNOTES

Author contributions: Turk M and Roberson T drafted the manuscript; Koratala A designed and reviewed the manuscript, and revised it for critical intellectual content; all authors have read and approved the final version.

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ORIGINAL ARTICLE

Observational Study

Elevated soluble fas blood concentrations in patients dying from spontaneous intracerebral hemorrhage

Leonardo Lorente, María M Martín, Antonia Pérez-Cejas, Luis Ramos-Gómez, Jordi Solé-Violan, Juan J Cáceres, Alejandro Jiménez, Agustín F González-Rivero

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Abstract

BACKGROUND

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there have been no data on the association between blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) and the prognosis of spontaneous intracranial hypotension (SIH) patients.

AIM

To determine whether there is an association between blood sFas concentrations

and SICH patient mortality.

METHODS
We included patients with severe and supratentorial SIH. Severe was defined as having Glasgow Coma Scale < 9. We determined serum sFas concentrations at the time of severe SICH diagnosis.

RESULTS
We found that non-surviving patients (n = 36) compared to surviving patients (n = 39) had higher ICH score (P = 0.001), higher midline shift (P = 0.004), higher serum sFas concentrations (P < 0.001), and lower rate of early hematoma evacuation (P = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; P = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

CONCLUSION
The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

Key Words: Spontaneous intracerebral hemorrhage; Soluble fas; Apoptosis; Patients; Mortality

Core Tip: Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) with SICH patient prognosis. The objective of our study was to determine whether there is an association between blood sFas concentrations and SICH patient mortality. The association of blood sFas concentrations with SICH patient mortality is a novel finding of this study.

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INTRODUCTION

Spontaneous intracerebral hemorrhage (SICH) leads to many disabilities and deaths annually worldwide[1]. Several studies of SICH patients undergoing surgical hematoma evacuation have shown apoptotic changes in brain samples from areas of hematoma compared with areas of the healthy brain[2-8]. Apoptosis can be activated by the release of mitochondrial cytochrome c into the cytoplasm (named the mitochondrial or intrinsic apoptosis pathway) or by the binding of a surface death receptor to its ligand (named extrinsic apoptosis pathway). The main surface death receptor is Fas, and its ligand is the FasL[2-8]. When binding between Fas and FasL occurs, a death signal appears and the the extrinsic pathway is activated. This death signal is responsible for the activation of caspase-8 (initiator caspase in the extrinsic apoptosis pathway), which leads to the activation of caspase-3 (the main effector caspase in extrinsic and intrinsic apoptosis pathways). Finally, caspase-3 is responsible for cell death[2-8]. Lower plasma Fas concentrations have been found in SICH patients than in healthy controls[9]. However, there are no data on the association between blood Fas concentrations and SICH patient prognosis.

Thus, the objective of this study was to determine whether there is an association between blood Fas concentrations and SICH patient mortality.

MATERIALS AND METHODS

Design and subjects

The following five Spanish Intensive Care Units recruited patients from 2016 to 2017 in this observational and prospective study: H General de La Palma, H Insular de Las Palmas de Gran Canaria, H Universitario de Canarias (San Cristóbal de La Laguna), H Universitario Nuestra Señora de Candelaria

(Santa Cruz de Tenerife), and H Universitario Dr. Negrín (Las Palmas de Gran Canaria). The study was performed with approval of the research ethic committee of each hospital, and written informed consent was provided by a family member of each patient.

We recruited 75 patients (29 females and 46 males) with severe and supratentorial SICH. Severe was defined as Glasgow coma scale (GCS) < 9[10]. We excluded patients aged < 18 years, pregnancy, malignant disease, or limited interventions order at hospital admission. In addition, we excluded patients with traumatic hemorrhage, hemorrhagic transformation of brain infarction, infratentorial hemorrhage or primary intraventricular hemorrhage (IVH). We also excluded patients in whom SICH was due to aneurysm, arteriovenous malformation, anticoagulant treatment, or fibrinolytic treatment.

We considered that SICH was due to hypertension if the patient was hypertensive and had no other cause of SICH. We considered that SICH was due to amyloid angiopathy if the patient was not hypertensive and any other cause of SICH was recorded. We considered that SICH was due to arteriovenous malformation or aneurysm if some of those findings were shown in computed tomography angiography. We considered that SICH was due to anticoagulant treatment or fibrinolytic treatment if some of those drugs were administered to the patient.

We registered the following data: Age, sex, GCS, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, fibrinogen, international normalized ratio, platelets, activated partial thromboplastin time, lactic acid, glycemia and creatinine[11]. We also registered volume (calculated by the formula $AxBxCx0.5$); site and cause of SICH; ICH score; and the existence of transtentorial herniation, hydrocephalus, IVH, or midline shift. In addition, we registered the existence of early hematoma evacuation (within first 24 h of SICH diagnosis) and of mortality during the first 30 d[12,13].

Blood samples and determination of serum Fas concentrations

We collected serum samples at the time of severe SICH diagnosis and froze the samples at -80 °C. We determined all soluble fas (sFas) concentrations at the same time with a Human Fas enzyme-linked immunoassay (ELISA) Kit (Elabscience, Houston, TX, United States), which had 19 pg/mL as the detection limit and < 6% as the intra- and inter-assay variation coefficients. This kit uses sandwich ELISA as the method. The micro ELISA plate provided in this kit was pre-coated with an antibody specific to human Fas. The optical density (OD) was measured with spectrophotometry at a wavelength of 450 ± 2 nm. The OD value was proportional to the concentration of human Fas. The concentration of human Fas in samples was calculated by comparing the OD of the samples with the standard curve. Some of those patients were included in our previous publication determining serum sFasL concentrations, and serum sFas concentrations were determined in the current work[14].

Statistical analyses

We described continuous variables as medians (interquartile ranges) and categorical variables as frequencies (percentages). We compared continuous variables by the Wilcoxon-Mann-Whitney test and categorical variables by the chi-square test. The estimation of 30-d mortality prediction for serum sFas concentrations was performed using receiver operating characteristic analysis. We constructed Kaplan-Meier curves of 30-d mortality in patients with serum sFas concentrations higher and lower than 63 ng/mL (which was the Youden J index). We analyzed the possible association of serum Fas concentrations and SICH patient mortality controlling for ICH score, midline shift, and early hematoma evacuation. Statistical analyses were performed using LogXact 4.1 (Cytel Co., Cambridge, MA, United States) and SPSS 17.0 (SPSS Inc., Chicago, IL, United States), and $P < 0.05$ was considered statistically significant.

RESULTS

We found that non-surviving patients ($n = 36$) with respect to surviving patients ($n = 39$) had higher age ($P = 0.001$), APACHE-II score ($P < 0.001$), ICH score ($P = 0.001$), ICH volume ($P = 0.04$), midline shift ($P = 0.004$), and serum sFas concentrations ($P < 0.001$). In addition, non-surviving patients with respect to surviving patients had lower GCS ($P < 0.001$) and lower rate of early hematoma evacuation ($P = 0.04$) (Table 1).

We found that serum sFas concentrations had an area under the curve for mortality prediction of 83% (95% confidence interval [CI] = 72%-90%; $P < 0.001$) (Figure 1). The mortality prediction for serum sFas concentrations cutoff point of 63 ng/mL had sensitivity of 72% (55%-86%), specificity of 77% (61%-89%), negative likelihood ratio of 0.4 (0.2-0.6), positive likelihood ratio of 3.1 (1.7-5.7), negative predictive value of 75% (63%-84%), and positive predictive value of 74% (61%-84%). We found in the Kaplan-Meier analysis that patients with serum sFas concentrations > 63 ng/mL showed higher death risk (hazard ratio = 4.7; 95%CI = 2.3-97; $P < 0.001$) (Figure 2). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95%CI = 1.014-1.129; $P = 0.01$) controlling for ICH score, midline shift, and early hematoma evacuation (Table 2).

Table 1 Clinical and biochemical characteristics of 30 d surviving and non-surviving patients with spontaneous intracerebral hemorrhage

Variable	Surviving, *n* = 39	Non-surviving, *n* = 36	*P* value
Sex, *n* (%)			0.35
Female	13 (33.3)	16 (44.4)	
Male	26 (66.6)	20 (55.6)	
Age in yr, *n* (median *P* 25-75)	57 (51-63)	68 (57-75)	0.001
Cause of SIH, *n* (%)			0.99
Hypertension	35 (89.7)	33 (91.7)	
Amyloid angiopathy	4 (10.3)	3 (8.3)	
Volume of SIH in cc, *n* (median *P* 25-75)	41 (23-66)	72 (29-98)	0.04
Transtentorial herniation, *n* (%)	2 (5.1)	2 (5.6)	0.99
Hydrocephalus, *n* (%)	17 (43.6)	23 (63.9)	0.11
Intraventricular hemorrhage, *n* (%)	13 (33.3)	20 (56.6)	0.07
Site of SIH, *n* (%)			0.91
Lobar	24 (61.5)	23 (63.9)	
Basal ganglia	7 (17.9)	7 (19.4)	
Thalamus	8 (20.5)	6 (16.7)	
Midline shift in mm, *n* (median *P* 25-75)	5 (0-8)	10 (5-15)	0.004
GCS, *n* (median *P* 25-75)	8 (6-8)	4 (3-7)	< 0.001
APACHE-II score, *n* (median *P* 25-75)	19 (15-21)	25 (23-28)	< 0.001
ICH score, *n* (median *P* 25-75)	2 (1-3)	3 (2-4)	< 0.001
aPTT in s, *n* (median *P* 25-75)	29 (26-30)	29 (24-33)	0.28
Platelets as $\times 10^3/mm^3$, *n* (median *P* 25-75)	208 (161-262)	200 (143-259)	0.83
Fibrinogen in mg/dL, *n* (median *P* 25-75)	402 (311-626)	487 (366-542)	0.42
INR, *n* (median *P* 25-75)	1.07 (0.94-1.21)	1.09 (0.90-1.21)	0.76
Lactic acid in mmol/L, *n* (median *P* 25-75)	1.60 (0.90-2.10)	1.75 (1.20-2.70)	0.07
Glycemia in g/dL, *n* (median *P* 25-75)	140 (120-194)	166 (133-211)	0.06
Sodium in mEq/L, *n* (median *P* 25-75)	140 (137-143)	139 (136-145)	0.79
Creatinine in mg/dL, *n* (median *P* 25-75)	0.80 (0.60-0.91)	0.80 (0.60-1.10)	0.90
PaO_2/FIO_2 ratio, *n* (median *P* 25-75)	296 (194-375)	270 (214-387)	0.83
Early hematoma evacuation, *n* (%)	15 (38.5)	6 (16.7)	0.04
sFas in ng/mL, *n* (median *P* 25-75)	22 (17-63)	141 (49-286)	< 0.001

APACHE II: Acute Physiology and Chronic Health Evaluation; aPTT: Activated partial thromboplastin time; FIO_2: Fraction inspired of oxygen; GCS: Glasgow Coma Scale; ICH: Intracerebral hemorrhage; INR: International normalized ratio; PaO_2: Pressure arterial of oxygen; SICH: Spontaneous intracerebral hemorrhage; SIH: Spontaneous intracranial hypotension.

DISCUSSION

Several studies of SICH patients have shown apoptotic changes in brain samples after hematoma evacuation[2-8]. However, there are no data on the association of blood concentrations of sFas with SICH patient prognosis. Our study reports the novel findings of the existence of higher serum sFas concentrations in non-survivor than survivor SICH patients and the existence of an association between serum sFas concentrations and 30-d mortality controlling SICH severity and early hematoma evacuation.

Fas is the main surface death receptor of the apoptosis extrinsic pathway. After binding to its specific receptor (FasL), a death signal appears that is responsible for the activation of caspase-8 activation[2-8].

Table 2 Multiple logistic regression analysis to predict 30 d mortality

Variable	Odds ratio	95%CI	*P* value
Serum sFas in ng/mL	1.070	1.014-1.129	0.01
ICH score as points	47.71	2.24-1012.34	0.01
Midline shift in mm	1.758	1.133-2.727	0.01
Early hematoma evacuation as yes *vs* no	0.002	0.001-0.210	0.01

CI: Confidence interval; ICH: Intracerebral hemorrhage.

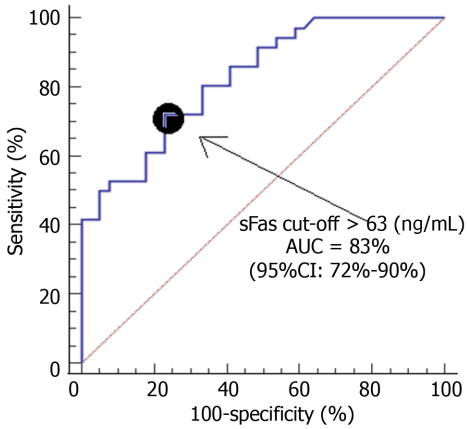

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Figure 1 Receiver operating characteristic analysis using serum soluble fas levels as a predictor of mortality at 30 d. AUC: Area under curve; CI: Confidence interval.

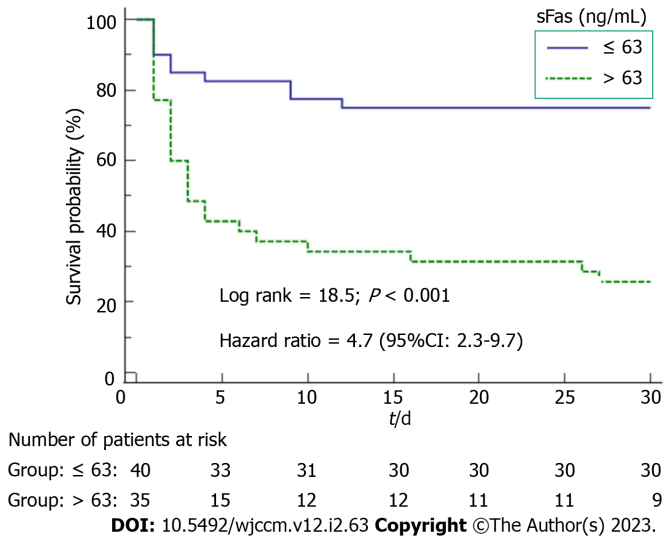

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Figure 2 Survival curves at 30 d using serum soluble fas levels of 63 ng/mL as the cutoff. CI: Confidence interval.

Afterwards, when this initiator caspase of the apoptosis extrinsic pathway (caspase-8) is activated, the activation of executor caspase (caspase-3) occurs. Finally, activation of this executor caspase is responsible for apoptotic cellular death[2-8]. Thus, it is possible that the findings of our study showing higher serum sFas concentrations in non-survivor with respect to survivor patients may reflect a lower apoptosis degree due to lower activation of the apoptosis extrinsic pathway in survivor patients. However, a limitation of our study was the fact that apoptotic brain damage was not assessed. In addition, the absence of serum sFas concentrations during patient evolution and in healthy subjects were other limitations. A promising finding is that the administration of Fas/FasL system inhibitors is associated with a reduction of neuronal cell death in rat models of brain ischemia[15-17]. Therefore, we

believe that the findings from our study showing higher serum sFas concentrations in non-survivor with respect to survivor SICH patients and those findings from brain ischemia animal models showing the reduction of neuronal cell death using Fas/FasL system inhibitors could motivate research on the Fas/FasL system and its modulation in SICH patients.

CONCLUSION

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

ARTICLE HIGHLIGHTS

Research background

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation.

Research motivation

There are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of extrinsic apoptosis pathway) with SICH patient prognosis.

Research objectives

To determine whether there is an association between blood sFas concentrations and SICH patient mortality.

Research methods

We included patients with severe and supratentorial SICH. Severe was defined as having Glasgow coma scale < 9. We determined serum sFas concentrations at the time of severe SICH diagnosis.

Research results

We found that non-surviving patients (n = 36) compared to surviving patients (n = 39) had higher ICH score (P = 0.001), higher midline shift (P = 0.004), higher serum sFas concentrations (P < 0.001), and lower rate of early hematoma evacuation (P = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; P = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

Research conclusions

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

Research perspectives

The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

FOOTNOTES

Author contributions: Lorente L conceived, designed and coordinated the study, made substantial contributions to the acquisition, analysis and interpretation of data, and drafted the manuscript; Martín MM, Ramos-Gómez L, Solé-Violan J, and Cáceres JJ made substantial contributions to the acquisition of data and provided useful suggestions; Pérez-Cejas A and González-Rivero AF determined the blood concentrations; Jiménez A made substantial contributions to the data analysis and interpretation.

Institutional review board statement: The Institutional Board of each hospital approved the study protocol: H. General de La Palma, H. Insular de Las Palmas de Gran Canaria, H. Universitario de Canarias (San Cristóbal de La Laguna), H. Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife), and H. Universitario Dr. Negrín (Las Palmas de Gran Canaria).

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

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

Data sharing statement: The datasets generated during the current study are available from the corresponding author

on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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SYSTEMATIC REVIEWS

Extracorporeal blood purification strategies in sepsis and septic shock: An insight into recent advancements

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Abstract

BACKGROUND

Despite various therapies to treat sepsis, it is one of the leading causes of mortality in the intensive care unit patients globally. Knowledge about the pathophysiology of sepsis has sparked interest in extracorporeal therapies (ECT) which are intended to balance the dysregulation of the immune system by removing excessive levels of inflammatory mediators.

AIM

To review recent data on the use of ECT in sepsis and to assess their effects on various inflammatory and clinical outcomes.

METHODS

In this review, an extensive English literature search was conducted from the last two decades to identify the use of ECT in sepsis. A total of 68 articles from peer-reviewed and indexed journals were selected excluding publications with only abstracts.

RESULTS

Results showed that ECT techniques such as high-volume hemofiltration, coupled plasma adsorption/filtration, resin or polymer adsorbers, and CytoSorb® are emerging as adjunct therapies to improve hemodynamic stability in sepsis. CytoSorb® has the most published data in regard to the use in the field of septic shock with reports on improved survival rates and lowered sequential organ failure assessment scores, lactate levels, total leucocyte count, platelet count, interleukin- IL-6, IL-10, and TNF levels.

CONCLUSION

Clinical acceptance of ECT in sepsis and septic shock is currently still limited due to a lack of large random clinical trials. In addition to patient-tailored therapies, future research developments with therapies targeting the cellular level of the immune response are expected.

Key Words: CytoSorb®; Hemadsorbers; Inflammatory mediators; Extracorporeal therapies; Sepsis

Core Tip: Sepsis is one of the leading causes of mortality in critically ill patients globally. Substantial progress is made in the field of extracorporeal therapies and sepsis. CytoSorb® is emerging as an adjunct therapy to improve hemodynamic stability. This device is an International Organization for Standardization certified, European Conformité Européenne mark-approved class IIb medical device that is designed to remove excess inflammatory cytokines from the blood. There are extensive published reports of its use in the field of septic shock with improved survival rates and other improved biochemical parameters. However, clinical acceptance is still limited due to a lack of large random clinical trials.

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INTRODUCTION

Sepsis is a global major life-threatening syndrome causing multiple organ dysfunction syndrome (MODS)[1]. The World Health Organization described the global estimate of sepsis morbidity and mortality[2] in 2017, as 48.9 million cases with 11 million sepsis related deaths. This estimate accounts for 20% of deaths worldwide[3]. In the United States, the incidence of severe sepsis and septic shock is reported as 300 cases per 100000 individuals, costing more than 20 billion dollars per year[4]. In 2005, there were 430 cases of severe sepsis per 100000 people in Sweden. Furthermore, in clinical cohort studies involving 198 European intensive care unit (ICU), the incidence of sepsis is 11.8% in Australia and New Zealand, 14.6% in France, 27.1% in the United Kingdom, and 30% in the SOAP study. Sepsis has steadily increased in most developed countries over the last several decades[5,6].

The definition of sepsis has evolved over the years and is currently defined as a life- threatening organ dysfunction caused by a dysregulated immune response of the host to infection[1]. Over stimulation of the immune response leads to a cytokine storm, which may lead to septic shock, capillary leakage, and microcirculatory disturbances finally resulting in MODS. The dysregulated reaction,

however, may also lead to a protracted phase of immunoparalysis, contributing to the risk of secondary, hospital acquired infections[7].

Conventional therapies for sepsis mainly focus on fluid resuscitation, source control measures and antimicrobial administration within 1 h of recognition[8]. New therapeutic strategies aim to restore the immune balance by eliminating/ deactivating inflammatory mediators[7,9]. Extracorporeal therapies (ECT), otherwise known as blood purification therapies target attenuation of the immune response by reducing the circulating levels of cytokines and triggers that potentiate the response (endotoxins, pathogen associated molecular patterns – (PAMPs), damage associated molecular patterns (DAMPs), and leukocytes), thereby trying to achieve immune balance/homeostasis[7].

ECT is a blood purification technique in which blood and its components are removed from the body, circulated in the EC circuit and treated with various technologies before being readministered to the patient[10]. Different ECTs include; hemofiltration, hemoperfusion, intermittent or continuous high volume hemofiltration (HVHF), hemadsorption and plasmapheresis[11].

The concept of ECT is based on the objective of nonspecific clearance of inflammatory mediators and/or toxins, attenuating the overwhelming systemic expression of inflammatory mediators in the early phase of sepsis[12]. As per the '*cytokine peak concentration*' hypothesis, eliminating the peak cytokine concentration during the early stage of sepsis can halt the inflammatory cascade, thereby limiting the organ damage and decreasing the incidence of MODS[13,14].

MATERIALS AND METHODS

An extensive literature search was conducted for articles published in last two decades that provided information on the use of ECT in sepsis, using the key words "sepsis", "septic shock", "extracorporeal therapy", "blood purification", and "CytoSorb®", that were in PubMed, MEDLINE, Cochrane Library, or Science Direct databases and with the filters "humans", "English language", "full text articles" (review articles, case reports, randomized controlled trials (RCTs) applied. Only articles published in peer-reviewed and indexed journals from 2002-2021 were selected; abstracts were excluded. The PRISMA diagram for inclusion and exclusion of articles is presented in Figure 1.

RESULTS

Pathophysiology of sepsis

Sepsis is a multi-layered disruption of the host immune balance. Its pathophysiology involves a complex interplay between the host and the infectious agent[15]. The first step in this process, is activation of the innate immune system (macrophages, monocytes, neutrophils and natural killer cells) which occur as a result of the binding of PAMPs and DAMPs such as adenosine triphosphate and mitochondrial DNA, to the specific pattern recognition receptors present on the immune cells, which include toll like receptors, C-type leptin receptors and nucleotide binding oligomerization domain like receptors[16]. This results in intracellular signal transduction and activation of pro-inflammatory cytokines, such as interleukin - IL1, IL6, IL12, IL18 and tumor necrosis factor alpha (TNF-α)[17]. Subsequently, cytokines cause activation of leukocytes, complement system, coagulation pathways, tissue factor production, chemokine expression and overexpression of endothelial adhesion molecules [15,16]. Following this negative feedback, a compensatory anti-inflammatory response syndrome (CARS) is initiated, which down regulates the components of the adaptive immune system[17]. Upregulation of both pro- and anti-inflammatory cytokines marks the early stage of sepsis[18]. A poorly regulated systemic inflammatory response syndrome (SIRS) and CARS can lead to a mixed antagonistic response syndrome leading to progressive tissue damage and potentially causing MODS[15,19].

Coagulopathy in sepsis occurs as a result of simultaneous activation of inflammatory and hemostatic pathways. It is thought to be driven by the release of tissue factor from damaged endothelial cells, leading to systemic activation of the coagulation cascade[20]. Activation of this cascade results in thrombin production, platelet activation and formation of fibrin clots leading to perfusion defects[16, 21]. In addition to this, procoagulant effects are further potentiated by suppression of natural anticoagulants such as protein C, anti-thrombin, and thrombomodulin along with tissue plasminogen activator, leading to microvascular coagulation and ultimately MODS[21,22]. Pathophysiology of sepsis is detailed[15,16,23] in Figure 2.

Management of sepsis

Sepsis is a medical emergency and measures taken in the initial hours after its recognition have a significant impact on the outcomes, including survival. In 2018, the Surviving Sepsis Campaign (SSC) guidelines introduced an "Hour-1-Bundle", replacing the previous recommendation of 3- and 6-hour bundles. The 'Hour-1 Bundle' consists of 5 clinical interventions, which prompt immediate initiation of sepsis management and fluid resuscitation measures[24]. Management of sepsis including screening

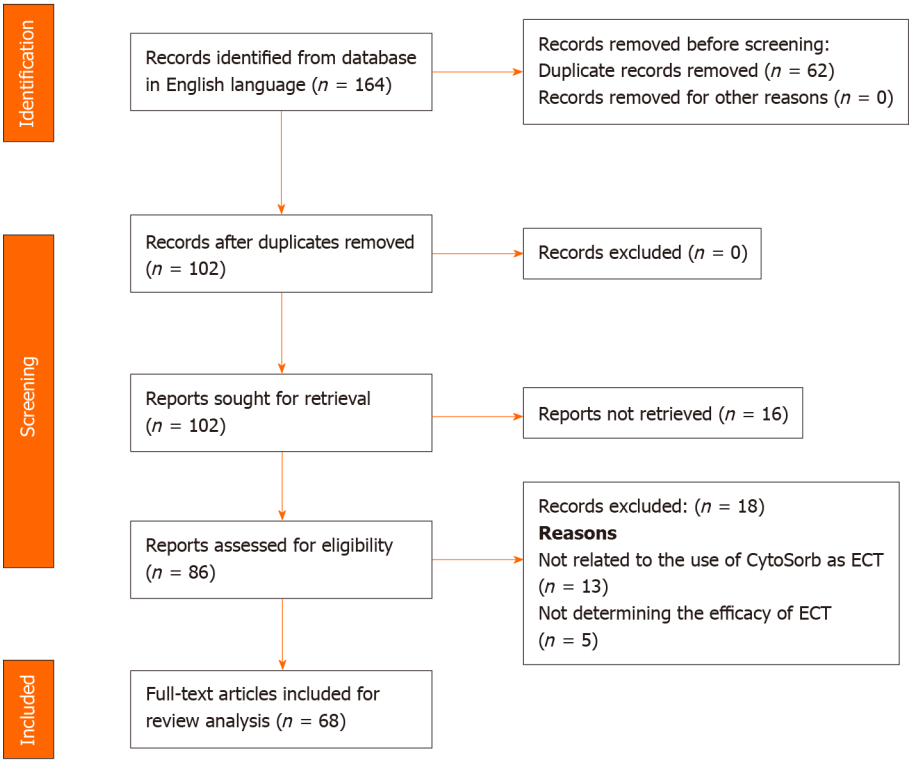

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Figure 1 PRISMA diagram. ECT: Extracorporeal therapies.

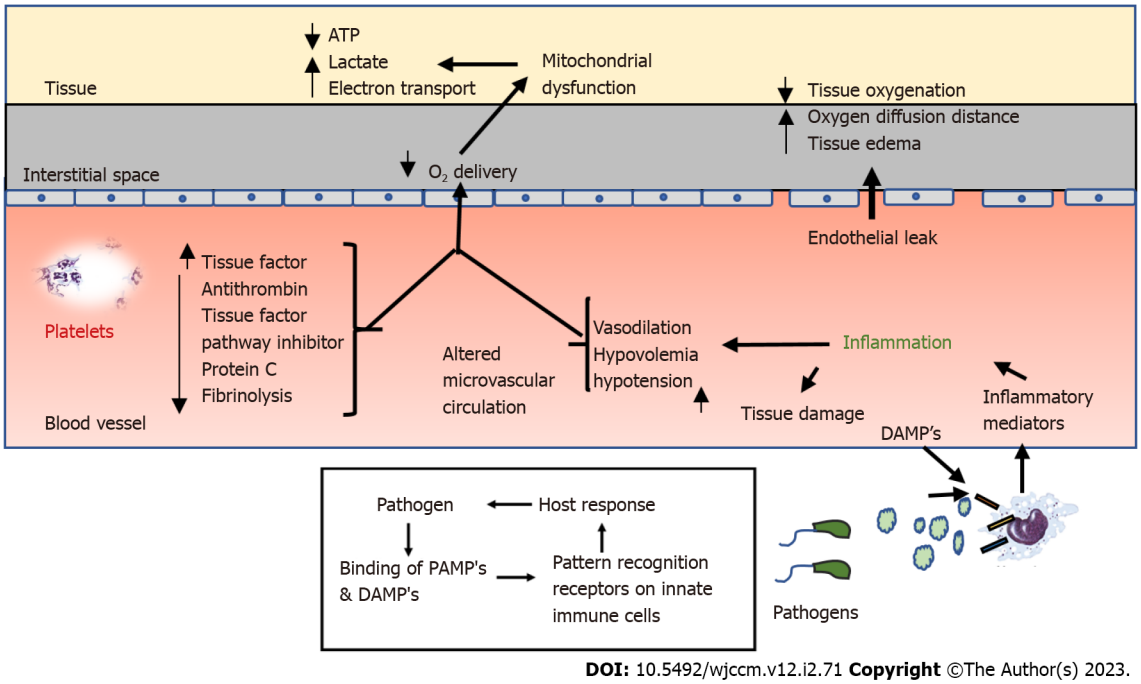

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Figure 2 Pathophysiology of sepsis. ATP: Adenosine triphosphate; DAMP: Damage associated molecular pattern.

and ICU standards of care is presented in Figure 3[7,16,25,26].

Blood purification therapies: MODS caused due to an excessive release of cytokines and inflammatory mediators is a major cause of ICU morbidity and mortality in sepsis[27]. Blood purification therapies (BPTs) are the strategies proposed to restore the immune balance by eliminating or deactivating the inflammatory mediators and originates as an off-shoot of renal replacement therapy (RRT). Various approaches have been identified to maximize the effect of RRT, which include HVHF, high cut-off membranes (HCO), hemadsorption techniques alone or in combination and coupled plasma filtration

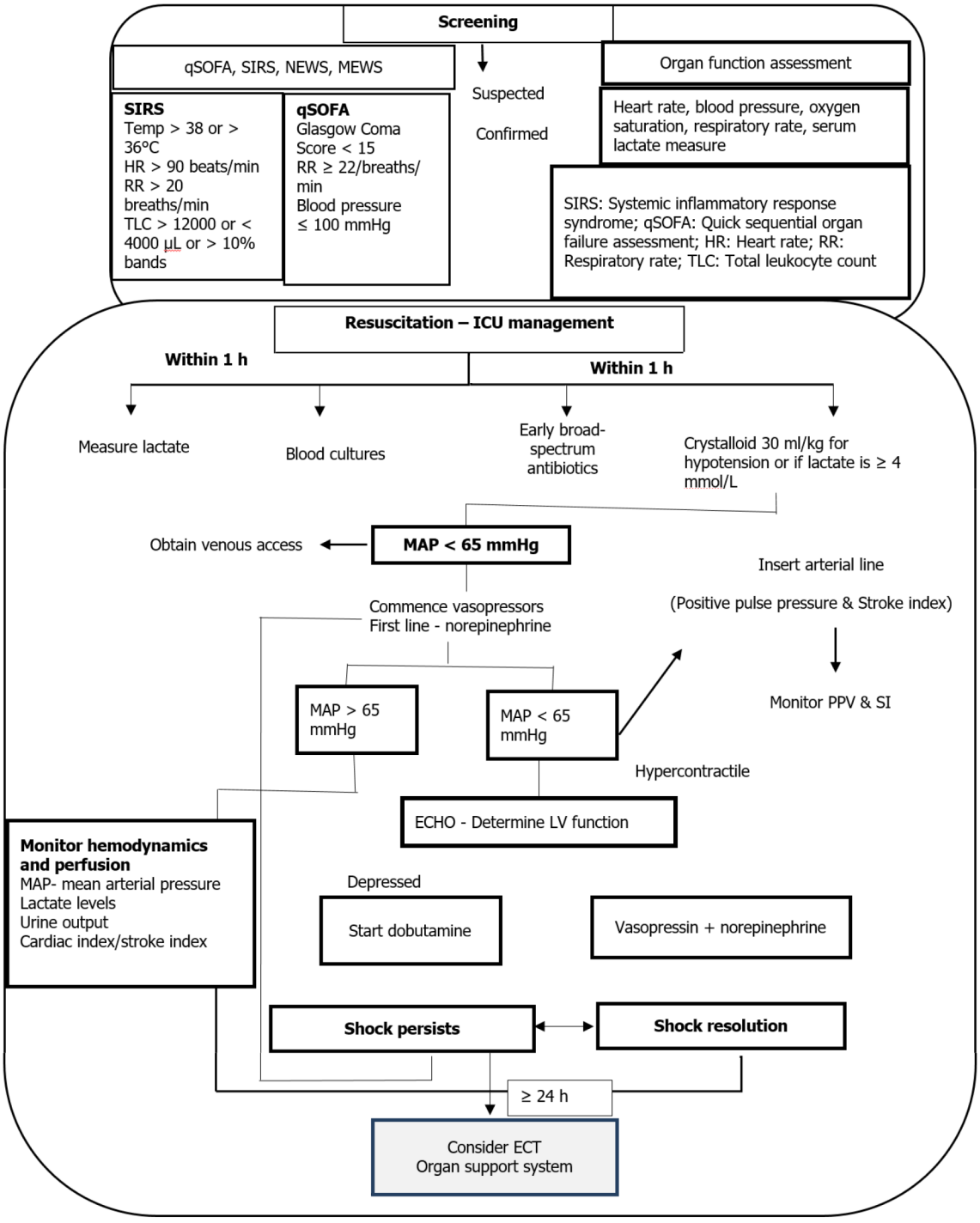

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Figure 3 Treatment algorithm for sepsis-screening to intensive care unit management. SIRS: Systemic Inflammatory Response Syndrome; NEWS: National Early Warning Score; MEWS: Modified Early Warning Score; qSOFA: Quick Sequential Organ Failure Assessment; Temp: Temprature; HR: Heart rate, RR: Respiratory rate; TLC: Total leukocyte count; MAP: Mean arterial pressure; PPV: Pulse pressure variation; SI: Stroke index.

adsorption (CPFA)[9,15,27]. Studies determining the efficacy of different modalities in cytokine and endotoxin removal are presented in Table 1[28-33].

EXTRACORPOREAL THERAPY IN SEPSIS

History of ECT

Extracorporeal BPTs such as hemodialysis, have been used traditionally to replace renal functions in critically-ill patients. Knowledge of solute and water transport through physico-chemical mechanisms in

Table 1 Studies showing efficacy of different devices for cytokine and endotoxin removal

Ref.	Study type	Population	Modality	Intervention	Outcomes
Tapia *et al* [28], 2012	Prospective cohort study	31 severe septic shock patients	HVHF, Cytokine removal	HVHF – single short term – 6 h at 40 mL/kg/h	25/31 responded to HVHF. Decrease in NE dose and improvement in hemodynamic, metabolic and respiratory parameters were significantly improved by 4 h
Joannes-Boyau *et al* [29], 2013	Prospective, randomized, open multicentre trial	137 septic shock patients (AKI < 24 h)	HVHF, Cytokine removal	HVHF – 70 mL/kg/h *vs* standard volume hemofiltration at 35 mL/kg/h	No difference in hemodynamic stability, severity scores, 28-d mortality, length of stay and vasopressor free days
Livigni *et al* [30], 2014	Prospective, randomized, multicentre parallel group trial	192 septic shock patients	CPFA, Cytokine & endotoxin removal	Conventional therapy (n = 93) *vs* CPFA (n = 91)	Decreased mortality in patients receiving high dose of CPFA. No difference in length of ICU stay and new organ failures in 30 d
Atan *et al* [31], 2018	Randomized controlled trial	76 critically ill patients with AKI	CVVH - HCOCytokine removal	CVVH-HCO (n = 38) – cut off point 100 kDa *vs* CVVH -Std (n = 38) – cut off point 30 kDa	No difference was observed in mortality, duration of hemofiltration, norepinephrine dose, serum albumin levels and filter life
Dellinger *et al*[32], 2018	Randomized, multicentre trial	449 septic shock patients	Polymyxin B hemoperfusion; Endotoxin removal	Polymyxin B hemoperfusion + Standard therapy *vs* Sham hemoperfusion + Standard therapy	No significant difference in 28 d mortality in overall population or in patients with MODS score of > 9
Kaçar *et al* [33], 2020	Prospective observational study	23 septic shock patients with AKI	HA 330 Cytokine removal	HA 330 hemoperfusion + CVVH for 2 h once daily for 3 d	Increase in pH was observed after 1st application HA330 hemoperfusion; CRP and PCT levels decreased significantly after 2nd application

HVHF: High volume hemoperfusion; CPFA: Coupled plasma filtration adsorption; CVVH: Continuous veno-venous hemoperfusion; HCO: High cut off membrane; ICU: Intensive care unit; NE: Norepinephrine; AKI: Acute kidney injury; CRP: C-reactive protein; PCT: Procalcitonin.

dialysis forms the basis of extracorporeal (continuous) renal replacement techniques (CRRT) and ECT. Observations of recovering ICU septic patients treated with RRT sparked the idea of tilizing ECT in sepsis[34,35]. Different theories have been postulated to explain the effect of blood purification in restoring hemodynamic stability. *Peak concentration hypothesis* suggests that eliminating the peaks of cytokine blood concentrations during the early phase of sepsis could halt the inflammatory cascade, resulting in improved immune-dysregulation[14,36]. Variations in interstitial and tissue concentrations of inflammatory mediators cannot be explained by this theory. To combat the failure of *peak concentration theory*, a new dynamic hypothesis "*threshold immunomodulation*" was developed by Honore and Matson, which correlated the removal of inflammatory mediators from the blood compartment to changes in interstitial and tissue mediator levels. According to this new theory, inflammatory mediators are gradually taken from interstitium and tissues after removal from the blood compartment until a threshold is reached, at which the inflammatory cascade comes to a halt preventing further organ damage. However, it is difficult to correctly determine this threshold as changes in inflammatory mediators in the interstitium and tissues might not be reflected accurately by changes in the blood compartment in different BPT[37]. To find out how blood purification affects the passage of mediators and cytokines from the tissue and interstitium into the blood compartment, a new hypothesis *i.e.*, "*mediator delivery*" hypothesis was proposed by Di Carlo and Alexander. This hypothesis suggested that use of high replacement volumes, (around 20 to 40 -fold increase in lymphatic volumes) might displace the inflammatory mediators in the blood compartment from where these could be removed during the blood purification process. Thus, high replacement volumes enhance the lymphatic transport between the blood compartments and tissue/interstitium[38]. However, Honore *et al*[37] developed a fourth cytotoxic hypothesis to explain the relationship between different compartments. This theory explained that removal of inflammatory mediators from central circulatory system required assistance of active transportation along with passive one. Peng *et al*[39] proposed a *cytokinetic theory* which suggested that the BPT restores immune function by regulating monocytes, neutrophils and lymphocytes at the cellular level. Many studies have reported that polymyxin B hemoadsorption could increase the expression of leukocyte surface markers such as HLA-DR making hemoadsorption a 're-programming system' for the leukocytes. Another unique element proposed in this theory is that the concentration gradient from plasma to infected tissues can be restored by removing mediators from the plasma in systemic inflammation. This concentration gradient has notable effects on leukocyte trafficking and bacterial clearance [11,36,39].

Mechanics and factors affecting ECT

Mechanisms involved in extracorporeal blood purification are either diffusion, convection or adsorption. With the diffusion process, the solute is transported through a semi permeable membrane down/across its concentration gradient, whereas in convection, solute transport happens as part of solvent drag, and ultrafiltration is driven by a transmembrane pressure gradient. In hemadsorption, blood is passed through sorbents which attract the solutes to adhere to them (adsorb), through a series of hydrophobic and ionic interactions[27,40]. Solute clearance by diffusion depends on molecular weight (MW), membrane permeability, dialysate flow and surface area. Various EC blood purification techniques are described in Figure 3[15,40,41].

Cytokine removal in sepsis

It has been postulated that sepsis induced organ injury can be mitigated by curtailing the inflammatory cascade. This could be achieved by disrupting the peak of inflammatory mediators[13]. BPT used for cytokine removal are the convection therapies [CRRT, HVHF, HCO, adsorption therapies (Polymixin B, CytoSorb® (hemadsorption)] and combination therapies[7,15].

HVHF: HVHF is defined as continuous hemofiltration at a rate of 50-70 mL/kg/h for 24 h or 100-120 mL/kg/h intermittently for 4-8 h followed by conventional renal dose hemofiltration[42]. Circulating inflammatory mediators are water insoluble with a MW of < 60 kDa (kilodaltons), and can thus be effectively removed from the plasma *via* the convection method. Additionally, these membranes have adsorptive properties which further enhance molecular clearance[12]. Recent meta-analysis studies have observed improvements in hemodynamic variables and reduced mortality in critically ill patients with HVHF therapy[28,43]. However, HVHF has also shown contradictory results with no improvement in mortality or hemodynamic variables in randomized trials[29,44-46]. Potential drawbacks of HVHF are the loss of small molecules (vitamins, nutrients, antibiotics) and large volume replacement which may increase treatment costs and the risk of electrolyte imbalance[12,47]. In order to avoid the drawbacks of HVHF, the concept of cascade hemofiltration was introduced which allows selective removal of middle weight molecules. It includes two hemofilters with different cut off values incorporated into a single EC unit, through which only middle molecular weight molecules are filtered and the lower molecular weight molecules are reinfused into the blood circuit. However, in the study conducted by Quenot *et al* [48] cascade hemofiltration failed to provide any beneficial effects in comparison to standard care.

Coupled plasma filtration and adsorption: In this technology, plasma is separated from the blood with the help of a high cut off filter and then passed through a sorbent cartridge for adsorption of cytokines and endotoxins. The filtrate plasma is then redirected to the dialyzer to combine with blood and used in RRT[7,49]. Several studies evaluating CPFA in sepsis and septic shock patients resulted in hemodynamic improvement compared to Continuous Veno-Venous Haemofiltration (CVVH). However, the evidence was weak as the patient sample size was small[50,51]. Primary studies on efficacy of CPFA in a large multi-centric trial showed no improvement in mortality rate, however, secondary analysis showed encouraging results with lower mortality in comparison to controls[30].

CytoSorb® hemoadsorber: Hemoadsorption is a technique where the sorbents contained in cartridges are placed in direct contact with the blood *via* an EC circuit, removing toxins and inflammatory mediators[12,36]. The rationale of using adsorption therapy is to restore the (proinflammatory and anti-inflammatory) immune balance[52].

Features: CytoSorb®(CytoSorbent, New Jersey, United States) hemoadsorption device is an International Organization for Standardization certified, European CE mark approved class IIb medical device, made up of biocompatible as well as hemocomaptible polystyrene divinylbenzene copolymer beads, designed to remove excess inflammatory cytokines from the blood (IL-1B, IL-6,8,10, TNFα monomer, TNFα trimer, IFN γ)[15,53,54]. It has a surface area of > 45000 m^2, so in principle has a far greater capacity for adsorption than with dialyzers/hemofilters and provides size-selective removal of hydrophobic subtstances with a molecular cut-off size of 60kDa, thus resulting in adsorption of both pro and anti-inflammatory mediators, toxins and drugs. However, endotoxins are an exception, as their MW is 100kDa[7,11]. CytoSorb® is compatible with both citrate anticoagulation and systemic heparin, and the duration of therapy is up to 24 h/sessions/d for 2-7 consecutive days depending on the clinical situation with blood flow ranging between 150-700 mL/min[55]. CytoSorb® also eliminates proteins (myoglobin, free hemoglobin dimer, ferritin, free hemoglobin tetramer), metabolites (bilirubin and bile acids), PAMPs (aflatoxin, *Staph. aureus* hemolysin, *Staph. aureus* toxic shock toxin, *Strept. pyogenes* exotoxin, *Clostr. perfringens* toxin and Shiga-like toxin), DAMPs (C5A, S100 and HMGB-1), which may in part be responsible for the dysregulated inflammatory response[7,53,54]. Due to the size-selectivity substances such as immunoglobulins, albumin and coagulation factors are not adsorbed in a significant manner by CytoSorb® as shown in studies[56,57] CytoSorb® can be used as a standalone therapy on cardiopulmonary bypass (CPB), or with CRRT and ECMO. CytoSorb® is approved for hemoperfusion/hemadsorption and for intraoperative use in CPB surgery for removal of $P2Y_{12}$-Inhibitor like Ticagrelor and/or the factor Xa-Inhibitor, Rivaroxaban[7,53,54].

Clinical evidence: Various clinical publications support the use of CytoSorb® in septic shock patients and have shown promising results prompting the need for RCTs to conclude on the benefits of blood purification with CytoSorb® in critically ill patients[58]. Brouwer *et al*[59] observed in their retrospective analysis on patients in septic shock requiring CRRT a significantly improved 28-d mortality by adding CytoSorb® as an adjunctive therapy, when they applied the statistical Inverse Probability Treatment Weighting method to compensate for baseline differences. In a follow-up long-term analysis of the same patient cohort, the authors concluded that the addition of CytoSorb® to CRRT improved survival from 28 d to 1 year. Lactate level > 6.0 mmol/L at the initiation of CytoSorb® therapy had a 79% positive predi -ctive value for mortality, underlining the need for timely intervention[60]. Rugg *et al*[61] retrospectively analysed data of septic shock patients who received CytoSorb® +RRT in comparison to matched CRRT only controls. Despite matching, CytoSorb® group showed even higher sequential organ failure assessment (SOFA) scores (13 *vs* 12) and mean norepinephrine requirements (0.54 μg/kg/min *vs* 0.25 μg/kg/min) at baseline compared to the control group. Moreover, catecholamine requirements as well as hospital mortality was reduced within 24 h in the CytoSorb® group compared to the control patients.

An international (130 centres from 22 countries) registry established in 2015 evaluated the use of CytoSorb® in critically-ill patients in the 'real world'. The interim analysis reported an observed mortality of 65% in comparison to acute physiology and chronic health evaluation II (APACHE II) predicted mortality of 78%. No significant reduction was observed in SOFA. Moreover, a marked reduction in IL-6 levels was observed[52].

In a prospective single center study including 20 patients with refractory septic shock, CytoSorb® therapy led to significant reductions in norepinephrine requirements improvements in lactate clearance and resolution of shock in 65% of patients[62].

Studies conducted in India by Mehta *et al*[53] also reported a favourable outcome in sepsis or septic shock patients with the use of CytoSorb® therapy. A retrospective observational study showed a decrease in total leucocyte count, reduction in biomarkers such as procalcitonin (PCT) (65%), C-reactive protein (CRP) (27%), serum lactate (27%), bilirubin (43%), IL-6 (87%), IL-10 (92%) and TNF (24%) levels and decrease in SOFA scores by 16.2% post therapy. Mehta *et al*[53] developed a CytoSorb® Scoring (CS) system that categorized patients in < 8, 8-13 or > 13, where 8-13 scores based on 5 parameters repres-enting 5 organ systems to determine the number of devices required for therapy. The score of 8-13 was observed as the most appropriate for initiating CytoSorb® therapy. Study results revealed that survivors had a mean score of 12, whereas non-survivors a mean score of 14.

Kogelmann *et al*[63] reported that the effects of hemadsorption therapy (hemodynamic stabilization and survival) using CytoSorb® was more pronounced in patients in whom therapy was started in < 24 h of sepsis onset, whereas a poor response was associated with a delay in therapy, in terms of vasopressor demand and survival. Further research is required to establish its use in treatment of sepsis[64]. CytoSorb® has shown promising results in sepsis both individually as well as an adjunct therapy by reducing SOFA scores, lactate levels, total leucocyte count, platelet count, IL-6, IL-10, TNF levels and improving survival[65-68] as presented in Tables 2[52,53,59,60-63,68,69] and 3[64,70-73].

However, other retrospective analysis did not support the above findings. Wendel Garcia *et al*[74] did not see differences in IL-6 or vasopressor needs in their analysis on the use of CytoSorb® in septic shock patients compared to historical control patients and even discussed an increased hazard of death associated with hemoadsorption. Similar Scharf *et al*[75] showed no difference in IL-6 reduction and hemodynamic stabilization, or mortality in patients with CytoSorb® treatment compared to a matched patient population.

De Wolf *et al*[76] in a recent meta-analysis suggested that the evidence with a low degree of certainty signified that administering CytoSorb® to critically ill patients with inflammatory conditions could even increase mortality. Adverse events were common, but they were not routinely evaluated and were also underreported. A need for high-quality RCTs to clarify mortality and adverse events related to CytoSorb® is suggested by the findings with significant uncertainty, which prevents drawing firm conclusions.

Regardless of the fact that all the included studies were not powered for mortality as an endpoint, it can also be discussed whether mortality is a reasonable endpoint for a single intervention in critically-ill patients with numerous potential causes for death.

However, considering the aspect that patient selection, timing and dosing was not always applied to the best possible manner or the current understanding respectively, might explain at least partly the contradictory results of the studies presented above. CytoSorb® should primarily be used in refractory cases where standard measures of care are not sufficient to stabilize the patient rapidly and start of the therapy should ideally be within the first 6-24 h after diagnosis of septic or vasoplegic shock. The therapy should be continued until sufficient stabilization. For this the adsorber should be replaced every 12-24 h depending on the degree of hemodynamic stabilization being observed. With regard to adequate timing, Kogelmann *et al*[77] evaluated a dynamic scoring system intended to support initiation of CytoSorb® in septic shock patients. The study reported that earlier treatment was associated with a better outcome. Additionally, outcomes improved if CytoSorb® was applied within 12 h after diagnosis in patients with the highest CS score > 8.

Table 2 Multiple logistic regression analysis to predict 30 d mortality

Ref.	Study design	Population	Intervention	Outcomes
Friesecke *et al*[62], 2017	Prospective, single center study	20 septic shock patients	CytoSorb hemoperfusion	Norepinephrinedose reduced after 6 and 12 h; Improved lactate clearance; SOFA scores unchanged; Shock reversal achieved in 65% of patients; 28-d survival – 45%
Kogelmann *et al*[63], 2017	Case series	26 septic shock patients	CytoSorb+CVVHD	Rapid hemodynamic stabilization; Reduction in Vasopressor dose by 67%; Decrease in blood lactate by 26.4%; Shock reversal in 38.5% patients; Decreased mortality than predicted by APACHE II; No adverse events reported
Friesecke *et al*[52], 2017	International registry	135 septic shock patients	CytoSorb hemoperfusion	Reduced observed mortality of 65% than predicted by APACHE II of 78%; Marked reduction in IL6 levels; No significant reduction in SOFA scores; Safe and well tolerated without any adverse events
Brouwer *et al* [59], 2019	Retrospective, investigator-initiated study	116 septic shock patients	CytoSorb +CRRT CRRT alone	In CytoSorb group, the mean predicted mortality rate was 74.5%, while 28 d mortality rate was 47.8%; In CRRT group, the mean predicted mortality rate was 67.9%, while 28-d mortality was 51.0%; CytoSorb group was associated with a reduced 28-d mortality in comparison to CRRT (53% *vs* 72.3%)
Brouwer *et al* [60], 2021	Long term follows up Retrospective cohort study	116 septic shock patients	CytoSorb +CRRT CRRT alone	CytoSorb was significantly associated with long term outcome compared to CRRT
Mehta *et al* [53], 2020	Retrospective, observational study	40 septic shock patients	CytoSorb hemoperfusion (Survivor group *vs* non survivor group)	Improvement in MAP (62.82 ± 9.73mmHg); Reduction in vasopressor dose; Reduction IL-6 levels (87%) and TNF levels (24%); Decrease in SOFA scores by 16.2%
Paul *et al* [68], 2021	Prospective, real time, observational multicentre study	45 septic shock patients	CytoSorb+ Standard therapy (Survivor *vs* non survivor group)	26 patients survived post therapy; Reduction in vasopressor dose (NE- 51.4%, Epinephrine – 69.4% and Vasopressin -13.9%); 52.3% reduction in IL-6 levels; Reduction in APACHE II and SOFA scores, 20.1 ± 2.47 and 9.04 ± 3.00 respectively
Akil *et al* [69], 2020		20 patients with pneumogenic sepsis and ARDS	CytoSorb + Combined high flow veno-venous ECMO (CytoSorb group); ECMO therapy alone (Control group)	The 30-d mortality rate was 0% in CytoSorb group, whereas 57% was observed in control group; Significant reduction in procalcitonin and C-reactive levels were observed in CytoSorb group in comparison to control group
Rugg *et al* [61], 2020	Retrospective single center study	42 septic shock patients compared to 42 matched controls	Cytosorb +RRT	Catecholamines requirements decreased to 0.26 μg/kg/min within 24 h of therapy with CytoSorb; In hospital mortality was significantly lower in CytoSorb group as compared to controls (35.7% *vs* 61.9%); Risk factors in CytoSorb group were high lactate levels and low thrombocyte counts proior to therapy. Lactate value of 7.5 mmol/L, predicted mortality with high specificicty (88.9%)

CVVHD: Continuous veno-venous hemodilation; NE: Norepinephrine; MAP: Mean arterial pressure; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation; IL: Interleukin; TNF: Tumor necrosis factor; ARDS: Acute respiratory distress syndrome; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy.

The CS still requires prospective validation and adapatibility. Nevertheless, more robust evidence is needed to better understand ideal patient selection, timing and dosing.

Novel use of CytoSorb®: CytoSorb® also has CE approval for the reduction of bilirubin and myoglobin in liver failure and severe trauma/rhabdomyolysis. It can also be used in severe acute pancreatitis and severe cardiogenic shock. Patients undergoing major aortic surgery with CytoSorb® incorporated in the CPB circuit demonstrated a promising therapeutic option for critically ill patients with multiorgan failure after cardiac surgery and may help in cytokine reduction with improved organ function[78]. In 2020, CytoSorb® was also approved for the removal for two antithrombotic drugs – ticagrelor and rivaroxaban in emergent and urgent cardiothoracic surgery, in order to reduce the risk of intra- and post-operative bleeding.

Jafron HA-330 and HA-380 adsorber: (Jafron Biomedical Co., Ltd.No.98, Technology Sixth Road, High-tech Zone, Zhuhai City, 519085, Guangdong, China).

The HA-330 (HA-380 is 15% bigger than HA-330) is a disposable hemoperfusion cartridge with an adsorbent material made up of *neutral microporous resin* and collodion coating. It is indicated for the removal of middle to large pathogenic substances from the blood (endogenous or exogenous), such as residual drugs, toxins and metabolic substances. It is used either as a stand alone or in combination with hemodialysis and hemoperfusion circuits. However, it is not clear if integration with ECMO is recommended or not.

Table 3 Studies determining efficacy of CytoSorb in coronavirus disease 2019 infection

Ref.	Study type	Population	Intervention	Outcomes
Alharthy *et al*[70], 2020	Retrospective case series	50 COVID-19 patients with AKI, ARDS, Sepsis and hyperinflammation	CytoSorb + CRRT [Survivors (n = 35) *vs* non survivors (n = 15)]	Decreased SOFA score, lactate levels, ferritin, D-dimers, CRP and IL-6 levels in th survivor group after 2 ± 1 sessions of CRRT + CytoSorb
Mehta *et al* [64], 2021	Case series	3 critically ill COVID-19 patients	CytoSorb hemoperfusion other prescribed medications (tocilizumab, antivirals, hydroxy-chloroquine, azithromycin)	Significant improvement in biochemical parameters and clinical outcomes post CytoSorb therapy; Reduction in CRP levels by 91.5%, 97.4% and 55.75%, respectively; Improvement in MAP by 18%, 23% and 17% by 7th day post therapy
Nassiri *et al*[71], 2021	Retrospective case series	26 COVID-19 patients with ARDS	CytoSorb hemadsorption therapy	21 patients survived; Significant decrease in NE requirement; PCT, CRP and ferritin reduced post therapy; Significant improvement in SOFA scores; Therapy was well tolerated
Paisey *et al* [72], 2021	Retrospective case series	15 severely ill COVID-19 patients	CytoSorb hemadsorption therapy	Adjunctive treatment with CytoSorb lead to reduction in ferritin, CRP, PCT and lactate levels
Song *et al* [73], 2021	Multicenter observational study	52 ICU COVID -19 patients on ECMO	ECMO + CytoSorb hemadsorption therapy	ICU mortality was 17.3% on day 30, 26.9% on day 90, and 30.8% at final follow up of 143 d; Lower baseline D-Dimer levels were observed among survivors (2.3 ± 2.5 *vs* 19.8 ± 32.2 μg/mL) compared to non survivors; Borderline association observed between baseline D-Dimer levels and mortality with a 32% increase in risk of death per 1 μg/mL increase

COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; SOFA: Sequential organ failure assessment; CRP: C-reactive protein; IL: Interleukin; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; MAP: Mean arterial pressure; NE: Norepinephrine; ECMO: Extracorporeal membrane oxygenation.

HA-330 (and HA-380) have limited options for circuit configurations and a shorter treatment time up to 4 h when used in conjunction with a dialyser. Moreover, HA-330 (and HA380) have a maximum blood flow and operating time depending on the mode of operation.

Both HA-330 and HA-380 adsorbers have a storage fluid considered to be extremely acidic, with a pH of 1.8, which, even after a careful and 45-min-long rinsing procedure, remains as low as pH 3.3. A case series conducted in septic pediatric patients with cancer and other hematological disorders has confirmed the efficacy of HA-330 and HA-380. However, detailed studies in a larger population was recommended by the authors[79]. Treatment with CytoSorb®, resulted in significant removal of IL-6 in a severely ill patient population with septic shock, ARDS, and multi-organ failure in a multicenter randomised study. This, however, had no effect on normalised IL-6-plasma levels[80,81]. A comparative in-vitro study was conducted on both the CytoSorbents and Jafron hemoadsorption technologies and showed that both systems can remove cytokines from whole blood, but the CytoSorb® 300 device appears to be more effective and dynamic in this regard. Therefore, in severe septic state where quick cytokine clearance is desired, it might be the preferred device[82]. HA-330 and HA-380 have very limited published articles (far less than 50) to support its therapeutic benefits and clinical experience.

Biosky MG 350 adsorber: (Biosun Medical Technology Co. Ltd, China). The Biosky MG350 adsorber is another disposable hemoperfusion cartridge made up of *microporous adsorptive resin*, recommended for application in sepsis and hyperinflammation. Published literature in the English language is extremely scarce, and currently limited to one case report. Sequential use of CytoSorb® and the MG350 filter was carried out in a coronavirus disease 2019 (COVID-19) patient with severe ARDS. After initial successful CytoSorb® use, an MG350filter was used in parallel to an ECMO circuit. The combination of an antibiotic regimen and Biosky filter resulted in decreased inflammatory markers (CRP, PCT, IL-6 and IL-2). However, the patient suffered with severe respiratory failure and later died[83]. Biosky MG350 has a blood flow of 400 mL/min with an operating time of 2 h depending on the mode of operation. Compared to other adsorbers, Biosky MG350 requires a long rinsing procedure (Table 4[84-88]).

Miscellaneous: Several other cartridges available for adsorption include Hemofeel (Toray, Tokyo, Japan), a polymethyl methacrylate hemofilter, and Theranova 400/500 dialysers developed by Baxter. Multiple other cartridges that have an affinity to bind to bacteria and viruses are also under investigation. The Seraph 100 Microbind Affinity blood filter (ExThera, California, United States) is an adsorbing technology which consists of non-porous heparin coated beads designed to reduce blood-borne pathogens during bloodstream infections. Hemopurifier (Aethlon Medical, California, United States) and FcMBL (Opsonix Inc, United States) is also other make that is also available[7].

Table 4 Multiple logistic regression analysis to predict 30 d mortality

Feature	CytoSorb 300[84,85,86]	Jafron HA-series (80, 130, 180, 230, 280, 330, 380) [87]	Biosky MG-Series[88]
Manufacturer	CytoSorbents™ Inc, United States	Jafron Biomedical Co., Ltd. No. 98, Technology Sixth Road, High-tech Zone, Zhuhai City, 519085, Guangdong, China	Biosun Medical Technology Co. Ltd, China
IFU version	October 1, 2021[87]	11-Sep-19	1-Aug-18
Adsorbent	Crosslinked Divinylbenzene	Neutral Macroporous Resin	Medical Neutral Macroporous Synthetic Resin
Coating	Polyvinylpyrollidone	Collodion	No data
Adsorbent Surface	> 45000 m^2	100000m^2	No data
Storage fluid	Isotonic saline	Water for injection	Sterile water
Use time/cartridge	24 h, Can be administered up to 7 consecutive days	Depending on mode of operation: Hemoperfusion 100-250 mL/ min; Dialysis < 320 ml/ min with use upto 4 h; CRRT 150-250 mL/min with use upto 12 h; CPB up to 700 mL/ min with use upto 2.5 h	120-180 min, Not suggested to use more than 3 times within 24 h
Blood flow	100-700 mL/min, Recommended > 150 mL/min	100-700 mL/min	100-400 mL/min; Highest rate is 250 mL/min
Pmax	760 mmHg	750 mmHg	750 mmHg
Mode of operation covered	Hemoperfusion, Intermittent hemodialysis, CRRT, Cardiopulmonary bypass (CPB) ECMO	Hemoperfusion; Hemodialysis; CRRT; CPB	Hemoperfusion; Hemodialysis; CRRT; CPB only as comment in anticoagulation, not in setup
Shelf life	3 yr	2 yr	2 yr
Safety report status	As of 2021: > 162000 treatments distributed without confirmed serious device related events	No data	No data

IFU: Instructions for use; CRRT: Continuous renal replacement therapy; CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenation.

Endotoxin removal in sepsis

Lipopolysaccharide (LPS) an endotoxin, is a component of gram-negative bacteria that induces an inflammatory response. A dysregulated host response to LPS might lead to multiple organ failure or fatal septic shock if unchecked. Endotoxin activity (EA) levels are measured on a scale of 0 to 1: low (< 0.4 units), intermediate (0.4-0.6 units), high (> 0.6 units). More than 80% of septic shock patients have intermediate or high EA levels indicating the function of endotoxin as a critical activator of the sepsis cascade. Clinical evidence for LPS is obtained from case series in critically ill patients reporting a reduction in endotoxin levels and improvement in hemodynamics with no significant adverse effects [89-91].

Polymyxin B: A polymyxin B-(PMX) immobilised fiber column (Toraymyxin: Toray, Tokyo, Japan) has been extensively used for endotoxin removal. The findings of a subsequent RCT in Europe, the EUPHAS study, which was carried out in Italy, were published in 2009, demonstrating that PMX has a significant effect on sepsis-related mortality[92]. The EUPHRATES RCT trial compared Polymyxin B hemoperfusion to a combination of sham hemoperfusion and standard therapy (n = 226) showing no significant difference in 28 d mortality among the overall population[32]. Subsequently, a post hoc analysis of the EUPHRATES trial demonstrated a significant reduction in 28 d mortality and improvement in MAP and ventilator free days in patients with an endotoxin assay of 0.6–0.9[93]. The ABDOMIX trial had inconclusive results on efficacy of the polymyxin B-immobilised fiber column for removing endotoxins and improving mortality rates in patients with septic shock[94].

Alteco LPS adsorber: The Alteco LPS adsorber (Alteco Medical; Sweden) is an endotoxin adsorber cartridge, consisting of polyethylene plates with peptides which have a high affinity to adsorb LPS. A multicentre feasibility trial of the Alteco LPS adsorber –the ASSET trial was terminated early due to patient recruitment difficulties[95].

Combined endotoxin and cytokine removal

oXiris membrane: The oXiris filter is a modified AN69ST membrane which has an affinity to adsorb both endotoxins and cytokines. Initially, it was approved in 2009 in Europe, and in 2017 the indication was extended for patients requiring blood purification, CRRT and in conditions with excessive levels of inflammatory mediators and endotoxins[96]. It was also authorised by the FDA for emergency use for

COVID-19 treatment[97]. However, its use is only indicated with the Prismaflex unit. Evidence supporting the use of oXiris comes largely from case series. In the study conducted by Shum *et al*[98], 6 patients with septic AKI received oXiris-CVVH and were compared to historical controls with a similar disease severity (n = 24). Results showed a significant reduction in SOFA scores by 37% after the use of oXiris-CVVH for 48 h whereas there was a 3% increase in the control group. However, there was no significant difference observed in length of ICU stay and hospital mortality. A single centred prospective study by Premužić *et al*[84] showed the efficacy of oXiris filters in reducing IL-6 and SOFA score severity in ICU patients. Improvement in respiratory status, chest X-ray severity score and other clinical symptoms were also reported in this study. Russell *et al*[85] used a hybrid purification system in fifteen critically ill sepsis patients. Treatment involved RRT with the oXiris filter and a CytoSorb® adsorbent cartridge also included in RRT system. Procalcitonin, IL6, cardiorespiratory function and endotoxins were monitored at baseline and at the completion of treatment. It was concluded that RRT with the oXiris filter and CytoSorb® cartridge were associated with improved hemodynamic stability, inflammatory response and renal function.

In an *in-vitro* comparison of three different blood purification devices – oXiris, polymyxin B, and CytoSorb®, oXiris showed a similar reduction in endotoxins and cytokines in comparison to polymyxin B and CytoSorb®, respectively[86]. Feri *et al*[99] pointed out the flaws in this *in-vitro* investigation, including the fact that the *in-vitro* comparison was carried out for two hours using 500 mL plasma solutions, pre-incubated with pathological quantities of inflammatory mediators. As stated by Feri *et al*[99], all the three devices (oXiris, polymyxin B, and CytoSorb®) work with whole blood and not just plasma, and the volume utilised by Malard *et al*[86] was very limited (500 mL), in humans the devices work with blood volume of 5 L. Furthermore, the concentration of inflammatory mediators was low, as was the duration of the experiment.

Feri *et al*[99] further stated that the actual application time of CytoSorb® and oXiris is 24 h and 72 h, respectively. Potential advantages and comparable results in endotoxin and cytokine clearance is limited to case series/reports, and no large, randomized trials exist thus far[96]. However, several ongoing trials have recently been completed and it is expected that oXiris may provide some new insights in the management of sepsis and septic shock. Studies showing the efficacy of oXiris in endotoxin and cytokine removal are presented in Table 5[49,96,98,100].

Novel therapeutic advances

Renal assisting device (RAD) is a cell-based therapy containing human proximal tubular cells. It was developed based on the concept that the kidney also have metabolic, immune and endocrine functions during sepsis[51]. RAD was found to be beneficial in replacing solute and water clearance along with active reabsorptive transport and metabolic functions[101]. However, its development was discontinued due to manufacturing and distribution issues. A selective cytopheretic device (SCD) is another therapeutic strategy targeting activated leucocytes. With a CRRT circuit, it results in sequestration of activated leucocytes. Evaluation of SCD was carried out in a randomized trial of 134 AKI patients. No significant differences in mortality were found between the treated (SCD) and control populations (CRRT)[102]. Molecular adsorbent recirculating system (MARS™) is another extracorporeal system which supports the liver by removing albumin-bound toxins from the blood. Short-term benefits of MARS have been evaluated in 3 prospective randomized studies showing improvement in survival rates of patients with hepato-renal syndrome and hepatic encephalopathy[103].

DISCUSSION

Based on SSC guidelines, evidence of ECT efficacy is evolving and has a sound rationale based on our current understanding of sepsis pathophysiology. Overall, however, hard evidence based on prospective RCTs is still scarce. As with every therapy proper patient selection, timing and dosing is crucial for therapeutic success. ECT has to be seen as an adjunctive therapy aiming at restoring homeostasis in hyperinflammatory conditions. In the light of the critically-ill patients with numerous co-morbidities usually treated with ECT in multi-nodal approach, one should not target mortality as the primary endpoint of such trials, but rather consider the improvements in organ dysfunction. Additionally, the challenge of patient heterogeneity usually mentioned in many of these trials and coming from the fact that sepsis is a syndrome rather than a specific disease, has to be taken into consideration for trial planning, too.

Challenges and limitations of ECT

In clinical practice, timing of ECT is still often delayed as doctors see it too much as a final rescue therapy. So better guidance in regard to patient selection, timing and dosing has to compiled and provided to the user at the bedside. Importantly and with regard to the different ECT systems available in the market, it has to be stated that clinical results, but particularly safety relevant aspects, are not transferable between various hemoadsorption products due to technical differences[104].

Table 5 Studies determing oxiris efficacy for removal of endotoxins and cytokines

Ref.	Study type	Population	Intervention	Outcomes
Shum *et al* [98], 2013	Prospective case series with historical controls	6 patients with septic AKI	oXiris + CVVH	Significant reduction in SOFA scores by 37% after 48 h of therapy
Ugurov *et al* [96], 2020	Single centre case series	15 COVID -19 patients	oXiris hemofilter	Early initiation of oXiris was associated with stable or reducing levels of IL-6,8,10 and TNFα
Zhang *et al* [49], 2021	Case series	5 COVID-19 patients	CRRT followed by oXiris hemofilter therapy	Reduced levels of cytokines, haemodynamic stabilization and improvement of organ function was observed with oXiris.
Rosalia *et al* [100], 2020	Prospective cohort study	44 COVID 19 cases	CVVH + oXiris	Reduction in CRP, ferritin, fibrinogen and other inflammatory mediators were observed

COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; SOFA: Sequential organ failure assessment; CRP: C-reactive protein; IL: Interleukin; CVVH: Continuous veno venous hemofiltration; TNFα: Tumornecrosis factor alpha.

Future directions

Hemodynamic improvements, length of ICU stay and decreasing mortality were among the frequently studied end-points in most of the studies that have evaluated different ECT modalities. Further sepsis trials should target patient populations as homogeneous as possible and therefore focus on patient pheno- and endotypes including biomarker-based approaches to try to obtain more consistent outcomes of the therapy, thereby increasing the understanding of optimal therapy management and reducing the possibility of conflicting results.

CONCLUSION

Substantial progress has been made in the field of ECT therapies and sepsis. Among the presented technologies in this review, CytoSorb® seems to currently represent the most investigated and clinically established procedure. However, more robust evidence is still needed. Additionally, the achievement of beneficial clinical effects of these adjunct modalities in routine use requires identification of the right patient, right timing and right dose. Therefore, high quality RCTs are needed to provide definitive answers for these questions and also to facilitate individualised ECT treatments of critically ill patients.

ARTICLE HIGHLIGHTS

Research background

Sepsis is one of the main causes of mortality in patients in critical care units worldwide, despite the fact that it can be treated with a variety of medications. Extracorporeal treatments (ECT), which aim to balance the dysregulation of the immune system by eliminating high quantities of inflammatory mediators, have drawn attention as a result of knowledge about the biology of sepsis.

Research motivation

The biology of sepsis has brought attention to extracorporeal therapies (ECT), which try to regulate immune system dysregulation by removing large amounts of inflammatory mediators.

Research objectives

To analyze new research on ECT use in sepsis and evaluate its impact on key inflammatory and clinical outcomes.

Research methods

To find the usage of ECT in sepsis, a thorough search of the English literature from the previous two decades was done for this review. The selection process excluded publications that had only abstracts and resulted in a total of 68 articles from peer-reviewed and indexed journals.

Research results

The findings demonstrated the emergence of ECT approaches such as high-volume hemofiltration, coupled plasma adsorption/filtration, resin or polymer adsorbers, and CytoSorb® as adjuvant therapy to enhance hemodynamic stability in sepsis. With findings on increased survival rates and decreased

sequential organ failure assessment scores, lactate levels, total leucocyte count, platelet count, interleukin-IL-6, IL-10, and TNF levels, CytoSorb® has the most published evidence in relation to its usage in the field of septic shock.

Research conclusions

The absence of significant random clinical trials currently limits the clinical adoption of ECT in sepsis and septic shock. Future research breakthroughs with treatments aiming at the cellular level of the immune response are anticipated, in addition to patient-tailored medicines.

Research perspectives

To achieve more consistent treatment outcomes, future clinical trials involving patients with sepsis should be as homogeneous as feasible and focus on patient phenotypes and endotypes, including biomarker-based techniques. This will not only increase our grasp of how to handle proper therapy, but it will also lessen the possibility of inconsistency.

FOOTNOTES

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LETTER TO THE EDITOR

The artificial intelligence evidence-based medicine pyramid

Valentina Bellini, Federico Coccolini, Francesco Forfori, Elena Bignami

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Abstract

Several studies exist in the literature regarding the exploitation of artificial intelligence in intensive care. However, an important gap between clinical research and daily clinical practice still exists that can only be bridged by robust validation studies carried out by multidisciplinary teams.

Key Words: Artificial intelligence; Intensive care; Intensive care unit; Evidence-based medicine; Clinical research

Core Tip: Artificial intelligence (AI) use in intensive care is now a reality. However, there is still an important discrepancy between the results found in the scientific literature and the day-to-day clinical implementation of this technology. One reason for this is that the AI evidence pyramid in intensive care has only just begun to emerge. We need to focus on the next steps in AI pyramid evidence, amplifying the external validation of models and increasing the number of randomized clinical trials. Only robust validation studies carried out by multidisciplinary teams will help bridge this existing gap between clinical research and clinical practice.

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TO THE EDITOR

We read with great interest the editorial by Luo *et al*[1] where the authors cogently present the main results regarding the use of artificial intelligence (AI) in the intensive care unit (ICU) for decision making and resource allocation. They simultaneously exposed the current limitations of the large-scale use of AI clinical tools in this setting. We share many of the reflections set out by Luo *et al*[1]. The presence of AI in medicine science and clinical practice has become a reality. Knowing how this new technology can assist the medical profession and how clinicians might take advantage of it are characteristics that are now required and are likely to be of assistance as far as personal career development is concerned[2]. However, the gap between the excellent results derived from biomedical research and the rare use in clinical practice is clear to everyone[3]. While this is probably the biggest deterrent to AI application on a daily professional basis, we must not stop considering it as a valuable ally. On the contrary, we need to ask clinical researchers to find answers for how these models can help intensivists carry out day-to-day activities.

Without external validation, the positive performance of these models in observational studies is no longer sufficient. This, however, should not lead to the erroneous conviction that AI implementation in the ICU should remain purely a scientific speculation, as its application outside the clinical reality regularly disproves this hypothesis. Intelligent vocal assistants and accurate search engines are just two examples of the efficient support offered to us by well-devised AI. The first results from clinical trials point in the same direction, with an example being the hypotension prediction index[4]. This is an algorithm implemented to predict hypotension, even before adverse events occur. Since its marketing, a number of clinical trials have tried to interpret its possible usefulness in clinical practice with most results showing a lower incidence of hypotensive events when compared with standard care[5-7].

We should bear in mind that anything stemming from evidence-based medicine (EBM) has a history based on the progressive collection of increasingly solid results, and the application of AI in the ICU follows the same path (Figure 1). We began with the intuition that AI might be useful in critical patients. Subsequently, stronger results, initially from retrospective followed by prospective observational studies, appeared. In the literature, a few clinical trials as well as sporadic systematic reviews and meta-analyses are available[8,9]. Presently, we are only halfway up the pyramid of the AI scientific evidence we initially imagined, and it is therefore logical that the use of AI tools is not widespread. This phenomenon is consistent with the concept of EBM. At this point, we need to focus on the second part of the pyramid, increasing the external validation of models and multiplying the number of randomized clinical trials.

Furthermore, we must not underestimate the fact that this gap can only be bridged by the intervention of multidisciplinary teams. As with the creation of the AI surgical department in anesthesiology[10], similar systems need to be considered for the ICU. Engineers, data scientists and intensivists must create units capable of managing each phase of the AI application in the ICU, from the design and then to the creation and exploitation of AI clinical instruments. This cooperation should also take place in the post-marketing phase, with constant verification of the quality and safety of AI tools together with continuous systems updates. In conclusion, it is not surprising that AI is not yet widely used in daily ICU activities. We are still at the very beginning of the EBM pyramid, and the gap between bytes and the bedside will only be bridged by robust validation studies carried out by multidisciplinary teams.

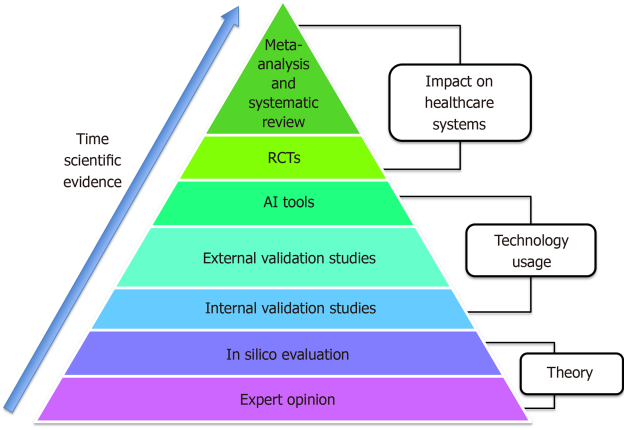

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Figure 1 A pyramid for artificial intelligence scientific evidence is proposed. Starting from the bottom and moving to the top, emerging results are becoming increasingly solid and strong. The two lowest rungs are the theory followed by the third, fourth and fifth steps that represent studies analyzing the use of artificial intelligence (AI) in clinical practice. From creation of the model with internal validation, we move towards external validation studies and the creation of usable

real instruments (AI tools). The penultimate step [randomized controlled trials (RCTs)] and the tip of the pyramid (meta-analysis and systematic reviews) represent the strongest methodological analysis to reach conclusions on the real impact of this technology on healthcare systems. If we then imagine the support base of the pyramid we have the necessary tools for each step of clinical research in AI applied to the intensive care unit: Electronic health record, solid big data systems, internet of things technologies and models of eXplainable AI.

FOOTNOTES

Author contributions: Bellini V, Coccolini F, Forfori F and Bignami E made substantial contributions to the conception and design of the study as well as the acquisition and interpretation of data; Bellini V and Bignami E drafted the article; Coccolini F and Forfori F made critical revisions related to important intellectual content within the manuscript; Bellini V, Coccolini F, Forfori F and Bignami E approved the final draft of the article.

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