Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Emergency Medicine 50 (2021) 683–692

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

The critical care literature 2020

Michael E. Winters, MD, MBA [a,*], Kami Hu, MD [a], Joseph P. Martinez, MD [a], Haney Mallemat, MD [b], William J. Brady, MD [c]

[a] Departments of Emergency Medicine and Medicine, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[b] Departments of Critical Care Medicine and Emergency Medicine, Cooper Medical School of Rowan University, Camden, NJ, USA
[c] Department of Emergency Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908, USA

ARTICLE INFO

Article history:
Received 22 August 2021
Received in revised form 17 September 2021
Accepted 21 September 2021

Keywords:
COVID-19
Mechanical ventilation
Septic shock
Cardiac arrest
Post-cardiac arrest
Vasopressors

ABSTRACT

Given the dramatic increase in critically ill patients who present to the emergency department for care, along with the persistence of boarding of critically ill patients, it is imperative for the emergency physician to be knowledgeable about recent developments in resuscitation and critical care medicine. This review summarizes important articles published in 2020 that pertain to the resuscitation and care of select critically ill patients. These articles have been selected based on the authors annual review of key critical care, emergency medicine and medicine journals and their opinion of the importance of study findings as it pertains to the care of critically ill ED patients. Several key findings from the studies discussed in this paper include the administration of dexamethasone to patients with COVID-19 infection who require mechanical ventilation or supplemental oxygen, the use of lower levels of positive end-expiratory pressure for patients without acute respiratory distress syndrome, and early initiation of extracorporeal membrane oxygenation for out-of-hospital cardiac arrest patients with refractory ventricular fibrillation if resources are available. Furthermore, the emergency physician should not administer tranexamic acid to patients with acute gastrointestinal bleeding or administer the combination of vitamin C, thiamine, and hydrocortisone for patients with septic shock. Finally, the emergency physician should titrate vasopressor medications to more closely match a patient's chronic perfusion pressure rather than target a mean arterial blood pressure of 65 mmHg for all critically ill patients.

1. Introduction

An emergency physician (EP) is often the first provider to evaluate, resuscitate, and manage a critically ill patient. Over the past two decades, the annual hours of critical care delivered in emergency departments across the United States has dramatically increased [1]. During the period from 2006 to 2014, the extent of critical care provided in the emergency department (ED) to critically ill patients increased approximately 80% [2]. During the same time period, the number of intubated patients cared for in the ED increased by approximately 16% [2]. In addition to seeing more critically ill patients, EPs are often tasked with providing critical care long beyond the initial resuscitation period. Prolonged ED boarding times for critically ill patients is associated with increased duration of mechanical ventilation, increased intensive care unit (ICU) length of stay, increased hospital length of stay, increased medication-related adverse events, and increased in-hospital, 30-day, and 90-day mortality [2-4]. As a result, it is imperative for the EP to be knowledgeable about recent developments in resuscitation and critical care medicine, so that the critically ill ED patient care receive current evidence-based care. This review summarizes important articles published in 2020 that pertain to the resuscitation and care of select critically ill patients. These articles have been selected based on the authors annual review of key critical care, emergency medicine and medicine journals and their opinion of the importance of study findings as it pertains to the care of critically ill ED patients. Topics covered in this article include coronavirus 2019 (COVID-19) infection, acute gastrointestinal bleeding, mechanical ventilation, vasopressor administration, sepsis, cardiac arrest, and post-cardiac arrest care. A summary of articles and key findings are provided in Table 1.

2. COVID-19

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – Preliminary Report. N Engl J Med. 2020. Published online July 17, 2020

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiology of COVID-19 infection and has rapidly spread throughout the world in 2020 [5,6]. While the majority of patients with COVID-19 infection have mild illness, many patients unfortunately develop

* Corresponding author.
E-mail address: mwinters@som.umaryland.edu (M.E. Winters).

https://doi.org/10.1016/j.ajem.2021.09.056
0735-6757/

Table 1
Summary of articles and key findings.

Article	Clinical Topic	Study Type	Key Findings
The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – Preliminary Report. N Engl J Med. 2020. Published online July 17, 2020	COVID-19	Multicenter, randomized, controlled, open-label trial	• Decreased 28-day all-cause mortality in patients who required respiratory support or supplemental oxygen and received dexamethasone.
HALT-IT Trial Collaborators. Effects of a high dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. Lancet. 2020; 395:1927–1936.	Acute Gastrointestinal Bleeding	Multicenter, randomized, double-blind, placebo-controlled trial	• No difference in death due to bleeding in patients randomized to receive TXA for acute gastrointestinal bleeding.
Lau JYW, Yu Y, Yang RS, et al. Timing of endoscopy for acute gastrointestinal bleeding. N Engl J Med. 2020; 382:1299–1308.	Acute Gastrointestinal Bleeding	Single-center, randomized trial	• No difference in 30-0 day all-cause mortality between patients randomized to receive urgent endoscopy (within 6 h) compared to those randomized to receive early endoscopy (within 24 h).
Writing Group and Steering Committee for the RELAx Collaborative Group. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS. JAMA. 2020; 324:2509–2520.	Mechanical Ventilation	Prospective, randomized, controlled study	• The use of a low PEEP strategy was non-inferior to a high PEEP strategy in ventilated patients without ARDS.
Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020; 382:999–1008.	Mechanical Ventilation	Prospective, multicenter, randomized trial	• No difference in 28-day all-cause mortality between patients with ARDS randomized to a conservative oxygen therapy group and those randomized to a liberal oxygen therapy group.
Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA. 2020; 323:938–49.	Vasopressors	Pragmatic, randomized trial	• No difference in 90-day all-cause mortality between patients randomized to permissive hypotension (MAP 60–65 mmHg) compared with those randomized to usual care for vasodilatory shock.
Panwar R, Tarvade S, Lanyon N, et al. Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock. A multicenter, prospective cohort study. Am J Respir Crit Care Med. 2020; 202:1407–18.	Vasopressors	Investigator-initiated, multicenter, prospective, observational trial	• Increased incidence of new acute kidney injury and major adverse kidney events in patients who experienced a deficit in mean perfusion pressure.
Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA. 2020; 323:423–431.	Septic Shock	Multicenter, open-label, parallel-group, randomized trial	• No difference in time alive and vasopressor-free days at day 7 for patients randomized to receive vitamin C, hydrocortisone, and thiamine compared to patients randomized to receive hydrocortisone.
Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020; 324:642–650.	Septic Shock	Multicenter, blinded, placebo-controlled, randomized, superiority trial	• No difference in the change in SOFA scores at 72 h for patients randomized to receive vitamin C, hydrocortisone, and thiamine compared to patients randomized to receive placebo.
Yannopoulos D, Bartos JA, Reveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single center, open-label, randomized controlled trial. Lancet. 2020; 396:1807–1816.	Cardiac Arrest	Phase 2, single-center, open-label, pragmatic, randomized trial	• Improved survival to hospital discharge for OHCA patients randomized to ECMO-facilitated resuscitation compared to patients randomized to receive standard ED-based ACLS resuscitation.
Pareek N,Kordis P, Beckley-Hoelscher N, et al. A practical risk score for early prediction of neurological outcome after out-of-hospital cardiac arrest: MIRACLE 2. European Heart Journal. 2020; 41:4508–17.	Post-Arrest Care	Prospective investigation of a cardiac arrest registry	• The $MIRA_2CLE_2$ score has a high specificity for predicting poor neurologic outcome in OHCA patients presumed due to a cardiac etiology.

progressive hypoxemic respiratory failure and require hospitalization [6,7]. For those that require admission to the ICU and mechanical ventilation, mortality remains very high. Though the pathophysiologic features of COVID-19 continue to be clarified, it is believed that the body's immune response may be a significant factor in disease progression and organ injury [6]. As such, numerous researchers have investigated a variety of anti-inflammatory treatments to attenuate the immune response and decrease morbidity and mortality due to COVID-19. Glucocorticoids are a common anti-inflammatory treatment used in critical illness and have been evaluated for respiratory conditions such as acute respiratory distress syndrome (ARDS). However, the benefit of glucocorticoids in the treatment of COVID-19 remains uncertain. The members of the RECOVERY Collaborative Group sought to evaluate several potential therapies in the treatment of hospitalized patients with COVID-19. These therapies included dexamethasone, lopinavir-ritonavir, azithromycin, convalescent plasma, and tocilizumab. The current preliminary report details the investigation of dexamethasone for COVID-19 and was published online in July 2020.

The RECOVERY trial was a multicenter, randomized, controlled, open-label trial performed in 176 sites in the United Kingdom. Patients included in the study were hospitalized with clinically suspected or laboratory confirmed infection with SARS-CoV-2 and had no medical history that placed them at risk with study participation. Patients enrolled in the study were randomized in a 2:1 ratio to receive standard care or standard care plus dexamethasone. Patients randomized to dexamethasone received 6 mg of dexamethasone per day (oral or intravenous) for up to 10 days or hospital discharge. The primary outcome was all-cause mortality at 28 days. Secondary outcomes included hospital length of stay, need for mechanical ventilation or renal replacement therapy, duration of mechanical ventilation, major arrhythmia, and cause-specific mortality. For patients who were intubated at the time of randomization, ventilator liberation at 28 days was also analyzed.

A total of 6425 patients were included in this preliminary report, with 2104 patients randomized to standard care plus dexamethasone and 4321 patients randomized to standard care alone. While the two groups were generally well matched, patients randomized to dexamethasone were slightly younger. In addition, those patients who were ventilated at the time of enrollment were approximately 10 years younger than those not ventilated and had been symptomatic for approximately 1 week longer. Notwithstanding, all-cause mortality at 28 days was statistically lower in patients who received standard care plus dexamethasone compared to patients who received standard care alone (22.9% vs 25.7%; rate ratio 0.83; 95% CI 0.75 to 0.93; $p<0.001$). The greatest improvement in all-cause mortality at 28 days for those patients who received dexamethasone was in those who were ventilated at the time of enrollment (29.3% vs 41.4%; rate ratio 0.64; 95% CI 0.51 to 0.81). Patients who had been placed on supplemental oxygen at the time of enrollment and were randomized to

dexamethasone also had a decrease in all-cause 28-day mortality compared with those on supplemental oxygen who received standard care alone (23.5% vs 26.2%; rate ratio 0.82; 95% CI 0.72 to 0.94). Importantly, there was no significant difference in all-cause 28-day mortality in patients who did not require supplemental oxygen or respiratory support. In fact, there was a trend towards worse outcomes in patients who received dexamethasone but did not require supplemental oxygen or respiratory support. With respect to secondary outcomes, patients randomized to standard care plus dexamethasone had a shorter hospital length of stay, were less likely to require renal replacement therapy, and more likely to be discharged from the hospital within 28 days. Furthermore, those who were ventilated and randomized to standard care plus dexamethasone were more likely to be liberated from mechanical ventilation by day 28 compared with those who received standard care alone. Four adverse reactions were reported in patients who received dexamethasone and included gastrointestinal hemorrhage, psychosis, and hyperglycemia.

The RECOVERY trial was one of the fastest, large-scale, randomized, controlled trials completed to date, with publication of these preliminary findings within 100 days of study creation. The authors should be applauded for their efforts, as this was one of the first studies in 2020 to demonstrate benefit of a therapeutic intervention in select patients with COVID-19 infection. Notwithstanding, the trial does have several limitations that should be highlighted. As noted, the trial was an open-label study and therefore subject to inclusion biases that can be seen with unblinded studies. In addition, there was no standardization of usual care across sites. Given that this trial was performed early in the pandemic, usual care likely changed over the duration of the trial. Furthermore, the study lacks long-term follow-up for patients who received dexamethasone. Knowledge of dexamethasone's effect beyond 28 days would be helpful in a patient population that has required prolonged ICU and hospital stays. Despite these limitations, the RECOVERY trial is one of the most important trials from 2020 and has served to change treatment for select patients with COVID-19 infection.

Take home point

- The EP should administer dexamethasone to patients with COVID-19 infection who require mechanical ventilation or supplemental oxygen for hypoxemic respiratory failure.

3. Acute gastrointestinal bleeding

HALT-IT Trial Collaborators. Effects of a high dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. Lancet. 2020; 395:1927–1936

Acute gastrointestinal bleeding is a common presentation to the ED. For patients with an acute upper gastrointestinal bleed, the case fatality rate can be as high as 10%, whereas the case fatality rate is approximately 3% for those with an acute lower gastrointestinal bleed [8,9]. Mortality increases several fold for those patients who rebleed after the initial gastrointestinal hemorrhage is controlled [10]. In recent years, the use of tranexamic acid (TXA) in emergency medicine has markedly increased. Tranexamic acid is an anti-fibrinolytic agent that reduces bleeding through stabilization of clot formation and has been shown to decrease bleeding and improve outcomes in select critical illnesses [11,12]. However, the effect of TXA in patients with acute gastrointestinal bleeding has not been assessed in a large, randomized trial. As such, the authors of the current trial sought to assess the effects of TXA on death and thromboembolic complications in patients with an acute gastrointestinal bleed.

The HALT-It trial is an international, randomized, multi-center, double-blind, placebo controlled trial performed in 164 hospitals in 15 countries. Patients included in the trial were adults 16 or 18 years of age (depending on the country) or older with a significant gastrointestinal bleed in whom the clinician was uncertain whether to administer TXA. The authors defined significant gastrointestinal bleeding as a "risk of bleeding to death and included patients with hypotension, tachycardia, signs of shock, or those likely to need transfusion or urgent endoscopy or surgery". Patients enrolled in the study were then randomized to an intervention group or a placebo group. Those in the intervention group received a loading dose of TXA followed by an infusion of TXA for 24 h. Those randomized to the placebo group received a loading dose of 0.9% sodium chloride followed by a maintenance infusion for 24 h. The initial primary outcome of the study was all-cause mortality at 5 days. However, the primary outcome was later changed to death due to bleeding within 5 days of randomization due to a large percentage of deaths among patients due to non-bleeding causes. Select secondary outcomes included death due to bleeding within 24 h and 28 days after randomization, all-cause and cause-specific mortality at 24 h, 5 days, and 28 days after randomization, rebleeding within 24 h, 5 days, and 28 days after randomization, blood product transfusion, and thromboembolic events.

A total of 12,009 patients were enrolled in the HALT-IT trial, with 5994 patients randomized to TXA and 6105 patients randomized to placebo. Importantly, 10,190 patients were enrolled prior to the change in primary outcome of the study. The primary outcome of death due to bleeding at 5 days after randomization did not differ between patients who received TXA and those who received placebo (3.7% vs 3.8%, RR 0.9; 95% CI 0.82 to 1.18). There was also no difference in the primary outcome when investigators analyzed prespecified subgroups based on the location of bleeding (upper vs lower) or the time to treatment. Furthermore, there was no difference in the primary outcome between patients who received TXA compared with those who received placebo when analyzed based on anticoagulant use, country income level, or systolic blood pressure. Similarly, the secondary outcomes of death from bleeding at 24 h and 28 days, all-cause mortality at 28 days, blood product transfusion, or the proportion of patients requiring intervention did not differ between groups. However, the risk of venous thromboembolism was significantly higher in those who received TXA compared with patients who received placebo (0.8% vs 0.4%; OR 1.85; 95% CI 1.15 to 2.98).

The HALT-IT trial is the largest, randomized trial to evaluate the use of TXA in patients with an acute gastrointestinal bleed. As noted, the trial did not demonstrate a reduction in death due to bleeding within 5 days or a reduction in meaningful secondary outcomes such as all-cause mortality, albeit with a higher risk of venous thromboembolism in those who received TXA. Limitations of the HALT-IT trial include the change in primary outcome near the end of the trial, the use of a clinical diagnosis of gastrointestinal bleeding and the potential for misclassification of the type of bleed by the bedside clinician, and the fact that patients without equipoise for TXA by the bedside clinician were excluded. Notwithstanding these limitations, the HALT-IT trial is an important contribution to the literature on gastrointestinal bleeding.

Take home point

- TXA should not be administered in the management of ED patients with acute gastrointestinal bleeding.

Lau JYW, Yu Y, Yang RS, et al. Timing of endoscopy for acute gastrointestinal bleeding. N Engl J Med. 2020; 382:1299–1308

The ideal time to perform endoscopy in the evaluation of patients with acute gastrointestinal bleeding remains uncertain. For patients with acute upper gastrointestinal bleeding, a recent consensus guideline recommends endoscopy be performed within 24 h of gastroenterologic consultation [13]. In contrast, other studies and clinical guidelines recommend that early endoscopy (i.e., within 12 h) be considered in hemodynamically stable patients with no significant comorbid conditions as well as those who are hemodynamically unstable with high-risk features for poor outcome [14,15]. While early endoscopy may lead to reduced hospital length of stay, it has been associated with increased mortality for patients in whom adequate hemodynamic

resuscitation has not been performed prior to endoscopy [14,16]. Given the current controversy on the optimal time to perform endoscopy for patients with acute gastrointestinal bleeding, the authors of the current study sought to evaluate whether endoscopy performed within 6 h after gastroenterologic consultation would improve outcomes compared to endoscopy performed within 6 to 24 h in patients with acute gastrointestinal bleeding who were at high risk of further bleeding or death.

The current study is a randomized trial performed in a single center in Hong Kong. Patients included in the study were adults greater than or equal to 18 years of age who presented either to the ED or after admission to a medical ward with overt signs of acute gastrointestinal bleeding (hematemesis, melena, or both) and had a Glasgow-Blatchford score of 12 or higher. The Glasgow-Blatchford score is a validated risk assessment score that ranges from 0 to 23 and is used to predict clinical outcomes and the need for intervention in patients with gastrointestinal bleeding. Higher Glasgow-Blatchford scores are associated with a higher risk for continued bleeding and death. Importantly, patients less than 18 years of age, were moribund from terminal illness, or remained in hypotensive shock after initial resuscitation were not included. Once enrolled, patients were randomized to either urgent endoscopy within 6 h from gastroenterologic consultation or early endoscopy the next morning and within 24 h from consultation. All patients received a high-dose intravenous proton pump inhibitor bolus followed by an infusion. Patients with suspected variceal bleeding also received intravenous antibiotics and a vasoactive medication. The primary outcome of this study was all-cause mortality within 30 days of randomization. Important secondary outcomes included further bleeding, ICU and hospital length of stay, blood transfusions, emergency surgery or angiographic embolization, and adverse events within 30 days of randomization.

Overall, 516 patients were enrolled in the current trial, with 258 patients assigned to both the urgent endoscopy group and early endoscopy group. Peptic ulcers were the most common source of bleeding in both groups, whereas esophagogatric varices were the source of bleeding in approximately 10% of patients in the urgent endoscopy group and in 7% of patients in the early endoscopy group. The mean time from presentation to endoscopy in the urgent group was 9.9 $\pm$ 6.1 h compared to a mean time in the early endoscopy group of 24.7 $\pm$ 1.7 h. Approximately 28% of patients in the urgent group underwent endoscopy within the planned 6-h time frame. Approximately 8% of patients in the early group underwent emergent endoscopy due to new-onset signs of bleeding. The primary outcome of all-cause mortality at 30 days did not differ between patients randomized to urgent endoscopy compared with patients randomized to early endoscopy (8.9% vs 6.6%; HR 1.35; 95%CI 0.72 to 2.54; $p = 0.34$). There was no statistical difference in further bleeding episodes between the groups. In addition, the groups did not differ in the duration of hospitalization, blood product transfusion, or the number of patients that required urgent surgery or angiographic embolization.

It can be difficult for the EP to determine when a patient should undergo endoscopy in the evaluation of acute gastrointestinal bleeding. The results of the current trial suggest that there is no difference in patient-centered outcomes for patients who undergo endoscopy within 6 h of gastroenterologic consultation compared with those who undergo endoscopy within 24 h. Importantly, the current trial is primarily limited by the exclusion of patients who remained hemodynamically unstable after initial resuscitation, a patient population that may benefit from emergent endoscopy especially in the setting of variceal hemorrhage. In addition, the trial was performed at a single center in Hong Kong that had access to 24-h experienced endoscopists, thereby limiting generalizability to other locations and patient demographics. Notwithstanding these limitations, the current trial contributes to the management of patients who present with acute gastrointestinal bleeding. Based on this trial, the EP should focus on resuscitation and stabilization of these patients. For adults who are hemodynamically stable, it is reasonable to perform endoscopy within 24 h of gastroenterologic consultation.

Take home point

- For adult patients with acute gastrointestinal bleeding who are hemodynamically stable, endoscopy can be performed within 24 h of gastroenterologic consultation.
- The EP should focus on ED resuscitation and stabilization of the patient with acute gastrointestinal bleeding.

4. Mechanical ventilation

Writing Group and Steering Committee for the RELAx Collaborative Group. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS. JAMA. 2020; 324:2509–2520

Rapid sequence intubation and initiation of mechanical ventilation are common critical care procedures for the EP. Although mechanical ventilation is often life saving for patients with acute hypoxic or hypercapnic respiratory failure, it can cause harm if not correctly managed. It is established that the use of lower tidal volumes (6–8 ml/kg predicted body weight) improve outcomes in patients with and without ARDS [17,18]. In addition to tidal volume, the EP must select an appropriate respiratory rate, fraction of inspired oxygen (FiO2), and positive end-expiratory pressure (PEEP) for mechanically ventilated ED patients. In contrast to tidal volume, the optimal level of PEEP remains unknown. In patients without ARDS, PEEP is used to improve lung aeration, reduce atelectasis, and prevent ARDS through the reduction of ventilator-associated pneumonia [19,20]. Similar to tidal volume, incorrect PEEP settings and titration can result in patient harm, as excessive pressures can adversely affect hemodynamics [21,22]. Given the current controversies on optimal PEEP, the authors of the current trial sought to determine whether a lower PEEP strategy would be non-inferior to a higher PEEP strategy for patients without ARDS.

The RELAx trial was prospective, randomized, controlled study performed in 8 ICUs in the Netherlands. Patients were enrolled in the study if they were initiated on invasive mechanical ventilation and were not expected to be extubated within 24 h of intubation. Patients were excluded from enrollment if they had been ventilated for more than 24 h or had confirmed or suspected ARDS. Once enrolled, patients were randomized within 1 h to either a low PEEP group or a high PEEP group. Patients randomized to low PEEP were initiated with a PEEP of 5 cm H2O and an FiO2 that ranged 0.21 to 0.6. If the patient's oxygen saturation (SpO2) remained greater than 92% or the partial arterial pressure of oxygen (PaO2) was greater than 60 mmHg, PEEP was decreased by 1 cm H2O increments until zero. If the patient's SpO2 was less than 92%, the FiO2 was first increased followed by an increase in PEEP. Patients randomized to high PEEP were initiated with a PEEP of 8 cm H2O and an FiO2 that ranged 0.21 to 0.6. Similar to the low PEEP group, if the patient's SpO2 was less than 92%, FiO2 was first increased followed by an increase in PEEP. Goal SpO2 for both groups was 92% to 96% with a goal PaO2 for both groups of 60 to 85 mmHg. The primary outcome of the RELAx trial was the number of ventilator-free days at day 28. Secondary outcomes included ICU and hospital length of stay, 28-day and 90-day mortality, number of days alive and not mechanically ventilated, number of pulmonary complications, and the need for rescue therapy for severe hypoxemia.

A total of 980 patients were enrolled in the RELAx trial, with 484 patients randomized to the low PEEP group and 496 patients randomized to the high PEEP group. Respiratory failure accounted for the most common reason for initiation of mechanical ventilation. Baseline characteristics were similar between groups. For the primary outcome of ventilator-free days at day 28, a ventilation strategy using low PEEP was non-inferior to a ventilation strategy using high PEEP (18 ventilator-free days vs 17 ventilator-free days; mean ratio 1.04; 1-

sided 95% CI 0.95 to infinity; $p = 0.007$ for noninferiority). With respect to the secondary outcomes, there was no statistically significant difference in duration of mechanical ventilation, ICU or hospital length of stay, 28-day and 90-day mortality, occurrence of pulmonary complications, or the use of rescue therapy for severe hypoxemia between groups.

The RELAx trial is one of the largest randomized trials to compare low and high PEEP strategies and demonstrated that the use of lower levels of PEEP were non-inferior to higher levels of PEEP in patients without ARDS. The current study is an important contribution to the ventilator management of patients without ARDS, the most common type of patient ventilated in the ED. The authors should be commended for this prospective, randomized trial on an important clinical question. Importantly, there are several limitations to the RELAx trial that should be highlighted. This was a unblinded trial, as the treating physicians were aware of level of PEEP applied to patients. In addition, many patients screened and enrolled were not randomized within the one-hour target of ventilation in the ICU. Finally, the authors included a large and heterogeneous group of patients without ARDS. It is possible that there are conditions that may benefit from a higher level of PEEP in patients not felt to have ARDS at the time mechanical ventilation is initiated.

Take home point

- When initiating mechanical ventilation, the EP can use lower levels of PEEP (i.e., 5 cm H2O) for patients without evidence of ARDS.

Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020; 382:999–1008

ARDS is a common indication for intubation, mechanical ventilation, and admission to the ICU [23]. In ARDS, mechanical ventilation can improve oxygenation with the application of titratable levels of PEEP and FiO2. As previously noted, increased levels of PEEP can be injurious to lungs and adversely affect hemodynamics [21,22,24,25]. Similarly, increased levels of FiO2 can also be harmful through free oxygen radical mediated pathways [26]. Unfortunately, the optimal oxygenation target to limit injury in patients with ARDS remains uncertain. As such, the authors of the current trial sought to compare a conservative and liberal oxygen strategy and better clarify oxygenation goals in ventilated patients with ARDS.

The $LOCO_2$ was a prospective, multicenter, randomized trial conducted in 13 ICUs in France. Patients included in the study were greater than or equal to 18 years of age who had been intubated and ventilated for ARDS less than 12 h prior to enrollment. Patients excluded from the study were those who had intracranial hypertension, cardiac arrest secondary to traumatic brain injury, or those who required long-term oxygen therapy or non-invasive ventilation as outpatients. Once enrolled, patients were randomized to either a conservative oxygen group, with a goal PaO2 of 55 to 70 mmHg, or a liberal oxygen group, with a goal PaO2 of 90 to 105 mmHg. These target oxygen goals were maintained for the first 7 days of mechanical ventilation or until extubation, whichever came first. Adjustments to FiO2 in increments of 0.05 to 0.10 could be made if the desired target PaO2 was not achieved. The primary outcome of the current study was death from any cause at 28 days. Secondary outcomes included death at 90-days, death in the ICU, cardiovascular complications, Sequential Organ Failure Assessment (SOFA) scores, neurologic complications, neurologic status, and respiratory weaning success at 28 and 90 days.

A total of 205 patients were enrolled in the $LOCO_2$ study, with 99 patients randomized to the conservative oxygen group and 102 patients randomized to the liberal oxygen group. There were no statistical differences in the baseline characteristics of both groups. As expected, there was a significant difference in mean values for PaO2, SpO2, and FiO2 between groups with lower overall values in the conservative oxygen group. For the primary outcome of death from any cause at 28 days, there was no statistical difference between patients randomized to the conservative oxygen group and those randomized to the liberal oxygen group (34.3% vs 26.5%; difference, 7.8 percentage points; 95% CI -4.8 to 20.6). In contrast, there was a trend towards higher mortality at 90 days in patients randomized to the conservative oxygen group compared to patients randomized to the liberal oxygen group (44.4% vs 30.4%, difference 14 percentage points; 95% CI 0.7 to 27.2). Furthermore, there were 5 episodes of mesenteric ischemia in patients in the conservative oxygen group. As a result of these findings, the $LOCO_2$ trial was terminated early.

The $LOCO_2$ trial was a well-conducted study that evaluated an important clinical question in the management of ventilated patients. As noted, there was no statistical difference in the primary outcome of 28-day mortality in patients randomized to either a conservative or liberal oxygen strategy, however there were concerning findings of increased 90-day mortality and increased episodes of mesenteric ischemia in patients who received a conservative oxygen strategy. Though no definitive cause could be determined, the authors of the study speculated that lower levels of oxygen may result in subclinical hypoxemia and patient harm. Several limitations of the $LOCO_2$ trial should be noted and include early termination of the study, unblinded study design, and the challenge of accurately monitoring patients with lower levels of oxygen. The accuracy of pulse oximeters decreases with lower levels of oxygen and it is possible that patients randomized to the conservative oxygen strategy with a lower target of 55 mmHg may have been exposed to more prolonged hypoxemia that those in the liberal oxygen strategy group. Notwithstanding these limitations the $LOCO_2$ is an important contribution to the literature and demonstrated that conservative oxygen strategy that targeted a PaO2 of 55 to 70 mmHg did not improve 28-day mortality, and may have harm in ventilated ARDS patients.

Take home point

- When managing the mechanically ventilated ED patient with ARDS, the EP should titrate supplemental oxygen to target a PaO2 of 90 to 105 mmHg given the trend towards worse outcome with lower PaO2 target values.

5. Vasopressors

Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA. 2020; 323:938–49

Vasopressors are commonly administered in the ED for patients with persistent hypotension and signs of poor perfusion despite initial resuscitation. Though vasopressor medications often increase systolic blood pressure and mean arterial pressure (MAP), they can also have adverse consequences on cardiac, metabolic, and immune function due to intense vasoconstriction [27,28]. Septic shock is the most common type of vasodilatory shock encountered in the ED. For patients in septic shock, the Surviving Sepsis Campaign (SSC) recommends a target MAP of 65 mmHg [29]. For older patients and those with chronic hypertension, the SSC recommends a higher MAP [29]. However, a relatively recent trial in 2016 demonstrated an association of increased vasopressor administration to target a higher MAP with increased mortality in patients older than 65 years of age [30]. Given the current controversies on the target MAP for older patients who require vasopressor support, the authors of the current trial sound to determine whether a reduction in exposure to vasopressors through permissive hypotension reduced 90-day mortality in ICU patients aged 65 years or older with vasodilatory shock.

The 65 trial was a pragmatic, randomized trial conducted in 65 ICUs in the United Kingdom. Patients were included in the trial if they were 65 years of age or older, admitted to a participating ICU, and were within 6 h of initiation of a vasopressor infusion for vasodilatory hypotension, had received adequate fluid resuscitation, and were

expected to need vasopressors for at least 6 more hours. Patients with contraindications to permissive hypotension, imminent risk of death, or received vasopressors for non-vasodilatory shock were excluded. Once enrolled, patients were randomized to a permissive hypotension group or a usual care group. Patients randomized to the permissive hypotension group received vasopressors to target a MAP between 60 and 65 mmHg. Those randomized to the usual care group received vasopressors at the discretion of the treating physician. The choice of vasopressors in both groups was left to the treating physician. The primary outcome of the 65 trial was 90-day all-cause mortality. Secondary outcomes included mortality at ICU discharge, mortality at hospital discharge, ICU length of stay, days alive and free of respiratory and renal support within the first 28-days, cognitive decline in survivors and 90 days and 1 year, and health-related quality of life in survivors at 90 days and 1 year.

A total of 2598 patients were enrolled in the 65 trial, with 1291 patients randomized to the permissive hypotension group and 1307 patients randomized to the usual care group. Both groups were well-matched with the exception of a higher proportion of patients in the permissive hypotension group that required assistance with activities of daily living (34.4% vs 30.9%). The average and peak MAPs in the permissive hypotension group were 66.7 mmHg and 84.9 mmHg, whereas the average and peak MAPs in the usual care group were 7.26 mmHg and 93.2 mmHg. Not surprisingly, patients in the permissive hypotension group had a lower median total dose and lower exposure to vasopressors compared with patients in the usual care group. With respect to the primary outcome of 90-day all-cause mortality, there was no difference between patients randomized to permissive hypotension compared to patients randomized to usual care (41% vs 43.8%; absolute difference − 2.85%; 95% CI -6.75 to 1.05; $p = 0.15$). Similarly, there were no differences between the groups for the secondary outcomes of ICU mortality, mortality at hospital discharge, ICU length of stay, days alive and free of respiratory and renal support at day 28, cognitive decline and health-related quality of life scores at 90 days and 1 year. Furthermore, there was no difference in adverse events between those randomized to permissive hypotension and those randomized to usual care. In a subgroup analysis of patients with chronic hypertension, the authors reported a decrease in 90-day mortality for those randomized to the permissive hypotension group compared with patients randomized to the usual care group (38.2% vs 44.3%; adjusted OR 0.67; 95% CI 0.49 to 0.85; $p = 0.047$).

The 65 trial is an important contribution to the 2020 critical care literature and addresses an important clinical question in the management of patients with vasodilatory shock. Groups were well-matched with respect to baseline MAPs prior to randomization, fluid balances, and other treatments for shock. The study did not find a statistical difference in 90-day all-cause mortality for patients randomized to a lower MAP target of 60 to 65 mmHg. The finding of reduced 90-day mortality in patients with chronic hypertension randomized to the lower MAP target range is hypothesis generating and requires further study. While the study suggests that a lower MAP target may be beneficial for older patients with chronic hypertension, it is important to note several limitations of the 65 trial. First, patients randomized to the permissive hypotension group spent approximately half of their treatment hours with MAPs greater than 65 mmHg. Second, the trial only included ICU patients. As an ICU-based study, patients likely received care with lower nurse to patient ratios with potentially greater attention in order to maintain the MAP within the narrow range of 5 mmHg in the permissive hypotension group. These factors may limit the generalizability to patients receiving vasopressors for vasodilatory shock in the ED. Additional limitations highlighted by the authors include the lack of blinding for study interventions and the failure to adjudicate attributable mortality. Based on these limitations, we feel it is reasonable to conclude that a MAP goal of 60 mmHg is likely safe in older patients with vasodilatory shock.

Take home point

- When managing older patients with vasodilatory shock, the EP determine an appropriate MAP target based on the patient and the clinical presentation.

Panwar R, Tarvade S, Lanyon N, et al. Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock. A multicenter, prospective cohort study. Am J Respir Crit Care Med. 2020; 202:1407–18

Vasopressors are typically administered and titrated to achieve a target MAP of 65 mmHg for most critically ill patients. For patients who have elevated blood pressure prior to the onset of critical illness, a target MAP of 65 mmHg may be insufficient to maintain adequate tissue perfusion. Relative hypotension, defined as the difference between the patient's pre-illness basal blood pressure and the achieved blood pressure while on vasopressor support, has been associated with adverse outcomes in critically ill patients [31,32]. Unfortunately, there are currently no prospective studies that assess the duration of relative hypotension and the impact on critically ill patients in shock. As such, the authors of the current study sought to assess the degree and duration of relative hypotension on the incidence of new acute kidney injury (AKI) and major adverse kidney events (MAKE) among ICU patients with shock.

The REACT Shock Study was an investigator-initiated, multicenter, prospective observation trial conducted in 7 mixed medical-surgical ICUs in Australia. Patients included in the study were 40 years of age or older who were within 48 h of ICU admission, were in shock and receiving vasopressors or inotropic medications for at least 4 h, and were receiving respiratory support with either high-flow oxygen therapy or positive-pressure ventilation. Patients who were considered moribund, in renal failure and in imminent need of RRT, had end-stage renal disease, lacked a central venous catheter, had active bleeding, were pregnant, or did not have at least two pre-illness blood pressure readings available were excluded. Importantly, the key blood pressure parameter for the REACT Shock Study was mean perfusion pressure (MPP), defined by the authors as the difference between MAP and central venous pressure (CVP). The MPP was obtained every 4 h up to 120 h while on vasopressors and compared with the patient's pre-illness MPP based on prior measurements. Relative hypotension was quantified for each patient using a time-weighted average MPP deficit, which was the percent difference between the pre-illness MPP and the vasopressor-achieved MPP. The primary outcomes of the study were the development of new significant AKI and MAKE within 14 days. Significant AKI was defined as a peak serum creatinine level greater than or equal to 2 times the baseline creatinine level, while MAKE within 14 days was comprised of death, new RRT, or doubling of the patient's pre-illness creatinine. Secondary outcomes included the maximum severity of AKI at 14 days, the receipt of RRT within 14 days, RRT-free days at day 28, new chronic kidney disease at 3 months, MAKE at 90 days, and all-cause mortality at 90 days.

A total of 302 patients were included in the REACT Shock Study. The majority of patients included in the study had septic shock and approximately 60% had chronic hypertension. There was a median of 36 h of vasopressor administration per patient and all but 2 patients experienced relative hypotension during their hospitalization. The median average MPP deficit was 19%. Overall, greater MPP deficits and longer periods of time spent with an MPP deficit greater than 20% were associated with an increased incidence of both new AKI and MAKE at 14 days. In fact, the odds of new AKI and MAKE at 14 days increased by 5.6% (95% CI 2.2 to 9.1; $p = 0.001$) and 5.9% (95% CI 0.4 to 2.4; $p = 0.002$) respectively for each percentage increase in the average MPP deficit. In addition, the odds of new AKI and MAKE at 14 days increased by 1.2% (95% CI 0.3 to 2.2; $p = 0.0008$) and 1.4% (95% CI 0.4 to 2.4; $p = 0.004$) respectively for each percentage increase in time spent with an MPP deficit greater than 20%. The authors also found an independent relationship between 14-day mortality and the time-weighted average MPP deficit and time spent with an MPP deficit greater than 20%.

The REACT Shock Study evaluates an important clinical question that pertains to appropriate MAP targets for critically ill patients receiving vasopressors. The study found a large percent of patients experienced periods of relative hypotension and this was associated with a higher incidence of new AKI and MAKE at 14 days, especially for those with MPP deficits in excess of 20%. Important limitations to the REACT Shock Study include its observational design, the lack of information provided on the number and classes of vasopressors used, and the absence of information on fluid resuscitation for these patients. Additional limitations include the reliability of pre-illness blood pressure readings, the use of MPP deficit as opposed to MAP deficit, and the use of a time-weighted average for MPP. Given these limitations, a causal relationship between relative hypotension, as measured by MPP deficit, and new AKI or MAKE at 14 days cannot be established.

Take home point

- The EP should titrate vasopressors to more closely match the patient's chronic perfusion pressure rather than target a MAP of 65 mmHg for all critically ill patients.

6. Sepsis

Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA. 2020; 323:423–431

Sepsis remains one of the most common critical illnesses diagnosed and treated by EPs. Despite advances in sepsis resuscitation over the past several decades, patients with septic shock continue to have significant morbidity and mortality [33,34]. Given the high mortality risk with septic shock, researchers continue to investigate novel therapies that may mitigate this risk. In 2017, investigators published results from a single-center, retrospective, before-and-after study of 94 patients with septic shock who had significant benefit following the administration of high-dose thiamine, vitamin C, and hydrocortisone [33]. As a result of this study, many clinicians began administration of these medications to patients with septic shock. However, there have been no randomized trials that evaluated these medications in patients with septic shock. To that end, the authors of the current study sought to compare the resolution of septic shock and days alive in patients randomized to receive high-dose thiamine, vitamin C, and hydrocortisone and those randomized to receive hydrocortisone alone.

The VITAMINS trial was a multicenter, open-label, parallel-group randomized trial conducted in 10 ICUs across Australia, New Zealand, and Brazil. Patients included in the trial were admitted to the ICU with a primary diagnosis of septic shock, a serum lactate greater than 2 mmol/L, a 2-point increase in SOFA score, and had at least 2 h of vasopressor administration. Importantly, patients had to be enrolled within 24 h of meeting septic shock criteria, as defined by the Sepsis-3 definition. Patients less than 18 years of age, had a diagnosis of septic shock for more than 24 h, had an additional indication to receive hydrocortisone, had a pre-existing do-not-resuscitate order, or had imminent death were excluded. Once enrolled, patients were randomized to an Intervention group or a Control group. Those randomized to the Intervention group received 1.5 g of vitamin C every 6 h, 50 mg of hydrocortisone every 6 h, and 200 mg of thiamine every 12 h. This intervention continued until vasopressors were discontinued. Patients randomized to the Control group received 50 mg of hydrocortisone every 6 h. The treating physician could administer thiamine at their discretion but were not permitted to administer vitamin C. The primary outcome of the VITAMINS trial was time alive and free of vasopressor support at 7 days after randomization. Secondary outcomes included 28-day and 90-day ICU and hospital mortality, 28-day cumulative mechanical ventilation-free days, 28-day RRT-free days, 28-day ICU-free days, and hospital length of stay.

A total of 216 patients were enrolled in the VITAMINS trial, with 109 patients randomized to the Intervention group and 107 patients randomized to the Control group. Ultimately, 211 patients were included in the final analysis. With respect to the primary outcome, there was no statistical difference in time alive and free of vasopressors at 7 days in patients randomized to the Intervention group compared to those randomized to the Control group (median of 122.1 h vs median of 124.6 h; median of all paired differences between groups, −0.6 h; 95% CI -8.3 to 7.2 h; $p = 0.83$). In terms of the secondary outcomes there was no difference in 28-day or 90-day hospital mortality, 28-day cumulative vasopressor-free days, 28-day mechanical ventilation-free days, 28-day or RRT-free days. There were only 3 adverse events that occurred in the VITAMINS trial, 2 of which occurred in the Intervention group (fluid overload, hyperglycemia) and 1 in the Control group (gastrointestinal bleeding).

The VITAMINS trial is the first randomized trial to evaluate the combination of vitamin C, hydrocortisone, and thiamine in patients with septic shock. In this trial, there was no difference in the primary or secondary outcomes for patients randomized to receive this combination of therapies compared with patients who received hydrocortisone. These findings conflict with the 2017 single-center, retrospective study by Marik and colleagues in which mortality was markedly reduced in patients with septic shock who received these therapies [33]. Important limitations to the VITAMINS trial include its open-label design and the lack of a blinded outcome assessment. In addition, the effects of vitamin C alone were not assessed, nor was the combination therapies of vitamin C, hydrocortisone, and thiamine compared to placebo. Furthermore, other aspects of care that may impact outcomes in patients with septic shock (i.e., target MAP, time to antibiotics) were not collected. Finally, the VITAMINS trial was not powered to assess mortality between the two groups. Nonetheless, the VITAMINS trial is an important contribution to the sepsis literature and suggests that the administration of vitamin C, hydrocortisone, and thiamine does not benefit patients with septic shock.

Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020; 324:642–650.

As discussed, patients with septic shock have high mortality. Previous studies have suggested that patients with sepsis may have deficiencies in both vitamin C and thiamine [35-38]. Additional studies have also suggested that vitamin C may have a synergistic effect with corticosteroids in patients with sepsis and septic shock [33,39]. Given the inconsistencies in the current literature and uncertainty of whether this combination therapy may be beneficial, the authors of the current trial sought to assess whether the administration of vitamin C, corticosteroids, and thiamine would reduce the SOFA score in patients with septic shock 72 h after enrollment.

The ACTS trial was a multicenter, blinded, placebo-controlled, randomized superiority trial conducted in 14 centers in the United States. Patients included in the study were greater than or equal to 18 years of age, has suspected or confirmed infection, and were receiving vasopressors as a result of sepsis. Patients who were less than 18 years of age, had an indication for any of the study drugs (i.e., corticosteroids), were receiving RRT, had glucose-6-phosphate dehydrogenase deficiency, had hemochromatosis, or were not expected to survive 24 h were excluded. Once enrolled, patients were randomized to an Intervention group or Placebo. Patients randomized to the Intervention group received 1500 mg of vitamin C, 50 mg of hydrocortisone, and 100 mg of thiamine every 6 h for 4 days. Patients randomized to the Placebo group received 0.9% normal saline in matching infusions. Patients in both groups received standard sepsis resuscitation that included early antibiotics, early source control, and maintenance of a MAP of at least 65 mmHg with IVFs and vasopressor medication. The primary outcome of the ACTS trial was the change in SOFA score between enrollment and 72 h. Secondary outcomes included renal failure, ventilator-free days during the first 7 days, shock-free days during the first

7 days, ICU-free days during the first 28 days, ICU all-cause mortality, all-cause mortality at hospital discharge.

A total of 205 patients were randomized in the ACTS trial, with 200 patients included in the primary analysis. Of these 200 patients, 101 were randomized to the Intervention group and 99 were randomized to the Placebo group. Baseline characteristics between the groups were well matched. With respect to the primary outcome there was no difference in the change in SOFA scores over 72 h between patients randomized to the Intervention group and those randomized to the Placebo group (mean difference − 0.8; 95% CI -1.7 to 0.2; $p = 0.12$). Similarly, there was no statistical difference between the groups with respect to the secondary outcomes of renal failure, 30-day mortality, or median number of ventilator-free days within the first 7 days. However, patients in the Intervention group did have a higher median number of shock-free days within the first 7 days compared with patients in the Placebo group (5 vs 4; median difference 1 day; 95% CI 0.2–1.8 days; $p < 0.01$). There were no serious adverse events related to the study protocol. Common adverse events included hyperglycemia, hypernatremia, and hospital-acquired infection.

Similar to the VITAMINS trial, the ACTS trial is another important randomized trial that evaluated the combination of vitamin C, hydrocortisone, and thiamine for patients with septic shock. In the current trial, which compared this combination therapy with placebo, there was no statistical difference in organ injury, as measured by the changes in SOFA scores, at 72 h after enrollment. In addition, there was no difference in 30-day mortality between the Intervention and Placebo groups. Limitations of the ACTS trial include the overall small number of patients randomized in the trial compared to those who were screened, the period of time to study drug administration from the initiation of vasopressor therapy (13.5 h), the percentage of patients who did not complete the full 4-day study protocol, and the lack of statistical power of the study to detect differences in mortality between the groups. Notwithstanding, the ACTS trial adds to the growing body of literature that does not indicate a benefit to the administration of this combination therapy for patients with septic shock. Until further studies are published that would contradict these findings, we feel that the administration of vitamin C, thiamine, and hydrocortisone should not be a component of the ED resuscitation of patients with septic shock.

Take home point

- Based on the VITAMINS and ACTS trials, the EP should not administer the combination of vitamin C, thiamine, and hydrocortisone to ED patients with septic shock.

7. Cardiac arrest

Yannopoulos D, Bartos JA, Reveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single center, open-label, randomized controlled trial. Lancet. 2020; 396:1807–1816

Survival to hospital discharge with meaningful neurologic recovery remains poor for patients who present to the ED with out-of-hospital cardiac arrest (OHCA). The majority of patients who do survive OHCA present with an initial shockable rhythm, such as ventricular fibrillation (VF) [40,41]. Unfortunately, up to 50% of OHCA patients with VF fail to respond to standard advanced cardiac life support (ACLS) treatment [42]. Extracorporeal membrane oxygenation (ECMO) is a resource-intensive intervention that has been used with increased frequency in recent years for select critical illnesses. The current literature on the use of ECMO for patients with cardiac arrest is primarily composed of retrospective studies that are subject to selection bias. As there remains limited high-quality evidence on the use of ECMO for OHCA patients, the authors of the current trial sought to compare survival to hospital discharge between OHCA patients who received ED-based standard ACLS resuscitation and those who received early ECMO-facilitated resuscitation.

The ARREST trial was a phase 2, single-center, open-label, pragmatic, randomized study performed at the University of Minnesota Medical Center and 3 emergency medical service agencies in proximity to the hospital. Patients included in the study were adults between the ages of 18 to 75 years of age who had OHCA with an initial rhythm of VF or pulseless ventricular tachycardia, did not achieve return of spontaneous circulation (ROSC) after 3 defibrillation attempts, could accommodate a mechanical CPR device, and had a transport time to the ED less than 30 min. Patients who achieved sustainable ROSC within the first 3 defibrillation attempts, those with blunt or penetrating trauma, those in whom cardiac arrest was due to drowning or overdose, were pregnant, had terminal cancer, had active gastrointestinal bleeding, were a patient at a skilled nursing facility, or had an existing DNR order were excluded from the present study. Once enrolled, patients were randomized to either ECMO-facilitated resuscitation or standard ED ACLS resuscitation. Patients who were randomized to ECMO-facilitated resuscitation were taken directly to the cardiac catheterization lab (CCL) regardless of whether a pulse was present. Upon arrival to the CCL, an arterial blood gas was obtained. If the PaO2 was less than 50 mmHg, a lactate was greater than 18 mmol/L, or the end-tidal CO2 concentration was less than 10 mmHg resuscitation efforts were terminated. If none of these conditions were met, patients were cannulated and placed on venoarterial ECMO, followed by an angiogram and revascularization if indicated. Patients randomized to standard ED ACLS resuscitation were taken to the ED, where resuscitation was continued for at least 15 min at the direction of the EP. If ROSC was achieved, the patient was transferred for angiography, revascularization, or circulatory support per study protocol. All patients who survived in both groups were transferred to a dedicated cardiac ICU. The primary outcome of the ARREST trial was survival to hospital discharge. Secondary outcomes included survival and functionally favorable neurologic status at hospital discharge, 3 months, and 6 months. Favorable neurologic survival was defined as a score of 3 or lower on the modified Rankin score (mRs).

A total of 30 patients were enrolled in the ARREST trial, with 15 patients randomized to ECMO-facilitated resuscitation and 15 patients randomized to standard ED ACLS resuscitation. Patient characteristics were well balanced between the groups, with a median age of 59 years and approximately 80% were male. Importantly, the study was terminated early by the Data Monitoring Safety Board due to significant differences in the primary and secondary outcomes between the groups at an interim analysis. With respect to the primary outcome, survival to hospital discharge was greater in patients randomized to ECMO-facilitated resuscitation compared with patients randomized to standard ED ACLS resuscitation (43% vs 7%; risk difference 36.2%, 95% CI 3.7–59.2; posterior probability of ECMO superiority 0.9861). The secondary outcomes of cumulative survival, mRs at hospital DC, 3 months, and 6 months were all improved in patients randomized to ECMO-facilitated resuscitation compared with those who received standard ED ACLS resuscitation. The authors reported no unanticipated serious adverse events in patients who received ECMO-facilitated resuscitation.

The ARREST trial is the first randomized trial of ECMO for OHCA patients with refractory VF and demonstrated markedly improved survival to hospital discharge for patients who received ECMO-facilitated resuscitation. While these results are promising, it is important to recognize the limitations of the ARREST trial. First and foremost, the study was terminated early after just 30 patients. Slight changes in survival in either group may have substantially changed the study results and conclusions. In addition, the study was a single-center study performed at a center that his highly experienced in ECMO. This raises the concern of generalizability to other centers with different patient populations and resources. To that end, nearly all patients in the ARREST trial had an OHCA in a public location and received bystander CPR. Despite

these limitations, the ARREST trial is an important contribution to the cardiac arrest literature.

Take home point

- If available, the EP should consider the early initiation of ECMO in the resuscitation of OHCA patients with refractory VF.

8. Post-cardiac arrest care

Pareek N, Kordis P, Beckley-Hoelscher N, et al. A practical risk score for early prediction of neurological outcome after out-of-hospital cardiac arrest: MIRACLE 2. European Heart Journal. 2020; 41:4508–17

The ability to predict meaningful neurologic outcome in ED patients resuscitated from OHCA is difficult. Accurate prognostication in this patient population is even more challenging with the application of targeted temperature management and sedation for mechanical ventilation. A standardized approach to appropriate post-cardiac arrest care is necessary to improve the chance of meaningful neurologic survival, but is resource intensive. Identification of patients who achieve ROSC from OHCA but are unlikely to survive with meaningful neurologic recovery is useful for the patient, their family, and for resource utilization. Unfortunately, there are currently no reliable and validated score to predict which patients with ROSC from OHCA will survive with meaningful neurologic outcome. As such, the authors of the current study sought to develop a practical risk score to predict poor neurologic outcome after OHCA.

The MIRACLE$_2$ study is a prospective investigation of the United Kingdom's King's Out of Hospital Cardiac Arrest Registry (KOCAR). Patients included in the present study were adults greater than or equal to 18 years of age who achieved ROSC from OHCA and either had evidence of ST elevation on the electrocardiogram (ECG) or a high clinical suspicion of a cardiac etiology. Patients less than 18 years of age, those with a non-cardiac etiology of OHCA, confirmed intracerebral bleeding, prior neurologic disability defined as a Cerebral Performance Category (CPC) of 3 or 4, and those with survival limiting disease were excluded. The authors then used multivariable logistic regression to identify predictors of poor neurologic outcome and derive a risk score. After derivation of the risk score, the authors used two independent cohorts for validation. The primary outcome of the study was poor neurologic outcome, defined as a CPC of 3 to 5 at 6-month follow up.

A total of 1055 patients suffered OHCA during the study period, of which 373 patients were included in the derivation cohort. The median age of patients in the derivation cohort was 64 years, with over 56% of patients sustaining OHCA at home and over 70% had an initial shockable rhythm. The primary outcome of poor neurologic outcome occurred in approximately 60% of patients in the derivation cohort. Seven independent predictors of poor outcome were identified by logistic regression and were assigned points for the MIRA$_2$CLE$_2$ score. These included unwitnessed arrest – 1 point, initial non-shockable rhythm – 1 point, non-reactivity of pupils – 1 point, pH less than 7.20–1 point, epinephrine administration (2 points), and age (60–80 years – 1 point; > 80 years – 3 points). Thus, the score ranges from 0 to 10. The MIRA$_2$CLE$_2$ score had an area under the curve (AUC) of 0.90 for the derivation cohort.

After the derivation cohort, the authors externally validated the MIRA$_2$CLE$_2$ score in two cohorts, 326 patients from a single center in Slovenia and 148 patients from a single center in London. The AUC for the MIRA$_2$CLE$_2$ score in the Slovenia cohort and the London cohort were 0.85 and 0.91, respectively. The authors then categorized patients into 3 risk categories based on the total MIRA$_2$CLE$_2$ score: Low – 0–2 points; Intermediate – 3–4 points; High – greater than or equal to 5 points). A MIRA$_2$CLE$_2$ score greater than or equal to 5 had a specificity of 90.3% and predicted poor neurologic outcome in nearly 50% of all patients.

The MIRACLE$_2$ trial is an important contribution to the post-cardiac arrest literature and offers a simple tool that might be used predict poor neurologic outcome for patients with ROSC from OHCA. Before widespread adoption of this score, it is important to highlight several limitations of the study. As noted by the authors, the score was derived and validated in retrospective cohorts from a cardiac arrest registry. In addition, the patients included in the cohorts all had a presumed cardiac etiology of their OHCA. In fact, many had an ST elevation myocardial infarction and an initial shockable rhythm, factors known to predict better outcomes in cardiac arrest patients. Furthermore, various components of the score (pupil reactivity, pH) were determined at the time of ICU admission for one of the validation cohorts. This may have adversely affected the performance of the score in this cohort. Notwithstanding these limitations, the MIRA$_2$CLE$_2$ score is simple to calculate and may offer additional information in the resuscitation of patients with OHCA.

Take home point

- At present, the MIRA$_2$CLE$_2$ score requires further validation and the EP should not use this tool as the sole data point to determine the prognosis of ED patients with ROSC from OHCA.

Funding

None.

Declaration of Competing Interest

The authors do not have any financial conflicts of interest.

References

[1] Herring AA, Ginde AA, Fahimi J, et al. Increasing critical care admissions from U.S. emergency departments, 2001-2009. Crit Care Med. 2013;41:1197–204.
[2] Mohr NM, Wessman BT, Bassin B, et al. Boarding of critically ill patients in the emergency department. Crit Care Med. 2020;48:1180–7.
[3] Mathews KS, Durst MS, Vargas-Torres C, et al. Effect of emergency department and ICU occupancy on admission decisions and outcomes for critically ill patients. Crit Care Med. 2018;46(5):720–7.
[4] Groenland CNL, Termorshuizen F, Rietdijk WJ, et al. Emergency department to ICU time is associated with hospital mortality: a registry analysis of 14,788 patients from six university hospitals in the Netherlands. Crit Care Med. 2019;47:1564–71.
[5] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
[6] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med. 2021;384:693–704.
[7] Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020;20:669–77.
[8] Hearnshaw SA, Logan RF, Lowe D, et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses, and outcomes in the 2007 UK audit. Gut. 2011;60:1327–35.
[9] Oakland K, Guy R, Uberroi R, et al. Acute lower GI bleeding in the UK: patient characteristics, intervention, and outcomes in the first nationwide audit. Gut. 2018;67:652–62.
[10] Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care. 2001;5:368–75.
[11] CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet. 2010;376:23–32.
[12] WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomized, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.
[13] Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the International Consensus Group. Ann Intern Med. 2019;171:805–22.
[14] Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107:345–61.
[15] Gralnek IM, Dumonceau J-M, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy guideline. Endoscopy. 2015;47:a1–a46.
[16] Laursen SB, Leontiadis GI, Stanley AJ, et al. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. Gastrointest Endosc. 2017;85 936.e3–944.e3.
[17] The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301–8.
[18] Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651–9.

[19] Neto AS, Filho RR, Cherpanath T, et al. PROVE Network Investigators. Associations between positive end-expiratory pressure and outcome of patients without ARDS at onset of ventilation: a systematic review and meta-analysis of randomized controlled trials. Ann Intensive Care. 2016;6:109.
[20] Manzano F, Fernandez-Mondejar E, Colmenero M, et al. Positive end-expiratory pressure reduces incidence of ventilator-associated pneumonia in non-hypoxemic patients. Crit Care Med. 2008;36:2225–31.
[21] Battaglini D, Ball L, Wittenstein J, et al. PEEP in thoracic anesthesia: pros and cons. Minerva Anestesiol. 2021;87:223–9.
[22] Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ, PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO Trial): a multicenter randomized controlled trial. Lancet. 2014;384:495–503.
[23] Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. Mayo Clin Proc. 2017;92:1382–400.
[24] Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369:2126–36.
[25] Marini M, Caretta G, Vagnarelli F, et al. Hemodynamic effects of positive end-expiratory pressure. G Ital Cardiol. 2017;18:505–12.
[26] Dias-Freitas F, Metelo-Coimbra C, Roncon-Albuquerque R. Molecular mechanisms underlying hyperoxia acute lung injury. Respir Med. 2016;119:23–8.
[27] Varpula M, Tallgren M, Saukkonen K, et al. Hemodynamic variables related to outcome in septic shock. Intensive Care Med. 2005;31:1066–71.
[28] Maheshwari K, Nathanson BH, Munson SH, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med. 2018;44:857–67.
[29] Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.
[30] Lamontagne F, Meade MO, Hebert PC, et al. Canadian Critical Care Trials Group. Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicenter pilot randomized controlled trial. Intensive Care Med. 2016;42:542–50.
[31] Panwar R, Tarvade S, Lanyon N, et al. Relative hypotension and adverse kidney-related outcomes among critically ill patients with shock. A multicenter, prospective cohort study. Am J Respir Crit Care Med. 2020;202:1407–18.
[32] Panwar R. Untreated relative hypotension measured as perfusion pressure deficit during management of shock and new-onset acute kidney injury-a literature review. Shock. 2018;49:497–507.
[33] Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest. 2017;151:1229–38.
[34] Shankar-Hari M, Phillips GS, Levy ML, et al. Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:775–87.
[35] Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020;324:642–50.
[36] Moskowitz A, Andersen LW, Huang DT, et al. Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. Crit Care. 2018;22:283.
[37] Marik PE, Hooper MH. Doctor-your septic patients have scurvy! Crit Care. 2018;22:23.
[38] Mallat J, Lemyze M, Thevenin D. Do not forget to give thiamine to your septic shock patient! J Thorac Dis. 2016;8:1062–6.
[39] Barabutis N, Khangoora V, Marik PE, Catravas JD. Hydrocortisone and ascorbic acid synergistically prevent and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction. Chest. 2017;152:954–62.
[40] Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S444–64.
[41] Yannopoulos D, Bartos JA, Aufderheide TP, et al. The evolving role of the cardiac catheterization laboratory in the management of patients with out-of-hospital cardiac arrest: a scientific statement from the American Heart Association. Circulation. 2019;139:e530–52.
[42] Yannopoulos D, Bartos JA, Reveendran G, et al. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single center, open-label, randomized controlled trial. Lancet. 2020;396:1807–16.