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SPECIAL FEATURE

Ventilator-Associated Pneumonia and Hospital-Acquired Pneumonia: Prevention and Treatment

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

Ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) account for approximately 22% of all hospital-acquired infections.[1] While the National Healthcare Safety Network reports declining rates of VAP, others cite a rate of approximately 10% of all ventilated patients with no declining trend.[2-4] Because VAP and HAP can significantly increase mortality rates, prolong ventilation duration, lead to longer hospital stays, create more serious complications, and increase the cost of care, all efforts leading to prevention and better treatment of VAP and HAP can improve outcomes in ICUs.[5-7]

VAP PREVENTION

When discussing VAP prevention, it is important to acknowledge that the literature revolves around a set of definitions that differ from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) definitions of VAP. These definitions, introduced by the CDC, emphasize the need for standardization of metrics used to assess the quality of care for ventilated patients.[8,9] As such, the CDC definitions are better tools for surveillance, quality improvement, and benchmarking quality of care rather clinical criteria for VAP diagnosis and treatment. The CDC definitions for ventilator-associated events (VAEs), as outlined by Klompas et al, include:

- **Ventilator-associated conditions (VAC):** Two or more days of stable or declining minimum positive end-expiratory pressure (PEEP) or minimum FiO_2, followed by a rising minimum PEEP (by 3 cm H_2O) or FiO_2 (by 0.2 points) for two or more days;
- **Infection-related ventilator-associated complication (IVAC):** Presence of possible infection indicators concurrent with VAC onset (temperature < 36° C or > 38° C or white blood cell count < 4,000 or > 12,000) *and* initiation of a new antibiotic that is continued for four or more days;

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• **Possible VAP:** An IVAC and Gram stain evidence of purulent sputum or pathogenic pulmonary culture;
• **Probable VAP:** An IVAC *and* either: 1) Gram stain evidence of purulent sputum *and* quantitative or semiquantitative growth of pathogenic organisms *or* 2) a positive test for respiratory viruses, *Legionella* species, pleural fluid cultures, or suggestive histopathology with or without abnormal Gram stain results.[9]

VAC and IVAC were developed for public reporting. However, it remains unclear how preventable VAC and IVAC are and how comparable they are from institution to institution. On the other hand, possible and probable VAP are meant for internal institutional quality improvement purposes and are not suitable for public reporting or benchmark comparisons. The Society for Healthcare Epidemiology of America recommends surveillance for VAE and all of the above definition tiers for all adult patients on the ventilator for four or more days, knowing that much of the data on VAP prevention come from literature using traditional definitions of VAP rather than CDC definitions of VAE.[9] Further, VAC may be a surveillance marker for broader nosocomial acute lung injury, including pneumonia, pulmonary edema, atelectasis, and acute respiratory distress syndrome (ARDS). As such, approaches shown to decrease VACs in general may be efficacious through means other than pneumonia prevention.

Specific recommendations for preventing VAP and the quality of evidence to support them are outlined in Table 1. Many of these focus on minimizing ventilator days; others focus on reducing the risk of introducing microbes into the trachea and lower airways. Data to support elevation of the head of the bed are mixed. Still, combining the studies in a meta-analysis demonstrated a positive effect on VAP rate.[10] Elevating the head of the bed is especially important for those receiving enteral nutrition. Some methods have been shown to improve outcomes but have not been strongly recommended or adopted because of concerns of potential risks. Included in this group is selective decontamination of the oropharynx, which has been shown to decrease mortality rates but in theory could increase the risk of antibiotic resistance or *Clostridioides difficile* infections.[11]

Other measures with unclear risk vs. benefit ratios that have not been strongly recommended include chlorhexidine oral care, prophylactic probiotics, ultrathin polyurethane endotracheal tube cuffs, and mechanical tooth brushing. Measures generally not recommended for prevention of VAP are silver-coated endotracheal tubes, kinetic beds, early tracheotomy, and early parenteral nutrition. In fact, initiation of early parenteral nutrition is associated with a higher risk of nosocomial infection and mortality compared to delaying it until day 8.[12]

Table 1. Recommended Approaches to Prevent Ventilator-Associated Pneumonia in Adults

Intervention	Quality of Evidence
Use noninvasive-positive pressure ventilation when possible for COPD and congestive heart failure	High
Minimize sedation	Moderate
Daily sedation vacation	High
Assess readiness to intubate on a daily basis	High
Daily spontaneous breathing trial with sedation turned off	High
Facilitate early mobility	Moderate
Endotracheal tubes with subglottic suction ports if intubation > 48-72 hours is anticipated	Moderate
Change ventilator circuit only if visibly soiled or malfunctioning	High
Elevate head of bed to 30-45 degrees	Low

Adapted from: Klompas M, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol* 2014;35: 915-936.

VAP/HAP TREATMENT

In reviewing the literature on the treatment rather than the prevention of HAP and VAP, one must return to the more traditional definitions of pneumonia. Definitions of VAP and HAP were left largely unchanged in the 2016 IDSA/ATS guidelines update.[13] Pneumonia is defined as a "new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation." HAP is a pneumonia that develops in the hospital and was not incubating at the time of admission. VAP is a pneumonia developing more than 48 hours after intubation. Without a gold standard for the diagnosis of pneumonia, there remains room for clinical judgment. In the IDSA/ATS guidelines, VAP is not included in the definition of HAP; thus, they are mutually exclusive groups, a definition of HAP that is not always consistent when reviewing the literature on the subject.[13]

On the other hand, the term healthcare-associated pneumonia (HCAP) has been excluded from the updated VAP/HAP guidelines. This is, in large part, because of increasing evidence showing that many patients previously defined as having HCAP are *not* at high risk for multidrug-resistant (MDR) pathogens and do not warrant exposure to broader antibiotic coverage. Instead, emphasis is placed on identifying risk factors for MDR pathogens in VAP and HAP. Similarly, while community-acquired pneumonia (CAP) is not covered in this review, the authors of the 2016 guidelines believed that specific risk factors for MDR pathogens (rather than simply looking at previous contact with the healthcare system) should be part of the guidelines for managing CAP.[13] In contrast, coma at the time of ICU admission decreases the chances of finding an MDR organism in VAP, probably related to the propensity for neurotrauma patients to develop VAP early in their hospitalization. MDR organisms in HAP, methicillin-resistant *S. aureus (*MRSA) in VAP or HAP, and resistant *Pseudomonas* organisms in VAP or HAP all share the risk factor of prior IV antibiotic use within 90 days. However, consistent data supporting other risk factors for these three scenarios are lacking. Besides prior IV antibiotic use within 90 days, other indications for treatment of MDR in VAP include septic shock, ARDS, five or more days of hospitalization prior to VAP onset, and acute renal replacement therapy prior to VAP onset.

What is the best way to obtain cultures in the patient with a new infiltrate? The IDSA/ATS guidelines recommend noninvasive sampling in VAP/HAP with semiquantitative cultures rather than bronchoalveolar lavage (BAL), protected specimen brush, or blind bronchial sampling (mini-BAL).[13] However, the European Respiratory Society and other international societies recommend using the invasive sampling techniques for VAP.[14,15] If someone happens to obtain invasive quantitative cultures, the IDSA/ATS guidelines recommend withholding antibiotics if the cultures return below the diagnostic threshold for VAP.

When VAP is suspected and before diagnostic microbiologic results have returned, empiric treatment is required. This treatment should include coverage for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli.[13] Empiric coverage for methicillin-sensitive *S. aureus* (MSSA) should include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem. MRSA rather than MSSA empiric coverage would be required for those with risk factors for MRSA (prior IV antibiotic use within 90 days, ICUs with > 10-20% *S. aureus* isolates resistant to methicillin) and would include vancomycin or linezolid. Empiric coverage for resistant *Pseudomonas* or other gram-negative organisms should include two antipseudomonal agents: one from the beta-lactam class (e.g., aztreonam, cefepime piperacillin-tazobactam, imipenem, ceftazidime, meropenem) and one from the nonbeta-lactam class (e.g., amikacin, colistin, ciprofloxacin, levofloxacin, polymyxin, gentamicin, tobramycin). The only double beta-lactam combination that could be considered is aztreonam with another beta-lactam, as aztreonam has a different bacterial cell wall target.[13] If the risk of resistant gram-negative organisms is low, then only one gram-negative agent is required, preferably an agent also effective against MSSA (if there are no risk factors for MRSA).

To avoid potential costs and side effects, such as renal failure and *C. difficile* infection, caveats to these recommendations include avoiding aminoglycosides and colistin when alternative agents are available. Generally, antibiotics to which the patient has been exposed recently should be avoided, with preference given to an agent from a different class of antibiotics. In addition, empiric coverage for both VAP and HAP should be guided by local antibiograms, which should be generated regularly and made available to clinicians.

Empiric coverage for HAP is similar to that of VAP. However, patients who are at high risk of mortality receive coverage for MRSA and MDR *Pseudomonas* — even if the MDR risk factors are not present. "High risk of mortality" is defined as the need for ventilator support due to HAP or the presence of septic shock.[13] Otherwise, clinicians should use double antipseudomonal coverage if the patient has bronchiectasis, cystic fibrosis, or another structural lung disease that raises the risk of resistant gram-negative infection.

Recommendations for coverage of specific organisms identified in VAP and HAP include using both inhaled and systemic antibiotics for treating gram-negative bacilli sensitive only to aminoglycosides or polymyxins (colistin or polymyxin B). *P. aeruginosa* VAP/HAP with

known antibiotic susceptibility should be treated with two antibiotics if the patient is still in septic shock or at high risk of death. Otherwise, monotherapy with an agent to which the organism is susceptible is recommended. The exception is that aminoglycosides should not be used as a sole antipseudomonal agent due to concerns about lung penetration.

Acinetobacter species are treated preferentially with a carbapenem or ampicillin/sulbactam if they are susceptible. Tigecycline is not recommended when *Acinetobacter* is the known pathogen. If sensitive only to polymyxins, *Acinetobacter* and other carbapenem-resistant pathogens should be treated with IV polymyxin (colistin or polymyxin B) and with inhaled colistin. If MSSA is the confirmed sole causative organism, coverage can be narrowed to oxacillin, nafcillin, or cefazolin. Nosocomial *Legionella* spp. VAP or HAP would be much less common but would require coverage to be tailored to include appropriate antibiotics (fluoroquinolones or azithromycin). Similarly, anaerobes are a less likely cause of VAP and HAP. However, in the setting of aspiration or recent abdominal surgery, one could consider including anaerobic coverage in the selection of antibiotics, knowing that adding specific anaerobic coverage for aspiration pneumonia may offer no clinical benefit.[16]

Generally, therapy duration is seven to eight days rather than a longer course for both VAP and HAP. However, for VAP due to nonfermenting, gram-negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Sphingomonas paucimobilis*, *Achromobacter xylosoxidans*, etc.), the risk of recurrence is higher with the seven-day course vs. the longer 10-15 day course.[13,17] Other situations in which a longer course of antibiotics should be considered include inadequate initial antibiotic treatment and severely immunocompromised patients.[15] Recently, Klompas et al suggested that VAP in stable patients on minimal ventilator support may perform just as well with a three-day course of antibiotics.[18] However, these findings need to be replicated before making firm recommendations to use the very short course. Because the clinical definitions of VAP and HAP as discussed earlier are very sensitive but have poor specificity, it is reasonable to consider a shortened course of antibiotics. Culture data and the patient's clinical course often can often help inform the diagnostic suspicion of VAP/HAP and early de-escalation of broad-spectrum antibiotic therapy. Still, differentiation between airway colonization and lower respiratory tract infection can be challenging.

In addition to clinical criteria, biomarkers (chiefly procalcitonin) may help guide length of therapy as well as timing of de-escalation. When possible, antibiotic therapy should be narrowed when culture and sensitivity results are available.

BIOMARKERS

Considering the frequent difficulty in distinguishing bacterial pneumonia from viral pneumonia or other pulmonary insults, interest in the use of biomarkers to help guide VAP and HAP management has increased in recent years. Biomarkers include procalcitonin (PCT), C-reactive protein (CRP), copeptin, soluble triggering receptor expressed on myeloid cells (sTREM-1), and others.

In general, sensitivity, specificity, and positive and negative predictive values of none of these biomarkers are adequate to make any of them useful in deciding whether to initiate antibiotic therapy.[13] Some have suggested that PCT may be helpful to decide when to stop empiric antibiotics when cultures return negative or to shorten the course of antibiotics in a patient who otherwise appears to be responding adequately. To reduce antibiotic use, some research supports stopping antibiotics when the PCT level declines to < 0.5 ng/mL or by more than 80% of the peak level, but the cohorts in those studies were relatively small.[19-22] Thus, the IDSA/ATS guidelines make a weak recommendation for using PCT levels in addition to clinical criteria to assist in deciding when to stop antibiotics.[13] Meanwhile, the 2017 European and Latin American society guidelines recommend considering PCT levels only if the anticipated duration of antibiotic therapy is longer than seven to eight days.[14,15] Other biomarkers, such as CRP, may not be as useful because of persistent elevation from noninfectious inflammatory disorders seen in the ICU, but may be considered when PCT testing is not available. If PCT levels remain elevated, one must consider that nonbacterial infections (such as *Pneumocystis jirovecii*, *Candida* species, and some parasites), as well as noninfectious conditions such as shock, burns, trauma, and chronic renal disease, can cause elevated PCT levels.

SUMMARY

VAP and HAP pose significant risks to hospitalized patients and increase the cost of care. It is essential to institute measures to reduce the risk of these pneumonias and to recognize and treat them early when they occur. Treatment is a balance of ensuring adequate antimicrobial coverage in those who already are seriously ill while not unduly exposing them to the risks of medication side effects and higher rates of resistant organisms that come with the use of broad-spectrum antibiotics. Following established guidelines discussed will lead to improved outcomes in ICUs and hospital wards. ■

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ABSTRACT & COMMENTARY

Presepsis Pathways: Can We Predict Mortality After Sepsis Hospitalization?

By Betty Tran, MD, MSc, Editor

SYNOPSIS: Using a latent profile analysis in observational cohort studies of patients hospitalized for sepsis, investigators identified subtypes of patients based on inpatient healthcare facility use in the year prior to sepsis hospitalization and correlated to 90-day mortality.

SOURCE: Prescott HC, et al. Paths into sepsis: Trajectories of presepsis healthcare use. *Ann Am Thorac Soc* 2019;16:116-123.

Sepsis is a heterogeneous condition, making it difficult to identify with certainty and treat successfully in many cases. As such, it remains a significant public health problem. Neither the incidence nor combined outcome of death or discharge to hospice changed much between 2009 and 2014, despite advances in medical knowledge, better clinical awareness, and changes in definitions and timely management.[1]

To elucidate clinically relevant contributors to sepsis heterogeneity, Prescott et al hypothesized that differences in sepsis outcomes may result from differences in a patient's clinical course leading up to a sepsis hospitalization. They studied three cohorts of patients hospitalized with sepsis: 1,512 participants in the U.S. Health and Retirement Study (HRS) in fee-for-service Medicare hospitalized 1998-2005 served as the derivation cohort, while 1,992 HRS cohort patients from 2006-2012 served as one validation cohort. Further, 32,525 Department of Veterans Affairs beneficiaries in 2009 served as a second validation cohort. The authors identified subgroups of patients with sepsis defined by their trajectory of presepsis inpatient healthcare facility use in the year before hospitalization. To identify these subgroups, the authors used a latent profile analysis, whereby the number of

subgroups is determined by minimizing within-group differences and maximizing between-group differences. The authors determined differences in patient characteristics between subgroups and measured their association with 90-day mortality was measured with adjustment for multiple variables, including sex, race, age, acute illness severity, chronic disease burden, and presepsis functional limitations.

Researchers found a three-class model that best characterized presepsis trajectories of healthcare use. Half of patients defined as low use did not spend any days in an inpatient facility. Patients defined as rising use increased their healthcare facility use in the months immediately preceding sepsis hospitalization (median = 55 days spent in a healthcare facility). Patients defined as high use spent a significant amount of time in inpatient healthcare facilities over the year (median = 119 days). None of these trajectories resembled the overall mean trajectory. The three-class model from the derivation cohort remained robust when applied to the validation cohorts in terms of patient characteristics and distribution.

Overall, the low use group was healthier. They demonstrated fewer functional limitations and comorbidities before developing sepsis. High use patients were chronically ill, exhibiting more presepsis disabilities and higher comorbidity burdens. Those in the rising use group were older than other patients but showed fewer functional disabilities and comorbidities than the high use class. The authors attributed most inpatient healthcare use to time spent in long-term acute care hospitals or skilled nursing facilities. Researchers observed no differences in mechanical ventilation or ICU use between classes.

Across all cohorts, 90-day mortality was highest in the rising use class. The low use class demonstrated the best survival rate. Adjusted odds of 90-day mortality were 1.3- to 2.2-fold higher in the rising use class vs. the low use class. Specifically, adjusted mortality for the rising use class was 58% vs. 39% for the low use class in the derivation cohort, 44% vs. 31% in the first validation cohort, and 27% vs. 23% in the second validation cohort. Across all cohorts, more rising use patients died in the first 30 days and used inpatient healthcare facilities more often during the 90 days after hospital admission for sepsis.

■ COMMENTARY

Often, the authors of sepsis studies focus on improving delivery of care during hospitalization, with increasing efforts devoted to highlighting posthospitalization rates of readmission and sequelae. This study is novel in that it focuses on presepsis risk factors that can affect sepsis-related outcomes. The results from this observational cohort study suggest that sepsis outcomes correlate to patients' overall health status before they are even hospitalized for sepsis; how this is linked to underlying sepsis pathobiology and the epidemiology of nosocomial exposures has yet to be elucidated. Notably, this study implies that the acuity of the change in host immunity in the rising use patients accounts for worse outcomes in this group, rather than the magnitude of healthcare facility use prior to sepsis hospitalization. Merely quantifying the amount of inpatient days in the year prior to sepsis hospitalization does not explain a patient's risk for sepsis-related mortality. This is supported by the finding that rising use patients experienced poorer outcomes than high use patients, and that none of the three trajectories resembled the pattern of mean use in all cohorts.

How can one explain higher mortality rates among rising use patients? The acute decline in host defense mechanisms may outpace any protective stress response. Recent high inpatient use can lead to microbiome disruption, making patients more vulnerable to sepsis. Also, recent exposure to antibiotics and nosocomial pathogens can increase the risk of sepsis.

The findings from this study could be used to identify high-risk patients through electronic health records to inform staff regarding care delivery and outcomes, researchers conducting clinical trials regarding types of patients enrolled, and translational investigators regarding whether the host response to sepsis is different based on presepsis trajectory. ■

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ABSTRACT & COMMENTARY

Saline vs. Balanced Crystalloids in Critically Ill Adults

By Drayton Hammond, PharmD, MBA, BCPS, BCCCP

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

SYNOPSIS: Balanced crystalloids appear to reduce in-hospital mortality in critically ill patients with sepsis or without traumatic brain injury and may reduce in-hospital mortality in the entire cohort of critically ill patients.

SOURCE: Xue M, et al. Effects of chloride content of intravenous crystalloid solutions in critically ill adult patients: A meta-analysis with trial sequential analysis of randomized trials. *Ann Intensive Care* 2019;9:30.

Critically ill patients with distributive shock are resuscitated most frequently with IV crystalloid and/or colloid solutions. For sepsis in particular, the current Surviving Sepsis Campaign guidelines provide a strong recommendation based on low quality of evidence for initial resuscitation with IV crystalloid fluid. The guidelines also offer a best practice statement for further fluid resuscitation based on reassessment of hemodynamic status with preferential use of dynamic markers of fluid responsiveness.[1] Guidelines for the management of distributive shock do not provide preferential recommendations for the type of IV crystalloid fluid. In the last five years, significant contributions to evolving and resolving the debate regarding balanced crystalloid vs. saline in critically ill patients with distributive shock have been made.[2-4] However, a contemporary meta-analysis that incorporates these data had not been performed.

Xue et al incorporated all randomized and cluster-randomized trials that compared balanced crystalloids (i.e., those with a near-physiological chloride concentration, such as PlasmaLyte and Ringer's lactate) to 0.9% saline provided as resuscitative or maintenance fluids in critically ill adults.[5] Articles indexed in Medline, EMBASE, Cochrane (Central) database, Elsevier, Web of Science, and ClinicalTrials.gov by June 2018 were considered for inclusion, resulting in eight trials with 19,301 patients. Four trials were assessed as low risk of bias. Their protocol was registered a priori in the PROSPERO database (CRD42018102661). Researchers performed subgroup analyses for subpopulations of critical illness (e.g., sepsis, traumatic brain injury [TBI]) for primary and secondary outcomes. The authors developed and evaluated fixed effect and random effect models for each outcome.

A difference in in-hospital survival favoring balanced crystalloids to 0.9% saline may exist (10.1% vs. 10.9%; risk ratio [RR], 0.92; 95% confidence interval [CI], 0.85-1.0; $P = 0.06$; I^2, 0%), although the results of a trial sequential analysis suggested the sample size was inadequate to detect a difference. Mortality at 30 and 60 days was similar between groups (RR, 0.92; 95% CI, 0.85-1.01; $P = 0.08$; and RR, 0.94; 95% CI, 0.87-1.02; $P = 0.13$, respectively). The evidence for the mortality outcomes was of low quality, according to GRADE criteria. Patients who received balanced crystalloids logged more days without renal replacement therapy (RRT; 25.6 days vs. 24.8 days; standard mean difference [SMD], 0.09; 95% CI, 0.06-0.12; $P < 0.001$), more days without using a ventilator (SMD, 0.08; 95% CI, 0.05-0.11; $P < 0.001$), and more days without using a vasopressor (SMD, 0.04; 95% CI, 0.00-0.07; $P = 0.02$). These patients also were at a lower risk of an increase in serum chloride levels (SMD, -1.23; 95% CI, -1.59 to -0.87; $P < 0.001$). Receipt of balanced crystalloids was associated with lower in-hospital mortality rates among septic patients (RR, 0.86; 95% CI, 0.75-0.98; $P = 0.02$) and non-TBI patients (RR, 0.90; 95% CI, 0.82-0.99; $P = 0.02$).

■ COMMENTARY

While surgical subspecialties of critical care have used balanced crystalloids as resuscitative and maintenance fluids predominately for years, recent interest in this practice from the medical critical care community has led to multiple randomized and cluster-randomized trials. This new research has helped reshape the landscape of IV fluid use in critical care. Of note, analyses were driven by the significant weight afforded to the recent cluster-randomized trial by Semler et al, which Xue et al determined to be of high risk of bias.[3] This systematic review and meta-analysis helps clarify subpopulations of critical care that appear most susceptible to improved outcomes from balanced crystalloid administration while leaving some questions unanswered or inadequately answered.

The two subpopulations of critical care for which balanced crystalloids were identified confidently as beneficial in reducing in-hospital mortality were those with sepsis and those without TBI, which makes sense pathophysiologically. Balanced crystalloids may help resolve the metabolic acidosis and acute kidney injury that often

happens during sepsis and septic shock. Conversely, 0.9% saline is more likely to raise serum sodium concentrations than balanced crystalloids, which may help alleviate raised intracranial pressure that often is present in TBI patients. Additionally, these outcomes may be achievable with relatively small volumes of IV fluids, as evidenced by 99% of patients in these studies receiving 2-3 L of IV fluids during the study period.

The authors described the overall primary outcome of in-hospital mortality as similar (RR, 0.92; 95% CI, 0.85-1.0; $P = 0.06$), which clinicians should note is based on $P > 0.05$ using frequentist statistics. Based on the point estimate and narrow confidence interval, there is a high probability (> 80% based on Bayesian statistics) that balanced crystalloids are associated with lower in-hospital mortality rates in the general critical care population. Additionally, although the authors chose not to include high-quality observational studies, those that have been published suggest a mortality benefit with balanced crystalloids.[5,6] Better end-organ function (evidenced by greater time without vasopressor, mechanical ventilator, and RRT support) corroborates this finding. More confident statements regarding mortality in the overall critically ill cohort and subgroups of interest should be expected following completion of two ongoing randomized, controlled trials.[7,8] At this point, clinicians should feel comfortable and justified using balanced crystalloids for resuscitative and maintenance fluids in critically ill patients (except for those with TBI). ■

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CME/CE QUESTIONS

1. **Which is true regarding the use of biomarkers in the management of ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP)?**
   a. In addition to clinical criteria, biomarkers are helpful when deciding whether to initiate antibiotics for possible VAP or HAP.
   b. Procalcitonin levels rise only with bacterial pneumonia.
   c. In addition to clinical criteria, procalcitonin levels may be helpful when deciding when to end a course of antibiotics that have been started for VAP or HAP.
   d. Compared to procalcitonin, C-reactive protein has been found to be more specific for VAP.

2. **In the study by Prescott et al, which of the following subtypes of patients (categorized by use of inpatient healthcare facilities in the one year prior to sepsis hospitalization) had the highest 90-day mortality after a sepsis hospitalization?**
   a. No use (none of the group spent any days in inpatient care)
   b. Low use (half of group spent zero days in inpatient care)
   c. Rising use (increased use in immediate preceding months)
   d. High use (marked use of inpatient services over the year)