AHC Media

Critical Care [ALERT]

Vol. 24, Issue 6, September 2016
AHCMedia.com

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Post-cardiac Arrest Targeted Temperature Management

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Dr. Radigan reports no financial relationships relevant to this field of study.

In 2015 alone, 326,200 patients experienced emergency medical services-assessed out-of-hospital cardiac arrest (OHCA), and 209,000 patients were treated for in-hospital cardiac arrest (IHCA).[1] Neurologic injury is the major cause of morbidity and mortality after cardiac arrest. It represents the cause of death in two-thirds of OHCA patients and one-fourth of IHCA patients.[2] Advances in post-cardiac arrest management, such as therapeutic hypothermia, have improved both neurological outcomes and mortality significantly.[3,4] One of the major advances that has improved neurological outcomes after cardiac arrest is the use of targeted temperature management (TTM).

Damage from cerebral anoxia is an extremely complicated process with many stages of injury. Within minutes of the anoxic insult, adenosine triphosphate and glucose are depleted, leading to mitochondrial damage, loss of calcium hemostasis, and eventual cellular necrosis and apoptosis.[5] Following reperfusion of the brain, anoxic injury is mitigated, but re-oxygenation promotes further development of reactive oxygen species and activates other inflammatory pathways, leading to cellular damage and death that may persist over hours to days after return of spontaneous circulation (ROSC). Hypothermia mitigates the post-cardiac arrest inflammatory cascade and aborts activated programmed cell death pathways. This subsequently prevents further damage, including intracranial hypertension and brain edema.

POST-CARDIAC ARREST CARE

Immediately after ROSC, identify and treat the precipitating cause of the arrest and prevent recurrent arrest. Identify acute coronary syndrome (ACS) immediately and treat it with emergency coronary angiography when indicated. Treat hypotension aggressively to maintain cerebral perfusion.[6] Optimize mechanical ventilation to minimize lung injury

Financial Disclosure: *Critical Care Alert*'s Physician Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Executive Editor Leslie Coplin, and Associate Managing Editor Jonathan Springston report no financial relationships relevant to this field of study.

Critical Care [ALERT]
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Critical Care Alert, (ISSN 1067-9502) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

GST Registration Number: R128870672.
POSTMASTER: Send address changes to *Critical Care Alert*, P.O. Box 550669, Atlanta, GA 30355.

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and ensure appropriate ventilation and oxygenation, thereby reducing the risk of multi-organ injury. Conduct a thorough neurological, with special attention to focal deficit and responsiveness. Recognize organ dysfunction and implement appropriate support immediately.

EVIDENCE FOR TARGETED TEMPERATURE MANAGEMENT

Although hypothermia as a medical intervention dates back to the time of Hippocrates, it has been difficult to study hypothermia after cardiac arrest, as most trials are limited by small numbers of participants. Recently, Arrich et al published a review of six randomized, controlled trials and found that 437 of the participants who underwent conventional cooling were more likely to reach a favorable neurological outcome (relative risk [RR], 1.94; 95% confidence interval [CI], 1.18-3.21) with a 30% survival benefit (RR, 1.32; 95% CI, 1.10-1.65).[7] Although there were no serious side effects, TTM was associated with an increased risk of pneumonia (RR, 1.15; 95% CI, 1.02-1.30) and hypokalemia (RR, 1.38; 95% CI, 1.03-1.84) in two trials. Despite insufficient evidence to show the effects of therapeutic hypothermia on the specific patient populations that included IHCA, asystole, or non-cardiac causes of arrest, based on the available data, researchers otherwise supported conventional cooling methods that induce mild therapeutic hypothermia to improve neurological outcomes after cardiac arrest.

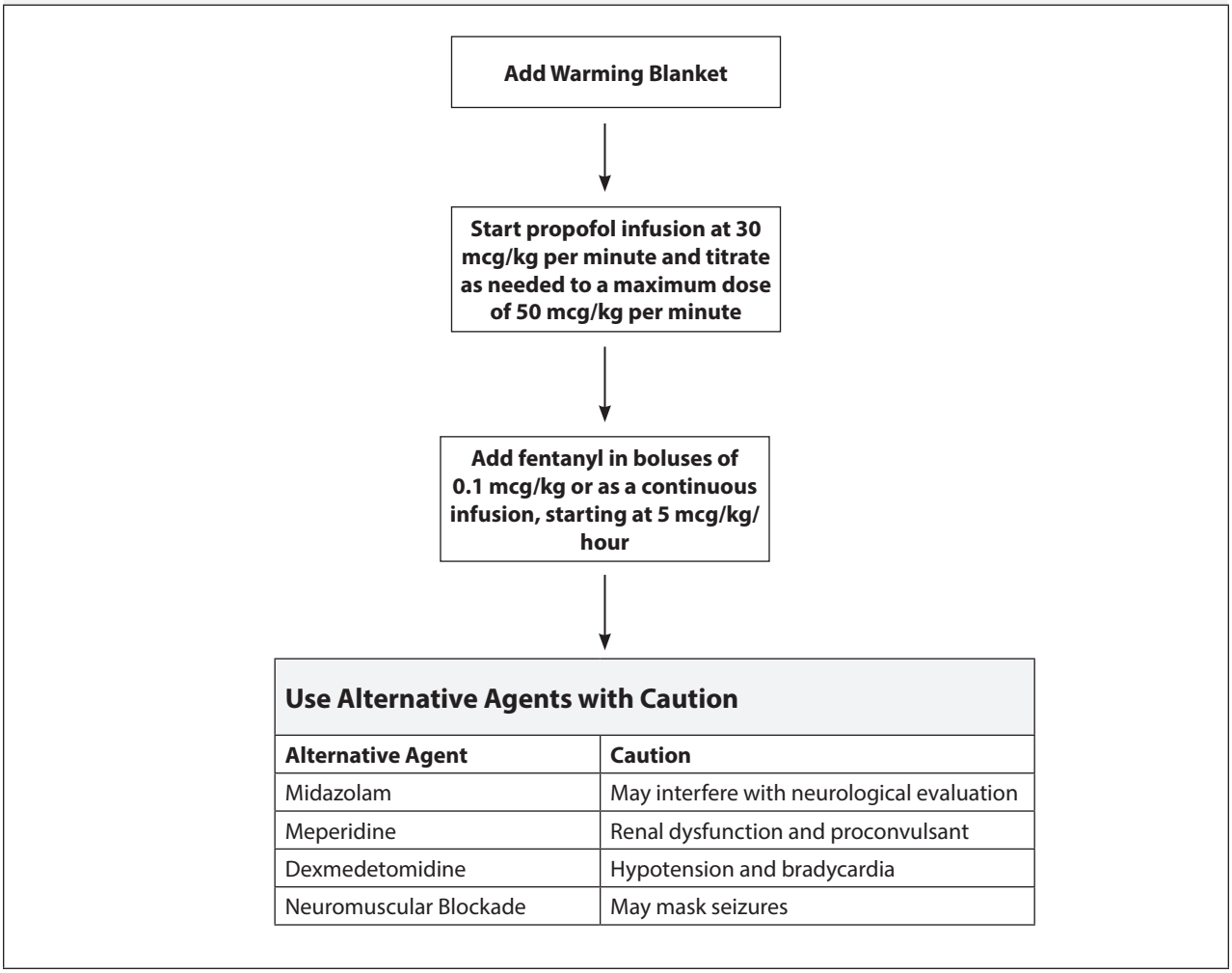
For patients presenting with OHCA and non-shockable rhythms, no randomized, clinical trials are available, and three observational studies found no difference in neurological outcome at hospital discharge for patients who underwent induced hypothermia.[8-10] Although Mader et al reported an increase in poor neurological outcomes at hospital discharge among OHCA survivors who had a non-shockable first documented rhythm, the analysis was questioned, as there was a lack of information on whether patients were eligible for hypothermia.[11] Furthermore, another study found that patients who underwent induced hypothermia were found to experience reduced mortality at six months.[9] For patients with IHCA, no randomized data are available, and one observational study found no benefit to hypothermia. Again, the results were confounded by a variety of issues, including lack of information on whether patients were appropriate candidates for hypothermia.[12] Although data on IHCA and OHCA with non-shockable rhythms may never be conclusive, Nielsen et al questioned previously established goal temperature guidelines and found no significant difference in mortality or poor neurological outcomes when comparing a targeted temperature of 33°C to 36°C in unconscious survivors presenting with OHCA and ROSC.[13] This new temperature target range is the reason the term "therapeutic hypothermia" was changed to "targeted temperature management."

AMERICAN HEART ASSOCIATION 2015 RECOMMENDATIONS

In reviewing all available studies, the 2015 American Heart Association (AHA) guidelines recommend that all comatose (i.e., lacking meaningful response to verbal commands) adult patients with ROSC after cardiac arrest should be started on TTM with a target temperature between 32°C and 36°C maintained for at least 24 hours.[6] Compared to the 2015 International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force guidelines and previous AHA guidelines, the 2015 AHA guidelines strongly push for initiating TTM even in adults experiencing cardiac arrest due to non-shockable rhythms and for adults who suffered from IHCA. By way of comparison, the ILCOR guidelines recommend TTM for adults with OHCA with initial shockable rhythms and suggest TTM for adults with OHCA with an initial non-shockable rhythm and for adults with IHCA with any initial rhythm.[14]

The AHA decided to advocate stronger recommendations based on recent clinical trials enrolling adults who developed all cardiac rhythms; it found that the evidence for adverse events was rare, that there was high neurologic morbidity and mortality associated with ROSC after cardiac arrest, and that a significant amount of data found that temperature was a significant variable for recovery after cardiac arrest. The AHA advocated stronger recommendations with the knowledge that there is

Figure 1. Protocol for the Treatment of Shivering



Use Alternative Agents with Caution

Alternative Agent	Caution
Midazolam	May interfere with neurological evaluation
Meperidine	Renal dysfunction and proconvulsant
Dexmedetomidine	Hypotension and bradycardia
Neuromuscular Blockade	May mask seizures

no significant difference in mortality or poor neurological outcomes when comparing a targeted temperature of 33°C to 36°C. Higher temperatures may be recommended for patients at higher risk of complications (e.g., bleeding, hypotension with uncontrolled infection) and lower temperatures for patients who have clinical features that may be worsened at higher temperatures (e.g., seizures, cerebral edema). Regardless, it is prudent that individual hospitals formulate a formal protocol that includes a consensus on specific inclusion and exclusion criteria (e.g., active bleeding, major head trauma, active do not resuscitate status, etc.) for initiation of TTM for that particular institution.

INITIATION OF TARGETED TEMPERATURE MANAGEMENT

Clinicians usually perform TTM in four different stages: initiation, maintenance, re-warming, and return to normothermia. Initiate control of the patient's temperature as soon as possible with a target temperature of 32°C to 36°C for 24 hours, followed by gradual re-warming (0.25°C/hour).[7] There are multiple strategies to induce therapeutic hypothermia, including ice bags, cold saline infusion using a pressure bag, cooling blankets, and temperature-regulated surface and endovascular devices that circulate cold water. Although the latter allows for easier temperature control, the particular device used depends on the institution. Regardless of the tactics, monitor patients using two temperature assessment methods. Place a feedback mechanism on the cooling device to actively control the patient's temperature. Ideally, one should measure using central venous temperature, but other options include esophageal, bladder, or rectal probes.[15] However, urine output that falls below 0.5 mL/kg per hour compromises the accuracy of bladder temperature. It also is important to note that rectal measurements may misrepresent core temperature by as much as 1.5°C. In general, do not use axillary and tympanic measurements. Re-warm the patient gradually, with a recommended incremental increase in temperature by 0.2°C to 0.25°C per hour.[13] If the patient is re-warmed faster than 0.5°C per hour, complications can occur and may include

Table 1. Clinical Findings Associated with Poor Neurologic Outcomes

- Absence of pupillary reflex to light 72 hours after cardiac arrest
- Absence of the N20 somatosensory evoked potential cortical wave 24-72 hours after cardiac arrest
- Persistent burst suppression or intractable staus epilepticus on electroencephalogram
- Persistent absence of electroencephalogram reactivity to external stimuli 72 hours post-arrest, especially in the setting of status epilepticus
- Extensive restriction of diffusion on brain MRI more than 48 hours after cardiac arrest
- Significant reduction of the gray-white ratio on brain CT within two hours of cardiac arrest
- Status myoclonus 72 hours after cardiac arrest
- Persistently elevated neuron-specific enolase 72 hours after cardiac arrest

*Adapted from 2015 AHA guidelines

electrolyte abnormalities, cerebral edema, and seizures. Since fever post-TTM is associated with worse outcomes, actively prevent fever in comatose patients after TTM.[6]

SEDATION AND SUPPRESSION OF SHIVERING

Shivering is the body's natural mechanism to re-warm the body. Actively suppress shivering during TTM. Typically, shivering develops between 35°C and 37°C. Minimize shivering by raising cutaneous temperatures with warming blankets. Magnesium sulfate also may raise the shivering threshold. Some institutions administer an initial 4 g bolus to patients undergoing TTM. Administer a low-dose sedative and an analgesic agent, usually propofol and fentanyl, to all patients receiving TTM (*see Figure 1*). Generally, agents with the shortest half-life are preferred since frequent neurological assessment is required. It is important to keep in mind that hypothermia reduces clearance of most sedatives, analgesics, and neuromuscular blockade agents (NMBAs).

CARE OF AND COMPLICATIONS IN POST-CARDIAC ARREST PATIENTS

Clinicians in the ICU always must be aware of how TTM can complicate the clinical care of the patient. Hypothermia is known to affect hemodynamics in several ways, including the development of tachycardia and hypertension at the start of TTM. Once the patient is effectively cooled, bradycardia, PR prolongation, QT prolongation, and junctional or ventricular escape rhythms may develop. Treat bradycardia only if it is associated with hypotension. Blood pressure may be high as a result of peripheral vasoconstriction and increased systemic vascular resistance. However, patients are more often hypotensive as a consequence of the post-resuscitation inflammatory response. Avoid hypotension and treat it with IV fluids and vasopressors as needed to maintain a systolic blood pressure ≥ 90 mmHg or a mean arterial blood pressure of > 65 mmHg.[6]

It also is important to maintain a goal oxygen saturation of 94-96%. Avoid excessive FiO_2 to prevent the development of reactive oxygen species, which can lead to further neurological damage.[6] Additionally, maintain normocarbia by avoiding both hyperventilation and hypoventilation. Most importantly, hypocarbia is associated with poor outcomes, so make sure to avoid it.

Since 12-22% of patients who are comatose after cardiac arrest experience seizures, non-convulsive status epilepticus, and other epileptiform activity, complete an EEG and interpret it promptly. Then, monitor the EEG frequently or continuously in comatose patients after ROSC.[6] Since hypothermia decreases insulin secretion and increases insulin resistance, hyperglycemia is common during TTM. Maintain blood glucose measurements between 140 and 180 mg/dL.[16] The risk for hypoglycemia is of greater concern during rewarming, when glucose levels may fall precipitously, especially in patients receiving IV insulin. Other common complications include mild coagulopathy as well as an increased risk of infection due to impaired cellular and antibody immunity. If a patient experiences significant bleeding, stop TTM and re-warm the patient to a core temperature of 36°C. Monitor fluid status and electrolytes, especially potassium, magnesium, and phosphorous, closely as many patients will develop cold diuresis. Always position the head of the bed at an elevation of 30 degrees to prevent aspiration and elevated intracranial pressure. It always is important to maintain stress ulcer prophylaxis, deep vein thrombosis prophylaxis, enteral feeding once bowel motility returns (usually after TTM), and early physical and occupational rehabilitation.

PROGNOSIS

Neurological complications are the most common cause of death after cardiac arrest.[2] Unfortunately, providing an accurate prognosis can be quite challenging. The most recent AHA guidelines suggest delaying neurological prognostication until at least 72 hours after return of normothermia.[6] Specific findings that may be useful to predict poor neurological outcomes are reviewed in Table 1. If the patient progresses to death or brain death, strongly consider organ donation.

TTM after cardiac arrest leads to improved neurological outcomes and mortality. Consider it in all comatose adult patients presenting with ROSC after cardiac arrest. ■

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ABSTRACT & COMMENTARY

The Use of Dexmedetomidine for Sedation May Lead to Earlier Extubation and Decreased Ventilator Adverse Events

By Samuel Nadler, MD, PhD

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Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: The choice of dexmedetomidine or propofol over midazolam may improve outcomes in patients mechanically ventilated for three or more days.

SOURCE: Klompas M, Li L, Szumita P, et al. Associations between different sedatives and ventilator-associated events, length of stay, and mortality in patients who were mechanically ventilated. *Chest* 2016;149:1373-1379.

It's common to treat critically ill patients on mechanical ventilation with sedative medications. Limited data exist to direct which sedatives are most appropriate to maintain patient comfort yet facilitate timely extubation and minimize adverse events. Previously, benzodiazepine infusions were most common. More recently, propofol and dexmedetomidine have supplanted benzodiazepine, based largely on two studies published in 2009 and 2012.[1,2]

Klompas et al examined how these recommendations generalize into routine practice. This is a retrospective study of 9,603 patients in a single academic center between July 2006 and December 2013. The inclusion criteria specified patients on mechanical ventilation for three or more days. Outcomes studied included time to extubation, time to hospital discharge, ventilator associated events (VAEs), and mortality. Proportional subdistribution hazard models were used to estimate the effect of sedative exposure on these outcomes.

Over the specified time period, researchers identified 86,714 ventilator days. The combination of benzodiazepines and propofol (42%) was the most common

sedation method, followed by benzodiazepines alone (21%), propofol alone (12%), and the combination of benzodiazepines, propofol, and dexmedetomidine (10%). Clinicians used dexmedetomidine alone in 0.3% of ventilator days, most commonly in the cardiac surgery ICU. Compared with regimens without benzodiazepines, there was a significantly higher risk of VAEs in patients on midazolam (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.1-1.7; $P = 0.002$). Compared with regimens without propofol, patients on propofol experienced a higher risk of VAEs (HR, 1.3; 95% CI, 1.1-1.6; $P = 0.003$), infection-related, ventilator-associated complications (IVACs) (HR, 1.6; 95% CI, 1.2-2.2; $P = 0.0009$), and possible or probable pneumonias (HR, 1.5; 95% CI, 1.0-2.2; $P = 0.003$). Direct comparisons of single agents did not reveal statistically significant HRs, although there was a trend toward decreased events in patients on dexmedetomidine. Overall, patients on dexmedetomidine were more likely to be extubated (HR, 2.05; 95% CI, 1.77-2.38; $P < 0.0001$) when compared to patients on regimens without dexmedetomidine and in single-agent comparisons. There were no differences in hospital discharges and mortality among different regimens.

■ COMMENTARY

This study represents a huge, albeit retrospective, cohort study of the effects of various sedative agents on patient outcomes in the ICU. It focuses on patients on prolonged mechanical ventilation, specifically three or more days. The use of proportional sub-distribution hazard models can correct for known confounding variables but cannot eliminate bias in this study.

It is important to note that investigators conducted this study using data on patients admitted between 2006 and 2013. Although efforts were made to correct hazard risks based on year of admission, the bulk of patients were admitted before most practitioners had transitioned away from the use of benzodiazepines. The SEDCOM and MIDEX/PRODEX trials were published in 2009 and 2012, respectively.[1,2] This is evident by the many patients on propofol and benzodiazepines and benzodiazepine-only regimens. Relatively few patients were on dexmedetomidine only or regimens including dexmedetomidine. Thus, this study may not represent contemporary practice patterns in the ICU.

There were significant differences in the type of ICU using each sedative. The greatest proportion of dexmedetomidine was used in the cardiac surgery (57%) and thoracic surgery (16%) units. While hazard risk adjustments were made for this confounding variable, these patients clearly are different from patients in medical units, which may bias results.

Ultimately, base the decision on which sedatives to use on relative risks and benefits. This study suggested dexmedetomidine-based sedation strategies might facilitate extubation and reduce VAEs and IVACs. However, this did not translate into shorter length of stay or hospital mortality. Greater rates of bradyarrhythmias have been noted with dexmedetomidine. Although Klompas et al did not address depth of sedation in this study, the SEDCOM and MIDEX/PRODEX trials did, and it may lead to improved patient arousability and ability to communicate with dexmedetomidine. This study did not address the cost-effectiveness of these regimens, as dexmedetomidine can be much more expensive than other agents. Thus, while the Klompas et al study hints that dexmedetomidine-based regimens may have benefits, one must consider the many other factors not examined in this study in choosing sedatives for patients on mechanical ventilation in the ICU. ■

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ABSTRACT & COMMENTARY

Is There Added Diagnostic Value in Tracheal Aspirate Culture in Mechanically Ventilated Community-onset Pneumonia?

By Kathryn Radigan, MD

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Dr. Radigan reports no financial relationships relevant to this field of study.

SYNOPSIS: Tracheal aspirate cultures identified plausible pneumonia pathogens in more than half of newly intubated mechanically ventilated patients suffering from severe community-acquired pneumonia.

SOURCE: McCauley LM, Webb BJ, Sorensen J, Dean NC. Use of tracheal aspirate culture in newly intubated patients with community-onset pneumonia. *Ann Am Thorac Soc* 2016;13:376-381.

Since community-acquired pneumonia (CAP) is common and often life-threatening, early and appropriate antibiotic treatment is essential. Although experts recommend tracheal aspirate to optimize the treatment of patients with CAP, there is no literature to support its diagnostic usefulness. To evaluate the use of tracheal aspirate culture in identifying pneumonia pathogens, McCauley et al identified all patients with suspected community-onset pneumonia with International Classification of Disease, Ninth Revision (ICD-9) codes and radiographic evidence of pneumonia within the EDs of two university-affiliated Utah hospitals. Between December 2009 and November 2010 and between December 2011 and November 2012, patients who were diagnosed with pneumonia and intubated within 24 hours of ED arrival were identified electronically. As a part of immediate post-intubation care, standing orders instructed the respiratory therapists to obtain a tracheal aspirate for culture. Semiquantitative cultures had to meet acceptability standards (< 10 epithelial cells per low-powered field) and be quantified as rare, 1+, 2+, 3+, or 4+, based on the number of quadrants on the agar plate that demonstrate growth. All organisms present in a semiquantitative amount > 1+ and any organism identified as predominant or only growth (regardless of the total amount of growth) were identified and included in the study. Investigators excluded organisms if identified as normal oral flora. The authors reviewed the electronic medical record to collect the results of other microbiological studies.

Of the 2,011 patients presenting with pneumonia, 94 were intubated and 84 received a tracheal aspirate. Of the 84 patients who underwent a tracheal aspirate, 47 featured a pulmonary pathogen identified by tracheal aspirate culture. Eighty patients also submitted blood cultures and 71 underwent pneumococcal and Legionella urinary antigen testing. Fifty-five patients underwent viral polymerase chain reaction (PCR) testing. Out of all the specimens evaluated by the variety of diagnostic mechanisms, researchers confirmed a microbiological diagnosis in 55 patients. The tracheal aspirate culture was the only positive test in 32 out of 82 patients. These patients otherwise would have been classified as culture-negative. Overall, 40 patients underwent de-escalation of antibiotic therapy, and 16 patients received targeted therapy.

Tracheal aspirate cultures added significant diagnostic value to other routine microbiological tests and identified many patients who otherwise would be considered culture negative.

■ COMMENTARY

Pneumonia is one of the leading causes of hospitalization and death in the United States and often associated with considerable morbidity and mortality, especially in older adult patients and those presenting with significant comorbidities.[1] Early and appropriate treatment has been shown to improve outcomes substantially.[2] This is especially important as the rates of drug-resistant pathogens and broad-spectrum antibiotic usage increase. Since it is difficult to achieve a microbiological diagnosis, McCauley et al examined the diagnostic usefulness of tracheal aspirate at the time of intubation in patients suffering from severe CAP.

Endotracheal aspirate, using a clean suction catheter, is a noninvasive method to obtain a deep respiratory sample in recently intubated patients. Bronchoalveolar lavage (BAL) or a protected specimen brush sample are alternative options to confirm the microbiological diagnosis in this setting. Interestingly, there has been extensive research into the use of tracheal aspirate cultures as a noninvasive method to diagnose ventilator-associated pneumonia (VAP). In this particular setting, it often is difficult to discriminate between organisms responsible for infection vs. colonization. Since the endotracheal aspirate cultures within the current study were performed immediately after intubation for severe CAP, one presumes there was not sufficient time for colonization. There also is concern that the results within this study were reported semi-quantitatively vs. quantitatively. At least in the diagnosis of VAP, one might believe that semi-quantitative cultures of endotracheal aspirate may be poorly concordant with quantitative cultures obtained via non-bronchoscopic BAL. Regardless, failure to identify potential multiple drug-resistant pathogens with semiquantitative cultures would be less concerning in a CAP population. In addition, even though there is concern that semiquantitative cultures may promote excessive antibiotic usage, there was substantial de-escalation of antibiotics in this study.[3]

Regardless of whether one favors semiquantitative cultures, researchers confirmed a microbiological diagnosis in almost two-thirds of patients with the tracheal aspirate culture. It was the only positive test in almost 40% of patients. Since evolving literature supports the notion that viruses cause CAP more often than bacteria,[4] results may have been even more striking if viral PCR had been completed in all patients as opposed to two-thirds. Nonetheless, one of the major benefits to this study is that endotracheal culture was a part of standing orders and initiated as a part of the immediate post-intubation care. As there is often a struggle

to order, collect, and process culture data in a timely manner, standing post-intubation orders may improve yield and confirm a microbiological diagnosis. As such, it is clear that tracheal aspirate cultures offer important additive diagnostic value to other routine tests performed in the setting of severe CAP while facilitating appropriate antibiotic therapy. Further studies may determine whether tracheal aspirate culture in patients suffering from severe CAP makes a significant difference in hospital stay, morbidity, or mortality. ■

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CME/CE QUESTIONS

1. **Neurologic injury is the cause of death in what proportion of all out-of-hospital cardiac arrest patients?**
   a. One-eighth
   b. One-third
   c. Two-thirds
   d. Three-quarters

2. **In post-cardiac arrest patients, one should control core temperature between:**
   a. 30°C and 32°C
   b. 32°C and 36°C
   c. 36°C and 38°C
   d. None of the above

3. **Compared to benzodiazepine-based sedation, regimens with dexmedetomidine were associated with:**
   a. higher hospital mortality.
   b. lower likelihood of extubation.
   c. longer hospital length of stay.
   d. None of the above

4. **The Klompas et al study reported:**
   a. higher likelihood of extubation with dexmedetomidine vs. propofol.
   b. improved hospital mortality of patients sedated with dexmedetomidine.
   c. improved hospital mortality of patients sedated with benzodiazepines.
   d. lower likelihood of extubation with dexmedetomidine vs. propofol.

5. **Tracheal aspirate culture was the only positive test in approximately what percentage of mechanically ventilated patients presenting with severe community-acquired pneumonia?**
   a. 20%
   b. 40%
   c. 60%
   d. 80%

6. **Colonization of the endotracheal tube with bacteria is most concerning when diagnosing:**
   a. community-acquired pneumonia.
   b. ventilator-associated pneumonia.
   c. viral pneumonia.
   d. None of the above