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Review

The critical care literature 2017

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ABSTRACT

An emergency physician (EP) is often the first health care provider to evaluate, resuscitate, and manage a critically ill patient. Between 2001 and 2009, the annual hours of critical care delivered in emergency departments (EDs) across the United States increased >200% [1]! This trend has persisted since then. In addition to seeing more critically ill patients, EPs are often tasked with providing critical care long beyond the initial resuscitation period. In fact, >33% of critically ill patients who are brought to an ED remain there for >6 h [1]. Longer ED boarding times for critically ill patients have been associated with a negative impact on inpatient morbidity and mortality [2]. During these crucial early hours of illness, detrimental pathophysiologic processes begin to take hold. It is during these early hours of illness where lives can be saved, or lost. Therefore, it is important for the EP to be knowledgeable about recent developments in critical care medicine. This review summarizes important articles published in 2017 pertaining to the resuscitation and care of select critically ill patients in the ED. We chose these articles based on our opinion of the importance of the study findings and their application to clinical care. The following topics are covered: sepsis, vasolidatory shock, cardiac arrest, post-cardiac arrest care, post-intubation sedation, and pulmonary embolism.

1. Introduction

An emergency physician (EP) is often the first health care provider to evaluate, resuscitate, and manage a critically ill patient. Between 2001 and 2009, the annual hours of critical care delivered in emergency departments (EDs) across the United States increased >200% [1]! This trend has persisted since then. In addition to seeing more critically ill patients, EPs are often tasked with providing critical care long beyond the initial resuscitation period. In fact, >33% of critically ill patients who are brought to an ED remain there for >6 h [1]. Longer ED boarding times for critically ill patients have been associated with a negative impact on inpatient morbidity and mortality [2]. During these crucial early hours of illness, detrimental pathophysiologic processes begin to take hold. It is during these early hours of illness where lives can be saved, or lost. Therefore, it is important for the EP to be knowledgeable about recent developments in critical care medicine. This review summarizes important articles published in 2017 pertaining to the resuscitation and care of select critically ill patients in the ED. We chose these articles based on our opinion of the importance of the study findings and their application to clinical care. The following topics are covered: sepsis, vasolidatory shock, cardiac arrest, post-cardiac arrest care, post-intubation sedation, and pulmonary embolism.

2. Sepsis

Freund Y, Lemachatti N, Krastinova E. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. JAMA 2017; 317(3): 301–8.

The definition of sepsis has changed. In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were published [3]. They replaced older definitions of sepsis and septic shock and eliminated the term “severe sepsis” [3]. In addition to redefining sepsis, the international task force proposed the use of a new Quick Sequential Organ Failure Assessment (qSOFA) score to identify non-intensive care unit patients at high risk of inpatient mortality. It was developed through analysis of several large hospital databases, searching for patients in whom infection was suspected. The qSOFA score ranges from 0 to 3 and comprises three variables: respiratory rate >21 breaths per minute, systolic blood pressure ≤100 mmHg, and altered mental status, defined as a Glasgow Coma Scale score <15. Each component of the qSOFA score is worth 1 point. Patients with a score of 2 or more have

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an inpatient mortality rate of at least 10%. Importantly, the qSOFA score has not been validated prospectively in the ED setting. Therefore, Freund and colleagues assessed the external validity of the Sepsis-3 criteria among patients presenting to the ED with suspected infection. They sought to compare the Sepsis-3 criteria with previous guidelines that use the systemic inflammatory response syndrome (SIRS) criteria and lactate level to identify patients with suspected infection.

The current study is a prospective, international, multicenter cohort study performed in 30 centers in Belgium, France, Spain, and Switzerland. The investigators enrolled consecutive adult patients who presented to the ED with suspected infection. Patients in whom infection was not confirmed, pregnant women, prisoners or patients in custody, low-acuity patients (localized infection without vital sign abnormalities), and those not admitted to the hospital were excluded. For those enrolled in the study, the EP collected the three components of the qSOFA score. Investigators also collected data, when available, to assess the severity of sepsis according to the previous definitions (i.e., SIRS criteria, lactate level) and components of the Sequential Organ Failure Assessment (SOFA) score. The primary endpoint of the current study was in-hospital mortality. Secondary endpoints included intensive care unit (ICU) admission, ICU length of stay >72 h, and the composite of death or ICU stay >72 h.

A total of 879 patients were included in the final analysis, 218 of whom had a qSOFA score ≥2. The overall in-hospital mortality rate for the cohort was 8%. Patients with a qSOFA score <2 had an in-hospital mortality rate of 3%, compared with patients who had a qSOFA score ≥2, who had an in-hospital mortality rate of 24% (absolute difference, 21%; 95% CI: 15%–26%). When investigators compared qSOFA, SOFA, and SIRS criteria for the prediction of in-hospital mortality, the areas under the receiver operating curves were as follows: qSOFA, 0.80 (95% CI: 0.74–0.85); SOFA, 0.77 (95% CI: 0.71–0.82); and SIRS, 0.65 (95% CI: 0.59–0.70). Overall, qSOFA was 70% sensitive and 79% specific for the prediction of in-hospital mortality, values greater than those for SOFA and SIRS. After adjusting for age and the site of infection, a qSOFA score ≥ 2 was associated with in-hospital mortality with a hazard ratio of 6.2 (95% CI: 3.8–10.3). There was no statistical benefit to the addition of lactate level to the qSOFA score.

Limitations of the study include the low numbers of patients who met the primary endpoint of in-hospital death, the significant number of records that were missing laboratory data needed to accurately calculate the SOFA score, and the exclusion of patients not admitted to the hospital. In addition, approximately 14% of patients were missing data required to calculate the qSOFA score. Notwithstanding these limitations, the study demonstrates that the qSOFA score had better prognostic accuracy for in-hospital mortality compared with the SIRS criteria and full SOFA score.

Importantly, there is no screening tool or test that rapidly identifies every ED patient with sepsis. Although the qSOFA score is simple and can be calculated easily, it does not diagnose patients with sepsis. Rather, compared with the conventional and commonly used SIRS criteria, it identifies patients at higher risk of in-hospital mortality. As ED decision makers determine which sepsis screening method to implement, they should consider the findings of this study, highlighting that qSOFA might have stronger prognostic accuracy for in-hospital mortality than the SIRS criteria.

Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017; 376: 2235–44.

Sepsis can present across a spectrum of severity that ranges from "simple" sepsis to septic shock with multiorgan failure. Depending on the severity of illness, sepsis mortality can be as high as 40% [3,4]. Early identification and resuscitation of patients with sepsis likely lower mortality and improve patient outcome. The tenets of ED sepsis resuscitation include the administration of appropriate antibiotics, aggressive fluid resuscitation, serial measurement of serum lactate values to assess perfusion, performance of appropriate body fluid cultures, and source control, when applicable. While early therapy is believed to improve outcomes, the time-to-therapy and its impact on survival remain debated. In addition, the components of sepsis resuscitation that most favorably impact outcome remain unknown. Seymour and colleagues investigated the timing of specific sepsis treatment bundles on risk-adjusted mortality rates in ED patients with sepsis and septic shock.

They conducted a retrospective analysis of hospital records in the New York State Department of Health database. Beginning in 2013, New York hospitals were required to implement sepsis protocols and report patient-level data for those with sepsis and septic shock. All protocols were required to include 3- and 6-hour bundles. Components of the 3-hour bundle were performance of blood culture before the administration of antibiotics, measurement of the serum lactate concentration, and administration of broad-spectrum antibiotics. Components of the 6-hour bundle were intravenous administration of a 30-ml/kg bolus of crystalloid fluid to patients with hypotension or a serum lactate concentration >4 mmol/L, initiation of vasopressor therapy for refractory hypotension, and remeasurement of the serum lactate concentration. Patients included in the study were older than 17 years of age, had severe sepsis or septic shock, and had care initiated in the ED within 6 h after arrival. Patients with advance directives that limited treatment, patients who declined enrollment, and patients whose 3-hour bundle was completed >12 h after initiation of the protocol were excluded. The primary outcome of the study was in-hospital mortality. The primary exposure was time to completion of the 3-hour bundle. The time to completion of the initial fluid bolus was measured only in patients who were hypotensive or had an initial serum lactate level ≥4.0 mmol/L.

A total of 49,331 ED patients from 149 hospitals were included in this study. Of these, 82.5% had the 3-hour bundle completed within 3 h. Among patients who had the 3-hour bundle completed, each hour of time to bundle completion was associated with a minimal increase in risk-adjusted, in-hospital mortality, with an odds ratio of 1.04 (95% CI: 1.02–1.05 [$p < 0.001$]). A longer time to the administration of antibiotics was associated with a similar increase in the hourly mortality rate, with an odds ratio of 1.04 (95% CI: 1.03–1.06 [$p < 0.001$]). For patients whose 3-hour bundle was completed between 3 and 12 h after presentation, the in-hospital mortality rate was higher, with an odds ratio of 1.14 (95% CI: 1.07–1.21 [$p < 0.001$]). Similarly, patients who received antibiotics between 3 and 12 h after presentation had an increase in mortality compared with those who received antibiotics within 3 h (odds ratio, 1.14; 95% CI: 1.06–1.22 [$p = 0.001$]). Interestingly, performance of blood cultures, measurement of lactate, and the time to completion of fluid therapy for applicable patients were not associated with in-hospital mortality.

This study has several limitations. Perhaps most importantly, it was not a randomized trial. Therefore, associations only between bundle completion and in-hospital mortality can be made. In addition, the authors did not assess the appropriateness of antibiotic therapy. In recent years, the appropriateness of antibiotic therapy has been shown to be an important determinant of sepsis mortality [5]. Finally, this study was performed using patients from a specific geographic region of the United States, so the results might not be generalizable to other locations.

Despite these limitations, this study makes an important contribution to the literature pertaining to ED sepsis care. Specifically, it highlights the importance of the early initiation of therapy for patients with sepsis or septic shock. Furthermore, it indicates that the administration of broad-spectrum antibiotics might be the most critical time-sensitive intervention to reduce sepsis-related mortality for ED patients. When designing and refining sepsis protocols, the EP should focus on the delivery of antibiotics as early as possible.

Leisman D, Huang V, Zhou Q, et al. Delayed second dose antibiotics for patients admitted from the emergency department with sepsis: prevalence, risk factors, and outcomes. Crit Care Med 2017; 45(6): 956–65.

As previously highlighted, the mortality rate among patients with sepsis and septic shock remains unacceptably high [6]. The early administration of appropriate antibiotics is one of the few time-sensitive interventions that can affect mortality [7,8]. While EPs are aware of the importance of administering the initial dose of broad-spectrum antibiotics to patients with sepsis, less is known about the second dose. Delayed administration of subsequent doses could negatively impact morbidity and mortality for ED patients, especially those who have long boarding times awaiting an inpatient bed. Leisman and associates sought to 1) quantify the frequency of delayed second-dose antibiotic administration in a sepsis or septic shock population, 2) identify risk factors for delays in care, and 3) conduct an exploratory analysis of in-hospital mortality, length of stay, need for mechanical ventilation, and ICU utilization associated with delays in the second dose of antibiotic therapy.

This retrospective cohort study was performed at a single, suburban, academic medical center in New York. Investigators used the hospital quality improvement database to identify and include all adult patients with sepsis and septic shock whose initial presentation was to the ED. The following patients were excluded: those who were younger than 18 years of age, had advance directives that precluded sepsis bundle application, declined interventions, did not receive the initial dose of antibiotics in the ED, died or were admitted to hospice before the second dose of antibiotics, or had antibiotic therapy discontinued before the second dose. The records of patients in the study were assessed for major delay in the second dose of antibiotic therapy, defined as 25% or more of the recommended dosing time interval. The primary outcome of the study was in-hospital mortality. Secondary outcomes were hospital length of stay, new mechanical ventilation after the second dose of antibiotics, and escalation of care to the ICU after initial admission. The Charlson Comorbidity Index (CCI) and qSOFA scores were calculated on all patients. Investigators also documented whether patients were already admitted and boarding in the ED.

A total of 828 patients were included in the study. Overall, 32.9% of them had a major delay in the second dose of antibiotics, with a median delay of 79% beyond the interval when the second dose was due. In fact, the more often an antibiotic needed to be dosed, the more likely it was to be delayed. For antibiotics with a recommended 6-hour dosing interval, 72% of second doses were delayed. For antibiotics with a recommended 8-hour dosing interval, 47% of second doses were delayed. Factors associated with a major delay in second doses of antibiotic included ED boarding (odds ratio, 2.67; 95% CI: 1.74–4.09 [$p < 0.001$]), initial 3-hour sepsis bundle compliance (odds ratio, 1.57; 05% CI 1.07–2.30 [$p = 0.020$]), and older age (odds ratio, 1.16; 95% CI: 1.01–1.34 [$p = 0.045$]). Forty-three percent of patients with a major second-dose delay were boarding in the ED, awaiting an inpatient bed assignment. After controlling for CCI, initial serum lactate value, and direct ICU admissions, a major delay in the second dose was found to be associated with an increased risk of in-hospital mortality (odds ratio 1.61; 95% CI: 1.01–2.57 [$p = 0.046$]) and an increased incidence of new mechanical ventilation (odds ratio 2.44; 95% CI: 1.27–4.69 [$p = 0.007$]).

Limitations of this study include its retrospective design, which precludes inference on causation, and the lack of information on the appropriateness of the chosen antibiotic, site of infection, and source control. Additional limitations include the fact that this was performed at a single center, thereby limiting generalizability, and the lack of data on vancomycin trough levels.

Though the results of the current study should be considered exploratory, the finding that one in three ED patients with sepsis experienced a delay in the second dose of antibiotics raises concern. This delay was associated with an increase in in-hospital mortality and need for mechanical ventilation. These findings highlight the importance of continued attention to sepsis care beyond the initial resuscitation bundles, especially in patients being boarded in the ED.

3. Vasodilatory shock

Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. N Engl J Med 2017; 377: 419–30.

Vasodilatory shock is the most common type of shock encountered by the EP and carries high rates of morbidity and mortality [9-11]. Patients with vasodilatory shock requiring high doses of vasopressor medications can have a 30-day mortality rate as high as 60% [12,13]. In vasodilatory shock, when intravenous fluid alone does not increase the mean arterial pressure (MAP) to goal, the EP initiates and titrates a vasopressor infusion. Currently, catecholamines (e.g., norepinephrine, epinephrine) and vasopressin are the two classes of vasopressor medications used in the treatment of vasodilatory shock [14]. In addition to the endogenous release of catecholamines, the body also activates the renin-angiotensin-aldosterone axis system (RAAS) during periods of hypotension and hypoperfusion. Angiotensin II, a hormone of the RAAS, has been shown to be a potent vasoconstrictor in various types of circulatory shock [15,16]. A recent pilot study by the authors of the article being summarized here demonstrated that angiotensin II increased MAP when administered to patients with vasodilatory shock who were receiving a catecholamine infusion [17]. Given the results of that pilot study, the authors sought to determine whether the addition of angiotensin II to existing vasopressors would improve blood pressure in patients with catecholamine-resistant vasodilatory shock.

The ATHOS-3 trial was an international, prospective, double-blind, randomized, placebo-controlled trial. Patients included in the study were at least 18 years of age and had persistent vasodilatory shock despite adequate intravenous fluid resuscitation (at least 25 ml/kg over the preceding 24 h) and administration of high-dose vasopressor medications. The authors defined "persistent vasodilatory shock" as a MAP of 55 to 70 mmHg that was not attributable to decreased cardiac output. "High-dose vasopressor infusions" were defined as >0.2 μg/kg of norepinephrine or an equivalent dose of another vasopressor medication. Patients were required to have received the high-dose vasopressor infusion for at least 6 h but not >48 h prior to inclusion. Patients with an acute coronary syndrome, burns covering >20% of total body-surface area, hepatic failure, mesenteric ischemia, active bleeding, neutropenia, bronchospasm, or abdominal aortic aneurysm and those receiving high-dose corticosteroid therapy or veno-arterial extracorporeal membrane oxygenation were excluded.

Once enrolled, patients were randomized in a 1:1 ratio to receive either angiotensin II or placebo. Those randomized to angiotensin II received an infusion at 20 ng/kg/min, which was then titrated during the first 3 h to a target MAP of at least 75 mmHg. During the first 3 h, doses of standard vasopressors were held constant. Beyond that point, angiotensin II or placebo, along with standard vasopressors, could be titrated to maintain a MAP between 65 and 75 mmHg. With the exception of specified personnel who prepared the angiotensin II or placebo infusion, all parties were blinded to treatment assignments. The primary outcome of the study was the achievement of a MAP of 75 mmHg or greater or an increase of at least 10 mmHg in MAP from baseline without an increase in the dose of standard vasopressors. Secondary outcomes were the mean change in cardiovascular or total SOFA score at 48 h, the mean change in norepinephrine or equivalent vasopressor dose, adverse events, and all-cause mortality at 7 and 28 days.

A total of 321 patients were included in the ATHOS-3 trial: 164 of them received angiotensin II and 158 received placebo. Not surprisingly, sepsis was the most common cause of vasodilatory shock, occurring in 81% of patients. In terms of primary outcome, more patients in the angiotensin II group reached a MAP of at least 75 mmHg or an increase of at least 10 mmHg above baseline compared with patients in the placebo group (69.9% vs. 23.4% [$p < 0.001$]; odds ratio, 7.95; 95% CI: 4.76–13.3). In addition, more patients in the angiotensin II group had a significantly greater increase in MAP during the first 3 h compared with patients in the placebo group (12.5 vs. 2.9 mmHg [$p < 0.001$]).

For patients in the angiotensin II group, the mean dose of standard vasopressors was routinely less than the mean dose of standard vasopressors for patients in the placebo group. With respect to secondary outcomes, patients who received angiotensin II had a greater improvement in the cardiovascular SOFA score and a larger decrease in norepinephrine dose than those who received placebo. The adverse event rate was similar between the groups and there was no statistical difference in all-cause mortality at 7 or 28 days.

The ATHOS-3 trial has several important limitations. Perhaps most importantly, it was a phase 3 manufacturer-sponsored trial. In fact, one of the study's authors is the chief medical officer of the pharmaceutical manufacturer. An additional limitation is the selection of MAP as the primary endpoint. While important, it can be argued that a MAP response within 3 h after drug infusion is not a patient-centered outcome (e.g., death) Unfortunately, the study was not powered to detect a mortality difference between angiotensin II and placebo. The study was also not powered to detect differences in ICU length of stay or ICU mortality. Furthermore, the rapid and robust response in blood pressure for many patients receiving angiotensin II likely led to the unintended unblinding of treating clinicians. Finally, it is interesting that the Food and Drug Administration's label for angiotensin II states that there is an increase in venous and arterial thromboembolic events with the administration of angiotensin II based on this trial, yet this information is not presented in the original study materials [18,19].

Regardless of their location or practice setting, EPs manage patients with vasodilatory shock on a daily basis. For patients who remain hypotensive despite receiving an appropriate amount of intravenous fluid, a vasopressor administration should be initiated to achieve an acceptable MAP. In the majority of patients, the initial vasopressor of choice is norepinephrine. For patients who remain refractory to norepinephrine and additional agents (epinephrine, vasopressin), angiotensin II *might* be beneficial. Though further study is clearly needed to demonstrate a meaningful patient-centered outcome, the positive results of the current trial will undoubtedly result in increased use of angiotensin II. The results of the ATHOS-3 trial are important for the EP to know for the treatment of vasodilatory shock.

4. Cardiac arrest

Anderson LW, Granfeldt A, Callaway CW, et al. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. JAMA 2017; 317(5): 494–506.

Despite advances in cardiopulmonary resuscitation, morbidity and mortality for patients who suffer sudden cardiac arrest remains high. Although there are many potential therapeutic interventions for patients with cardiac arrest, significant uncertainty remains regarding the benefit of select interventions (e.g., vasopressors, antiarrhythmic medications, advanced airway placement). In 2010, the American Heart Association (AHA) de-emphasized the management of oxygenation and ventilation using an endotracheal device [20]. It its latest guidelines, the AHA did not provide a clear recommendation for the optimal strategy for airway management (e.g., bag-valve-mask, advanced airway device) for patients with cardiac arrest [21]. Although recent literature demonstrated harm when advanced airway devices are used to manage out-of-hospital cardiac arrest, there is very little evidence on the use of these devices during the management of in-hospital cardiac arrest [22-24]. Anderson and associates sought to investigate whether tracheal intubation arrest would lead to worse outcomes following in-hospital cardiac arrest.

The current study is a retrospective review of patients included in the AHA-sponsored Get-With-The-Guidelines Resuscitation Registry (GWTG-R), a prospective database documenting in-hospital cardiac arrest at US hospitals. Patients included in the study were 18 years of age or older, had an in-hospital cardiac arrest, and received chest compressions. Patients were excluded if they had an advanced airway in place at the time of their cardiac arrest, if they were visitors or employees of the hospital, or if data regarding their cardiac arrest management (e.g., the timing of intubation) were missing. The authors defined cardiac arrest as a clinical state of pulselessness requiring chest compressions or defibrillation and prompting a hospital-wide or unit-based emergency response. Tracheal intubation was defined as placement of an orotracheal endotracheal tube or a tracheostomy tube. The primary outcome of the study was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation (ROSC) and favorable functional outcome at hospital discharge, as measured by the Cerebral Performance Category score.

A total of 108,079 patients from 688 US hospitals were included in the analysis. Of these patients, 76,579 were intubated, 71,615 of them within the first 15 min after cardiac arrest. Overall, 22.4% of patients survived to hospital discharge. A significantly lower rate of survival to discharge was observed in patients who were intubated during the first 15 min compared with those who were not intubated (17% vs. 33%; relative risk, 0.58; 95% CI: 0.57–0.59 [$p < 0.001$]). In terms of secondary outcomes, 62.5% of patients achieved ROSC. As for survival, patients intubated within the first 15 min had a lower rate of ROSC than those who were not intubated (59% vs. 69%; relative risk, 0.75; 95% CI: 0.73–0.76 [$p < 0.001$]). Neurologic outcome for survivors was also lower in those intubated within the first 15 min compared with those not intubated (11.2% vs. 25.7%; relative risk, 0.55; 95% CI: 0.54–0.56 [$p < 0.001$]). Based on a planned a priori subgroup analysis, the authors reported a lower rate of survival among patients with a shockable rhythm who were intubated compared with those who had an initial nonshockable rhythm and were intubated.

Limitations of the current study include its retrospective study design and limitations of the information contained within the GWTG-R. The registry does not capture information about the experience of the health care providers who manage resuscitation attempts, the cause of cardiac arrest, the quality of chest compressions, or the indication for intubation.

Despite these limitations, the study by Anderson et al. is the largest one to date of in-hospital cardiac arrest patients and demonstrates an association between tracheal intubation and worse patient outcomes. As stated by the authors, there are several possible reasons for this association: interruption of high-quality chest compressions during endotracheal intubation, excessive ventilation once the endotracheal tube is placed, unrecognized esophageal intubation leading to poor oxygenation and ventilation, and interruption of defibrillation to place the endotracheal tube. EPs are often called upon to respond to inpatient cardiac arrests, especially in critical access hospitals. Therefore, it is important for them to know this study and to be aware of the association of lower survival rates with early endotracheal intubation in the management of patients who experience in-hospital cardiac arrest.

Huis In't Veld MA, Allison MG, Bostick DS, et al. Ultrasound use during cardiopulmonary resuscitation is associated with delays in chest compressions. Resuscitation 2017; 119: 95–8.

Point-of-care ultrasound (POCUS) can be a helpful diagnostic and prognostic tool in the management of patients in cardiac arrest. It can identify potentially reversible causes of cardiac arrest (e.g., pericardial tamponade, pneumothorax) and focus treatment (e.g., thrombolytic administration for massive pulmonary embolism) [25-28]. An important tenet of cardiac arrest resuscitation is limiting interruptions in high-quality CPR. Current guidelines recommend that interruptions in CPR (e.g., for rhythm analysis) be no longer than 10 s [29]. Prolonged pauses in CPR lead to reduced coronary perfusion, decreased rates of ROSC, and decreased rates of survival to hospital discharge [29]. The impact of POCUS on interruptions in CPR is currently unknown. Huis In't Veld and associates sought to evaluate the impact of POCUS on the duration of pulse checks in patients with cardiac arrest.

This prospective cohort study was conducted in the adult emergency department at a single, urban, academic, tertiary care medical center. Patients included in the study were 18 years of age or older and either presented to the ED in cardiac arrest or experienced cardiac arrest

during their ED course. In addition, these patients had to be placed in one of three resuscitation rooms with continuous video monitoring equipment. Patients younger than 18 years of age, those who did not have a documented pulse check, and those not placed in the designated resuscitation rooms were excluded. For enrolled patients, investigators reviewed the cardiac arrest videos and recorded whether POCUS was used, the duration of pulse checks, and whether a procedure was performed (e.g., central line placement, endotracheal intubation). A pause was defined as the time compressions ceased until the time they were resumed. The primary outcome of the study was the duration of pulse checks with the use of POCUS.

Twenty-three patients were enrolled in the study and they had a total of 123 pulse checks. The mean duration of pulse checks without POCUS was 13.0 s (95% CI: 12–15) compared with 21.0 s when POCUS was performed (95% CI: 18–24). The use of POCUS significantly increased the duration of pulse checks by 8.4 s (95% CI: 6.7–10.0 [$p < 0.001$]). No findings on POCUS lad to the performance of a procedure (e.g., pericardiocentesis) or change in management. Age, body mass index (BMI), and the performance of a procedure (e.g., endotracheal intubation) were not associated with a statistically significant increase in the duration of pulse checks.

Important limitations of this study include its small sample size, the performance at a single center, and the use of transthoracic ultrasound images in contrast to transesophageal ultrasound. Perhaps most importantly, the authors were not able to assess the impact of prolonged pulse checks associated with POCUS on the mortality rate.

POCUS is a powerful diagnostic tool for the EP. This study is the first to demonstrate a potential adverse effect of POCUS when used during cardiac arrest resuscitation. Although its sample size is small, the study highlights the delicate balance between performing a diagnostic procedure and ensuring the delivery of high-quality CPR. Additional studies are needed to determine the impact of prolonged pulse checks on the mortality rate. It is important for the EP to be familiar with the results of this study and to continue limiting interruptions in high-quality CPR.

5. Post-cardiac arrest care

Moler FW, Silverstein FS, Holubkov R, et al. Therapeutic hypothermia after in-hospital cardiac arrest in children. N Engl J Med 2017; 376: 318–29.

Fever is common in the post-cardiac arrest patient and is associated with adverse patient outcome [30]. Therapeutic hypothermia, now referred to as targeted temperature management (TTM), is currently recommended for comatose adult and pediatric patients with out-of-hospital cardiac arrest [31,32]. While TTM is given a Class IIa recommendation in current guidelines, it is important to note that the evidence supporting its use in children is limited and based largely on extrapolations from the adult post-cardiac arrest literature [31]. A recent prospective, randomized trial compared hypothermia (32 to 34C) with normothermia (36 to 37.5) in children between the ages of 2 days to 18 years and found no difference in survival or neurologic outcome [33]. In contrast, Lin and colleagues demonstrated a modest improvement in survival in pediatric patients treated with TTM [34]. As a result of the current controversies surrounding the use of TTM in children sustaining out-of-hospital and in-hospital cardiac arrest, Moler and colleagues sought to compare the efficacy of therapeutic hypothermia with therapeutic normothermia in comatose children and adolescents resuscitated from in-hospital cardiac arrest.

The randomized THAPCA-IH trial was conducted at 37 children's hospitals in the United States, Canada, and the United Kingdom. Patients included in the current study were children and adolescents between the ages of 48 h and 18 years, who received CPR for at least 2 min during an in-hospital cardiac arrest and who remained ventilator dependent after ROSC. Patients were excluded if they had a score of 5 or 6 on the Glasgow Coma Scale motor-response subscale, were unable to undergo randomization within 6 h following ROSC, had active or refractory severe bleeding, or had a preexisting illness associated with life expectancy <12 months. Patients included in the study were randomized in a 1:1 ratio to receive either therapeutic hypothermia or therapeutic normothermia. The target temperature for those receiving therapeutic hypothermia was 33C and 36.8C for those randomized to therapeutic normothermia. TTM was maintained for 120 h in each group. The primary outcome of the study was survival with favorable neurobehavioral outcome at 12 months. Favorable neurologic outcome was assessed using the Vineland Adaptive Behavior Scales. Secondary outcomes were 12-month survival and change in neurobehavioral function.

Though 746 patients were eligible for enrollment, only 329 patients underwent randomization (166 patients to the therapeutic hypothermia group and 163 to the therapeutic normothermia group). Importantly, the trial was terminated early due to futility. An interim analysis of efficacy revealed no difference in the primary outcome of favorable neurologic outcome at 12 months: 36% in the therapeutic hypothermia group and 39% in the therapeutic normothermia group (relative risk, 0.92; 95% CI: 0.67–1.27 [$p = 0.63$]). In addition, there were no significant differences in the secondary outcomes of 12-month survival or change in neurobehavioral function at 12 months. Finally, there were no differences between the two groups in the incidence of arrhythmias or infection within 7 days following randomization.

The primary limitation of the THAPCA-IH study is that the trial was terminated before reaching its target enrollment (558 patients). Nonetheless, it is unlikely that the results would demonstrate any benefit had the authors been able to achieve their target enrollment number. An additional limitation of this study is that it took a relatively long time to achieve target temperature in those receiving therapeutic hypothermia (median, 6 h). When comparing this trial with evaluations of the use of TH in adults, it is important to note that very few patients in the current trial had a shockable rhythm. Finally, the duration of hypothermia in the current trial (120h) is significantly longer than the duration of hypothermia used in adults (24 to 48 h).

Significant uncertainty remains on the use of TTM for pediatric patients who experience out-of-hospital or in-hospital cardiac arrest. Although the current study evaluated the use of TTM in an in-hospital patient population, it contributes significantly to the pediatric post-arrest literature. Based on the results of this study and its cohort (THAPCA-OH), therapeutic hypothermia cannot be recommended for the pediatric patient with ROSC following cardiac arrest.

6. Post-intubation sedation

Stephens RJ, Ablordeppey E, Drewry AM, et al. Analgosedation practices and the impact of sedation depth on clinical outcomes among patients requiring mechanical ventilation in the ED: a cohort study. Chest 2017; 152(5): 963–71.

The administration of analgesic and sedative medications is a critical component in the care of intubated and ventilated patients. In fact, their use is known to affect the duration of mechanical ventilation, the length of ICU stay, and possibly the mortality rate [35,36]. Despite the growing body of literature highlighting potential adverse outcomes of inappropriate doses of these medications in ICU patients, very little literature exists on analgesic and sedation practices in ventilated ED patients. Stephens and colleagues sought to characterize modern ED analgosedation practices as well as examine the relationship between ED sedation depth and patient mortality.

This secondary analysis of a prospective, observational cohort study was performed at a single, academic, tertiary medical center. Patients were included if they were 18 years of age or older and mechanically ventilated in the ED through an endotracheal tube. Patients were excluded if they were chronically ventilated, had a tracheostomy, died or were taken off the ventilator within 24 h, were transferred to another hospital, or had neurologic injury or cardiac arrest as the reason for

intubation and mechanical ventilation. The authors assessed sedation depth using the Richmond Agitation-Sedation Scale (RASS), a well validated tool that assesses the degree of sedation and ranges from −5 (unarousable) to +4 (combative). Deep sedation was defined in the current study as a RASS score of −3 to −5. The primary outcome was in-hospital mortality, with secondary outcomes of ventilator-free days, hospital-free days, and ICU-free days. The authors also planned to analyze patients intubated and ventilated for trauma and medical conditions as well as those who received no sedation in the ED.

A total of 414 patients were included in the final analysis of this study. The majority of patients underwent rapid sequence intubation with ketamine or etomidate as a sedative agent and succinylcholine or rocuronium as the paralytic agent. In terms of sedation practices, approximately 85% of patients received fentanyl, 61% received midazolam, 47% received propofol, and 16% received ketamine. Importantly, 14% of patients received no analgesic medication and 15% received no sedative medication in the ED. Sixty patients (14.5%) died while in hospital. The ED RASS score was significantly deeper in patients who died compared with those who survived to hospital discharge (−4 vs. −3 [$p < 0.001$]). In fact, deeper ED RASS scores were associated with increased mortality, even when the authors adjusted for potential confounders (adjusted odds ratio, 0.77; 95% CI: 0.54–0.94). Secondary outcomes of ICU-free, ventilator-free, and hospital-free days were longer in those who received deeper levels of sedation. Finally, deeper ED sedation remained associated with higher mortality regardless of whether the patient was intubated and ventilated for a trauma or medical condition.

This study has several limitations. Notably, it is a single-site study, so the results might not be generalizable to other institutions or practice settings. In addition, the authors reported that the depth of sedation was recorded inconsistently. When necessary, they used the first ICU RASS score as a surrogate of ED sedation depth. Deep sedation might simply be a marker for increased illness severity, that is, it might occur more often in critically ill patients despite the administration of medications. Finally, and as the authors point out, patient-level or medication-level variables could have been in play but not accounted for in their analyses.

Despite these limitations, this study provides important information about sedation practices in ventilated ED patients. Many EPs recognize the risks of inadequate analgesia and sedation, but they might not appreciate that overly aggressive sedation could cause patient harm. It is critical to administer appropriate doses of sedative medications and closely monitor the depth of sedation in intubated ED patients.

7. Pulmonary embolism

Konstantinides SV, Vicaut E, Danays T, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol 2017; 69: 1536–44.

Emergency physicians routinely diagnose patients with acute pulmonary embolism (PE) and initiate therapy. Thrombolytic therapy is recommended as a Class 2c intervention for patients with massive PE and hypotension [37]. Massive PE is an infrequent diagnosis in the ED. ED patients are more often diagnosed with an intermediate-risk (a.k.a submassive) PE. Patients with intermediate-risk PE have evidence of acute right-heart strain (i.e., elevated troponin, elevated BNP, right ventricular dilation) with normal blood pressure measurements. The use of thrombolytic therapy in patients with intermediate-risk PE remains controversial. In the recent PEITHO trial, patients with intermediate-risk PE who received the thrombolytic medication tenecteplase had a lower 7-day all-cause mortality rate and less hemodynamic decompensation than patients who received placebo [38]. In addition to the controversy regarding short-term benefit of thrombolytic therapy in intermediate-risk PE, there is also debate as to whether this treatment reduces common long-term sequelae of PE (e.g., pulmonary hypertension, right heart failure). Konstantinides and associates sought to investigate the long-term prognosis of patients with intermediate-risk PE and the effect of thrombolytic treatment on their persistent symptoms or late complications.

This was a planned, long-term follow-up study of patients from 28 sites included in the original PEITHO trial, a multicenter, double-blind, placebo-controlled randomized study that enrolled 1006 patients with PE and right ventricular dysfunction confirmed by echocardiogram or elevated troponin biomarkers. Patients in the current study had hemodynamic, clinical, and vital status recorded 24 months or more after randomization in the PEITHO trial. This information was obtained during a follow-up appointment at a participating site. When possible, echocardiographic assessment was also performed during the follow–up visit. Outcomes included long-term mortality rate, the presence of persistent symptoms, and late complications (residual pulmonary hypertension or right ventricular dysfunction, chronic thromboembolic pulmonary hypertension, and New York Heart Association Class III or IV heart failure).

Of the 1006 patients in the PEITHO trial, 709 were included in the current analysis. The overall mortality rate for patients who received tenecteplase was 20.3% compared with 18.0% among patients who received placebo ($p = 0.43$). The most common persistent symptom was dyspnea, which occurred in 36% of patients who received tenecteplase and 30.1% of patients who received placebo ($p = 0.23$). There were no statistical differences in the incidence of residual pulmonary hypertension, persistent right ventricular dysfunction, New York Heart Failure Association Class III or IV heart failure, or chronic thromboembolic pulmonary hypertension.

Several limitations should be noted. Patients from only 28 of the 76 sites in the PEITHO trial were enrolled in the follow-up analysis, which is two-thirds of the original study population, raising the possibility of selection bias. Furthermore, not all survivors underwent clinical examination or echocardiographic assessment. As a result, the current study cannot be used to definitively determine the prevalence of persistent symptoms or pulmonary hypertension in patients with intermediate-risk PE. Finally, the overall low incidence of chronic thromboembolic pulmonary hypertension limits the ability of the current study to determine if thrombolytic therapy decreases the incidence of this complication.

The ED treatment of patients with acute PE continues to evolve. Thrombolytic therapy can be used in the ED to treat patients with massive PE and hypotension. Many EPs believe that the use of thrombolytics in patients with intermediate-risk could be beneficial in decreasing the disabling long-term symptoms and complications of pulmonary hypertension. The results of the current study are important and demonstrate that the use of thrombolytic therapy in this patient population did not affect long-term mortality or reduce the incidence of dyspnea, persistent right ventricular dysfunction, or pulmonary hypertension.

8. Summary

The 2017 medical literature provided numerous pearls for EPs in their care of select critically ill ED patients. For patients with sepsis, qSOFA appears better than the traditional SIRS criteria in identifying patients at higher risk of in-hospital mortality. In addition, it is critical to focus on the early administration of appropriate antibiotics as well as the second dose of antibiotics for septic patients boarding in the ED. For patients with vasodilatory shock that is resistant to escalating doses of vasopressors, angiotensin II may be beneficial in improving the MAP. When the EP responds to an inpatient cardiac arrest, he or she should be cautious about early endotracheal intubation, because it may be associated with worse patient outcome. When treating the patient with out-of-hospital cardiac arrest, it is vital to limit interruptions in high-quality CPR. When using POCUS during cardiac arrest resuscitation, the EP should pay attention to the duration of the examination and its potential impact on pulse check duration. In the pediatric patient with ROSC following inpatient cardiac arrest, the use of therapeutic hypothermia does not seem to improve outcomes. Post-intubation analgesia and sedation remain vital components of the ED care of ventilated

patients. Oversedation is common in the ED and might be associated with worse outcomes. Finally, the use of thrombolytic therapy in patients with intermediate-risk PE did not reduce the incidence of long-term symptoms, right ventricular dysfunction, or pulmonary hypertension.

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Conflict of interest

The authors do not have any financial conflicts of interest.

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