REVIEW

CME MOC

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Hospital-acquired and ventilator-associated pneumonia: Diagnosis, management, and prevention

ABSTRACT

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) cause significant inpatient morbidity and mortality. They are especially challenging to diagnose promptly in the intensive care unit because a plethora of other causes can contribute to clinical decline in complex, critically ill patients. The authors describe the diagnosis, management, and prevention of these diseases based on current guidelines and recent evidence.

KEY POINTS

Noninvasive testing such as blood and sputum cultures and the staphylococcal nasal swab should be conducted in a patient with suspected HAP or VAP to isolate the culprit organism and tailor antibiotic therapy.

Procalcitonin testing should not be used to decide whether to start antibiotics but can be used in conjunction with clinical judgment to decide course duration.

Patients with suspected HAP or VAP who are immunocompromised, hemodynamically unstable, or unable to produce timely lower respiratory tract samples for microbiologic testing merit empiric antibiotic treatment with a regimen based on individual risk factors and local antibiotic resistance.

Nursing care bundles addressing aspiration risk factors can reduce the incidence of HAP and VAP in the hospital.

doi:10.3949/ccjm.87a.19117

Although guidelines are available for managing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)[1,2] and our understanding of these diseases is growing, their incidence does not seem to be decreasing.[3]

And the toll is high. About 10% of patients put on mechanical ventilation develop VAP,[3] and the mortality rate in VAP has been estimated at 13%.[4] Together, HAP and VAP accounted for 22% of hospital-acquired infections in a 2014 survey of 183 US hospitals.[5] Patients with VAP face a longer hospital course and incur higher healthcare costs than similarly ill patients without VAP.[1]

This review discusses the diagnosis, management, and prevention of HAP and VAP using the 2016 guidelines from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS),[1] as well as recent literature regarding controversial topics such as the role for procalcitonin testing and adjunctive inhaled aminoglycosides.

TERMS

HAP is a new pneumonia (a lower respiratory tract infection verified by the presence of a new pulmonary infiltrate on imaging) that develops more than 48 hours after admission in nonintubated patients.

VAP, the most common and fatal nosocomial infection of critical care, is a new pneumonia that develops after 48 hours of endotracheal intubation. Importantly, by the time of VAP onset, patients may have already been extubated.

'Healthcare-associated pneumonia' is no longer recognized

Of note, the term "healthcare-associated pneumonia" (HCAP) has been removed from the 2016 guidelines.[1]

HCAP was defined in the IDSA/ATS 2005 guidelines as pneumonia developing in a person hospitalized for more than 48 hours in the last 90 days, residing in a nursing home or extended-care facility, or receiving home infusion therapy, wound care, or chronic dialysis.[6] As patients who frequently interface with the healthcare system were suspected of harboring multidrug-resistant organisms, the empiric antibiotic regimen recommended for HCAP mirrored that recommended for HAP and VAP.

But a systematic review and meta-analysis of 24 studies revealed that these criteria for HCAP did not reliably correlate with the presence of multidrug-resistant organisms.[7] Mortality in HCAP was not associated with multidrug-resistant organisms, but rather was associated with patient age and comorbidities.

The designation of HCAP was ultimately determined to have minimal practical value in decision-making about empiric antibiotic selection and overall prognostication. Patients who would have previously qualified for a diagnosis of HCAP should instead be treated as having community-acquired pneumonia unless they have specific individual risk factors that call for broad-spectrum empiric antibiotic treatment (see below).

By the time of VAP onset, patients may have already been extubated

ASPIRATION IS AN IMPORTANT CAUSE OF HAP AND VAP

Aspiration is an important contributor to the pathogenesis of HAP and VAP. Further, proton-pump inhibitors and histamine-2 receptor blockers, by suppressing acid production, can allow nosocomial pathogens to colonize the oropharynx and endotracheal tube and be aspirated.[2] VAP-specific risk factors such as age, recent surgery, and admission for neurologic causes or cardiovascular failure all increase the risk of aspiration.[8,9]

CHALLENGING TO DIAGNOSE

HAP and VAP can be challenging to diagnose promptly, owing to limited diagnostic tests and a broad differential diagnosis for patients who develop increasing oxygen requirements, leukocytosis, and secretions in the intensive care unit (ICU). Respiratory decline accompanied by fevers and a productive cough—or following a witnessed or suspected aspiration event in the hospital—can suggest developing pneumonia. While scoring systems such as the Clinical Pulmonary Infection Score are used to guide the management of community-acquired pneumonia, the IDSA/ATS guidelines suggest using clinical criteria alone for the management of HAP and VAP.[1,10]

According to the guidelines, the diagnosis of HAP and VAP requires all of the following:

- New lung infiltrates on chest imaging
- Respiratory decline
- Fever
- Productive cough.

Absence of a new infiltrate significantly lowers the probability of VAP and can guide the clinician to alternative causes of inpatient respiratory decline, including pulmonary embolism.[1]

Noninvasive tests

Once an infiltrate is observed and HAP or VAP is suspected as the cause of respiratory decline, several noninvasive tests are recommended to isolate a pathogen and promptly tailor empiric antibiotics to the culprit organism.

Blood cultures are recommended for all patients diagnosed with HAP or VAP.[1] Fifteen percent of patients with VAP are bacteremic, and up to 25% of blood cultures from this group demonstrate pathogens reflective of a secondary, nonpulmonary source of infection.[1]

Thus, blood cultures can be useful to identify the pathogen responsible for HAP or VAP, especially if respiratory cultures are unrevealing, and also to inform the clinician as to the presence of additional concomitant infections unrelated to the respiratory tract. For example, *Candida* and *Enterococcus* species are not known to cause pneumonia, and so detecting these pathogens in the bloodstream may direct the clinician to a separate and previously unsuspected site of infection such as a catheter-related bloodstream infection.

Sputum cultures should be obtained in patients with HAP and in nonintubated patients with VAP who are capable of producing

a sufficient sample, characterized by few to no squamous epithelial cells on Gram stain.

For patients who cannot produce an adequate sputum sample, semiquantitative sputum samples obtained by noninvasive methods (eg, endotracheal aspiration) are preferred over quantitative samples obtained by noninvasive or invasive methods such as bronchoscopy and blind bronchial sampling (mini-bronchoalveolar lavage) in an effort to reduce cost and patient harm associated with quantitative and invasive testing.[1] Quantitative testing may be falsely unremarkable if antibiotics have been started before sample collection and may erroneously trigger the cessation of appropriate therapy. Further, no improvement in mortality rate, length of ICU stay, or duration of mechanical ventilation has been observed in patients who underwent invasive sampling.[1]

However, invasive sampling may be merited for an immunocompromised patient or a patient experiencing continued clinical decline despite appropriate antibiotics and with a negative noninvasive evaluation, given its improved diagnostic yield.[11]

Should invasive sampling be attempted, high cellularity (> 400,000 cells/mL) and the presence of more than 50% neutrophils in bronchoalveolar lavage fluid can implicate VAP.[12,13] The IDSA/ATS guidelines suggest discontinuing antibiotics if the final bronchoalveolar lavage culture results demonstrate fewer than 10^4 colony-forming units/mL, though it should be noted that the yield of bronchoscopic cultures dramatically decreases after 72 hours of antibiotic exposure.[1] Negative bronchoscopic cultures obtained from a patient on empiric antibiotic therapy may rule out multidrug-resistant organisms but do not entirely rule out pneumonia.

Polymerase chain reaction (PCR) testing has been increasingly employed to diagnose pathogens responsible for HAP and VAP and to guide antibiotic stewardship measures.

The *Staphylococcus aureus* nasal swab, a PCR-based test, demonstrated a high negative predictive value for methicillin-resistant *S aureus* (MRSA) colonization in a patient population with a 10% prevalence of MRSA.[14] The sensitivity of this test is higher when used for HAP (sensitivity 85%, specificity 92%) than for VAP (sensitivity 40%, specificity 94%). Given that a patient's nasal colonization pattern reliably predicts which *Staphylococcus* species could be responsible for an ongoing pneumonia, the nasal swab has been widely used as an antibiotic stewardship tool, prompting safe discontinuation of anti-MRSA agents when negative, particularly in the context of HAP.[14]

The respiratory viral panel, a PCR-based nasopharyngeal swab, should be used especially during influenza season to identify viral causes of HAP and VAP for which antibiotic therapy may not be necessary.[1]

Within the first 2 days in the hospital, pneumonia is most likely attributable to community-acquired organisms. After 48 hours, culprit organisms include pathogens to which the patient was exposed in the hospital.[1]

Antibiotic use within the 90 days preceding new pneumonia is the only known risk factor consistently correlated with MRSA and multidrug-resistant *Pseudomonas aeruginosa* HAP and VAP.[1] Patients with the following risk factors may be additionally predisposed to VAP due to multidrug-resistant organisms:

- Cystic fibrosis or bronchiectasis
- Septic shock
- Acute respiratory distress syndrome
- Renal replacement therapy before VAP
- At least 5 days of hospitalization.[1]

Viruses cause up to 20% of cases of HAP and VAP.[15] An observational study of 262 patients with HAP determined that respiratory syncytial virus, parainfluenza virus, and rhinovirus were the most common causative pathogens, and 8% of all HAP cases were caused by bacterial and viral coinfection.[15]

Procalcitonin testing can help differentiate viral from bacterial pathogens in patients with HAP or VAP and potentially identify cases of coinfection. While any infectious pneumonia can elevate this serum biomarker, typical bacteria tend to lead to higher procalcitonin levels than atypical bacteria or viruses.[16] Cytokines, associated with bacterial infections, enhance procalcitonin release, whereas interferons, associated with viral infections, inhibit procalcitonin release.

Procalcitonin testing is not perfect, however, as procalcitonin is not elevated in up to 23% of typical bacterial infections.[16] A systematic review and meta-analysis of 15

In the absence of a new infiltrate, consider other causes of inpatient respiratory decline, including pulmonary embolism

randomized controlled trials in ICU patients evaluated procalcitonin guidance in initiating antibiotics compared with clinical judgment alone and noted no difference in short-term mortality. However, procalcitonin-guided cessation of antibiotics was associated with a lower mortality rate than cessation of antibiotics based on clinical judgment alone.[17]

In keeping with these results, the IDSA/ATS guidelines state that procalcitonin should not replace clinical judgment to decide on antibiotic initiation for patients with a diagnosis of HAP or VAP, but can be monitored over the course of therapy to note a trend, and can be used in conjunction with clinical judgment to de-escalate and eventually discontinue antibiotics.[1]

Our understanding of the use of procalcitonin in HAP and VAP management is still in its infancy. There is no consensus on this subject, but we offer the following, based on our own experience and the relationship between procalcitonin levels and cytokines and interferons:

- Elevated procalcitonin in a patient with a PCR-proven viral infection such as influenza can suggest bacterial superinfection and merit continuation of antibiotic therapy.
- A low-positive or negative procalcitonin level in a patient with PCR-proven viral infection may lend confidence to the diagnosis of viral HAP or VAP and prompt safe discontinuation of antibiotics.
- A negative procalcitonin in a patient with a clinical history suggesting alternative causes of respiratory decline or marked improvement with diuresis can also support antibiotic cessation.

Understanding of the use of procalcitonin in HAP and VAP is still in its infancy

MANAGEMENT OF HAP AND VAP

Although delaying the start of antibiotic therapy is associated with a higher risk of death in the context of sepsis, recent studies argue that antibiotics may not be immediately required in every patient with suspected HAP or VAP.

Two different strategies—clinical and bacteriologic—can be used in this decision. In the clinical strategy, antibiotics are started in patients with a new pulmonary infiltrate concerning for HAP or VAP if they meet 2 of the following 3 criteria: fever, productive cough, and leukocytosis. In the bacteriologic strategy, antibiotics are held until quantitative cultures of lower respiratory tract samples confirm a diagnosis of HAP or VAP.

A single-center observational study[18] comparing these 2 strategies noted that, while patients managed with the clinical strategy were rapidly started on antibiotics, they experienced a lower chance of receiving initially appropriate therapy, a longer duration of treatment, and a significantly higher rate of in-hospital mortality, possibly due to selection of resistant organisms. However, certain patients do merit prompt and aggressive antibiotic therapy even before culture results become available: those with hemodynamic or respiratory instability, those with immunocompromised status, and those for whom timely sampling of lower respiratory tract secretions is not feasible.[1]

Initial empiric coverage of MRSA, gram-negative bacteria

Once the decision to treat a patient with suspected HAP or VAP is made, an institution-specific antibiogram should guide the selection of an empiric antibiotic regimen that best addresses local organism prevalence and antibiotic resistance patterns.[1] If such an antibiogram is not readily available, a regimen with empiric coverage of methicillin-susceptible *S aureus* and gram-negative bacilli such as *P aeruginosa* should be selected, eg, piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem.

One antipseudomonal agent or two? Patients who recently received intravenous antibiotics or are at high risk of death merit double coverage of *P aeruginosa* with antibiotics from 2 different classes for empiric treatment of HAP. Placement in an ICU where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy is an additional indication for the initiation of 2 antipseudomonal agents to treat VAP.[1] Patients with *P aeruginosa* pneumonia complicated by bacteremia who receive empiric antipseudomonal combination therapy have a lower mortality rate than those who receive antipseudomonal monotherapy.[19] Combination therapy ensures timely initiation of at least 1 active agent. Patients who receive

antipseudomonal monotherapy may experience delays to the initiation of an appropriate antipseudomonal agent if resistance to the chosen agent is present.

Is MRSA coverage needed? Not all patients with HAP or VAP need empiric MRSA coverage. Vancomycin or linezolid should be initiated only in those who received intravenous antibiotics in the last 90 days, are hospitalized in a unit where at least 20% of *S aureus* isolates are methicillin-resistant or where the prevalence of MRSA is unknown, or are at high mortality risk.[1]

Additionally, despite the role of aspiration in the development of HAP and VAP, empiric anaerobic coverage is not always indicated. This is because over the first 48 hours of hospitalization, bacterial colonization of the oropharynx and endotracheal tube evolves from a predominance of streptococcal and anaerobic species to a predominance of gram-negative, nosocomial flora.

Role for inhaled antibiotics. The guidelines discourage the use of intravenous aminoglycosides and polymyxins, given concerns for nephrotoxicity in critically ill patients with HAP or VAP. However, for VAP due to pathogens susceptible only to aminoglycosides or polymyxins, inhaled aminoglycosides or colistin can and should be used in conjunction with their intravenous formulations.[1]

Systemic aminoglycosides achieve low concentrations in respiratory secretions and in epithelial lining fluid of the lung, resulting in subtherapeutic levels that may encourage the development of multidrug-resistant organisms.[20] Inhaled antibiotics are not associated with the degree of nephrotoxicity seen in patients given the equivalent intravenous formulations, and their addition to systemic antibiotics may allow for higher drug concentrations at the site of infection, which in turn may help improve clinical cure rates and reduce the duration of mechanical ventilation.

Adjunctive inhaled antibiotics have not been demonstrated to affect overall mortality rates in VAP. The relationships between adjunctive inhaled antibiotics and ICU length of stay, hospital length of stay, and prevalence of multidrug-resistant organisms have yet to be elucidated.

Final tailored regimen

Regardless of the empiric regimen initiated, culture susceptibilities can allow for appropriate tailoring of antibiotics to the culprit organisms responsible for HAP and VAP.

Aspiration events that precipitate HAP and VAP are inherently polymicrobial. Thus, even if sputum cultures demonstrate only 1 pathogen, the final antibiotic regimen used to treat a patient with suspected aspiration should still include coverage of oral and enteric flora, including gram-negative and anaerobic bacteria.

Duration of treatment

The duration of the antibiotic course in uncomplicated HAP and VAP is 7 days, as longer courses have not been shown to reduce rates of recurrent pneumonia, treatment failure, duration of mechanical ventilation, hospital length of stay, or mortality.[1] If a patient is hemodynamically stable, is needing less oxygen, and is tolerating oral intake, oral antibiotics can be used to complete a course of therapy for uncomplicated HAP or VAP.

HAP and VAP associated with pulmonary or extrapulmonary complications, such as empyema or bacteremia, merit longer course durations specific to these issues. Pneumonias due to *Pseudomonas* or *Acinetobacter* species are also considered complicated and merit at least 2 weeks of antibiotic therapy due to the risk of relapse associated with shorter course durations.[21] Follow-up chest imaging during the same admission is not indicated unless the patient continues to decline. In such a case, repeat radiography or computed tomography of the chest may detect a pulmonary complication requiring procedural intervention or, alternatively, may guide the clinician to search for unrelated causes of decline if signs on imaging are improved.

Infectious disease consultation for evaluation and antibiotic management can be helpful in an immunocompromised patient or a patient experiencing continued clinical decline on appropriate antibiotic therapy. Pulmonary consultation is indicated for patients who develop complications requiring procedural intervention such as empyema and in patients who merit invasive sampling of the lower respiratory tract.

Preventing HAP and VAP is as important as diagnosing and managing them

PREVENTING HAP AND VAP

Preventing HAP and VAP is as important as diagnosing and managing them and depends upon multiple approaches to address individual aspiration risk factors and nosocomial transmission of disease.

Preventing colonization and aspiration

Regular oral care, assessment of the need for proton-pump inhibitor and histamine-2-receptor blocker therapy, and early identification and treatment of dysphagia—especially in the elderly and in patients with recent stroke or surgical procedures—are key features to preventing oropharyngeal colonization of pathogenic organisms, aspiration, and ensuing HAP or VAP. A systematic review and meta-analysis including 2 studies of critically ill, nonventilated patients reported significant risk reduction in HAP through the use of chlorhexidine oral cleansing, electric toothbrushing, and oral hygiene instruction.[22]

Data supporting oral care in VAP prevention are more robust, with several institutions worldwide reporting reduced VAP incidence in association with ICU "bundles" including an oral care component.

Several institutions report decreased incidence of VAP using ICU care 'bundles'

One institution implemented a protocol involving twice-daily chlorhexidine oral cleansing in addition to elevating the head of the bed to more than 30 degrees, once-daily respiratory therapy-driven weaning attempts, and conversion from a nasogastric to an orogastric tube as feasible for all ventilated trauma patients.[23] One year after this protocol was implemented, the incidence of VAP had declined, and patients without VAP accrued fewer total ventilator days, ICU days, and hospital days, although their mortality rate was no lower than in patients with VAP.

Other strategies to reduce aspiration risk include maintaining tracheal cuff pressure, eliminating nonessential tracheal suction, and avoiding gastric overdistention. A 20-bed academic medical ICU developed a task force and an educational session to raise awareness about aspiration prevention with subsequent assessments of compliance with these strategies.[24] These interventions increased compliance dramatically over a 2-year time span, during which the center noticed a 51% decrease in VAP incidence as well as decreased ventilator days and healthcare costs. Standardized use of aspiration-prevention strategies and didactic modules, championed by an invested multidisciplinary team, can collectively reduce aspiration risk and associated pneumonia.[1]

Managing the microbiome

Probiotics and antibiotics in HAP and VAP prevention are still under evaluation. In theory, probiotics could reduce VAP by improving intestinal barrier function, increasing host cell antimicrobial peptides, and regulating the composition of intestinal flora to reduce overgrowth and colonization by pathogenic organisms.[25] However, large, randomized controlled trials should be conducted to determine the clinical efficacy of this strategy.

The French Society of Anesthesia and Intensive Care Medicine and the French Society of Intensive Care 2017 guidelines recommend selective digestive decontamination with a topical antiseptic administered enterally for up to 5 days to prevent HAP and VAP.[26]

These guidelines cite meta-analyses of randomized controlled trials demonstrating a relationship between selective digestive decontamination and decreased mortality as well as decreased acquisition of multidrug-resistant organisms, but acknowledge that the role of selective digestive decontamination may be limited in units that already face high prevalence of multidrug-resistant organisms. A theoretical risk of increased *Clostridioides difficile* incidence with routine selective digestive decontamination use has yet to be explored.

These seemingly opposing strategies of HAP and VAP prevention require further investigation.

Infection control

In addition to addressing individual patient risk factors for HAP and VAP, clinicians should address potential for nosocomial transmission of pathogens typically responsible for pneumonia.

Timely vaccinations for both patients and providers reliably reduce transmission of influenza, *Haemophilus influenzae*, and *Streptococcus pneumoniae* pneumonia.[27] While these pathogens are not commonly associated with the hospital setting, transmission from patients hospitalized with community-acquired pneumonia or from ill healthcare providers to oth-

ers on the same unit has been reported and may precipitate HAP and VAP.

Hospital-wide respiratory hygiene measures such as hand hygiene and the use of masks or tissues for patients with a cough can reduce the spread of respiratory pathogens. Observational studies suggest some benefit to routine stethoscope and procedural equipment cleaning, though single-patient stethoscopes and universal gown-glove contact isolation are primarily supported by theoretical benefit.

ONGOING EFFORTS

As we continue to face HAP and VAP in our hospital systems, ongoing efforts to improve their diagnosis, management, and prevention will be critical to reduce morbidity and mortality related to these nosocomial infections.

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