Hospital-Acquired Pneumonia: Pathophysiology, Diagnosis, and Treatment

Alicia N. Kieninger, MD[a], Pamela A. Lipsett, MD[b],*

Pneumonia is one of the most common nosocomial infections occurring in hospitalized patients. Hospital-acquired pneumonia (HAP) is pneumonia that occurs more than 48 hours after admission[1] and without any antecedent signs of infection at the time of hospital admission. The distinction of HAP from community-acquired pneumonia is important, as patients with HAP are susceptible to pneumonia from a different and potentially more virulent spectrum of organisms. Health care–associated pneumonia is a similar entity, occurring in patients who have been hospitalized in the last 90 days; live in nursing facilities; have received recent intravenous antibiotics, chemotherapy, or wound care; or who attend a hemodialysis clinic.[2] Based on their prior exposures, these patients have been found to be at risk for the same pathogens prevalent in HAP, and clinicians consider them the same disease. Treatment recommendations then take these risks into account. Ventilator-associated pneumonia (VAP), a subset of HAP, is pneumonia that stems from extended mechanical ventilation. Normally, pneumonia is categorized as VAP if it occurs after 48 hours of mechanical ventilation, but within 72 hours of the start of ventilation. If pneumonia occurs before 48 hours or after 72 hours, the cause is presumed to be unrelated to mechanical ventilation.

The impact of pneumonia on health care is significant in terms of morbidity, cost, and likely patient mortality.[3–5] To best prevent and treat HAP, it is important to have an understanding of the risk factors and pathophysiology leading to HAP. In addition,

[a] Department of Surgery, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Osler 603, Baltimore, MD 21287-4685, USA
[b] Department of Surgery, Anesthesiology and Critical Care Medicine, and Nursing, Johns Hopkins University Schools of Medicine and Nursing, 600 North Wolfe Street, Osler 603, Baltimore, MD 21287, USA
* Corresponding author.
E-mail address: plipsett@jhmi.edu (P.A. Lipsett).

knowledge of the varying diagnostic and treatment regimens may lead to improvements in patient care and outcomes. This understanding takes on increased importance as the focus of medicine shifts toward decreasing preventable complications.

EPIDEMIOLOGY
Incidence

HAP represents one of the most common nosocomial infections, with significant impact on patient morbidity and mortality, as well as on the cost of health care. Accounting for 15% of all hospital-acquired infections, nosocomial pneumonia is a frequent lethal complication of hospitalization.[6] At a rate of 3 to 10 cases per 1000 hospital admissions, HAP may increase a patient's hospital stay by more than a week, resulting in up to $40,000 in additional costs and a threefold increase in mortality.[1,3,5,7] VAP represents a large and important subset of HAP. The overall risk of VAP is estimated at 3% per day for the first 5 days of mechanical ventilation, 2% per day for days 6 through 10, and 1% per day for every day beyond 10 days of mechanical ventilation, with each day of mechanical ventilation adding infectious risk.[1]

Risk Factors

The pathogenesis of HAP is multifactorial. The concomitant illnesses of hospitalized patients place them at risk for nosocomial infections. Alterations in patient immune function allow pathogens to cause invasive infections that would not occur in healthy individuals. Many hospitalized patients experience poor nutrition, increasing their risk of infection.[8] Severe illness and hemodynamic compromise have also been associated with increased rates of HAP.[9]

Aspiration of oropharyngeal secretions plays a significant role in the development of HAP.[10] As many as 45% of all healthy individuals may aspirate during sleep. However, the combination of depressed immune function, impaired mucocilliary clearance of the respiratory tract, and the presence of more pathogenic organisms makes aspiration a significant contributor to HAP.[6,11] Supine positioning contributes greatly to this aspiration risk and has been demonstrated to increase the rate of HAP among hospitalized patients.[12,13]

The oropharynx of hospitalized patients is colonized by enteric gram-negative pathogens. Risk factors for these pathogens include prolonged hospital length of stay, cigarette smoking, increasing age, uremia, prior antibiotic exposure, alcohol consumption, endotracheal intubation, coma, major surgery, malnutrition, multiple organ-system failure, and neutropenia.[6] Additionally, the use of stress ulcer prophylaxis, such as histamine blockers and proton pump inhibitors, is now a mainstay treatment for intensive care unit (ICU) patients. While histamine blockers and proton pump inhibitors are effective in preventing gastrointestinal bleeding, their use is also associated with increased gram-negative colonization of the aerodigestive tract,[1] increasing the risk of HAP due to these organisms. Finally, foreign bodies, such as endotracheal and nasogastric tubes, provide a source for further colonization and act as physical conduits for the migration of pathogens to the lower respiratory tract.[1]

PATHOPHYSIOLOGY
Microbiology

The causative organisms for HAP differ significantly from those typically responsible for community-acquired pneumonia.[1,14–16] The clinical setting in which HAP arises is likely to influence the likely causative organisms. Not only does this change in microbiology affect the appropriate treatment, but it also has implications on morbidity and

mortality. HAP arising early (<5 days) in the hospital course is associated with a better prognosis than late-onset HAP.[1] Thus, HAP can be divided into two categories: early onset (arising less than 5 days into a hospital course) and late onset (arising 5 days or later into a hospital course). These two categories can then be further subdivided into categories of patients with prior antibiotic exposure and patients without prior antibiotic exposure.

Early-onset HAP in patients with no prior antibiotic exposure tends to mirror community-acquired pneumonia. The most common pathogens include *Enterobacteraciea, Haemophilus influenzae, Streptococcus pneumonia,* and methicillin-sensitive *Staphyloccous aureus.*[15] Patients with recent antibiotic exposures are susceptible to the above organisms, in addition to non–lactose fermenting gram-negative bacilli. Late-onset HAP in patients with no prior antibiotic exposure presents with similar bacteria. However, occasionally these patients present with gram-negative bacilli resistant to first-generation cephalosporins. The preceding three categories of microbes involve generally antibiotic-sensitive organisms. The final category, late-onset HAP with prior antibiotic exposure, presents a greater problem in both the prediction of and empiric treatment of likely pathogens. As many as 40% of these patients present with potentially multidrug-resistant pathogens, including *Pseudomonas aeruginosa, Acinetobacter baumannii,* and methicillin-resistant *Staphylococcus aureus* (MRSA).[15]

Gram-Positive Bacteria

The common gram-positive cocci causing pneumonia in hospitalized patients are *S pneumoniae* and *S aureus. S pneumoniae* colonizes the upper airways and is a common causative organism of community-acquired pneumonia.[16] For this reason, *S pneumoniae* is more likely to be associated with early-onset HAP than late-onset HAP.[15,17] *S pneumoniae* is rarely resistant to traditional beta-lactam antibiotics. *S aureus* also frequently colonizes the upper airways, particularly the nasal passages. Younger patients hospitalized with traumatic brain injuries are at increased risk of pneumonia due to *S aureus.*[18] This organism can cause pneumonia at any point in the hospital course. Early on, most isolates are sensitive to penicllinase-resistant beta-lactam antimicrobials (methicillin-sensitive *S aureus*). However, patients who have been hospitalized for longer periods or exposed to prior antimicrobial therapy are at increased risk for MRSA.[18]

MRSA is a gram-positive coccus that frequently colonizes the nares of hospitalized patients and is seen even now as a community-acquired pathogen. Risk factors for MRSA pneumonia include chronic obstructive pulmonary disease (COPD), longer duration of mechanical ventilation, prior antibiotic exposure, prior use of corticosteroids, and prior bronchoscopy.[16] Its resistance mechanisms develop via a penicillin-binding protein that causes decreased affinity for beta-lactam antimicrobials, leaving a narrow spectrum of treatment options for MRSA.[1]

Gram-Negative Bacteria

Early-onset HAP is associated with *Hemophilus influenzae* and lactose-fermenting gram-negative bacilli, such as *Enterobacteraciae*. As with *S pneumoniae*, *H influenzae* is a common cause of community-acquired pneumonia and is easily eradicated when treated.[17] *Enterobacteraciae* are lactose-fermenting enteric gram-negative bacilli. This group of organisms includes *Echerichia coli, Klebsiella* spp and *Enterobacter* spp. Overgrowth of these organisms can be associated with prior antibiotic therapy, and their virulence may increase in critical illness. *Enterobacteraciae* spp are increasingly demonstrating extended-spectrum beta-lactamase activity (ESBL). While these organisms were frequently treated with broad-spectrum beta-lactam antimicrobials,

plasmid-mediated resistance to these agents is increasing.[19] ESBL-producing strains are considered resistant to all beta-lactam agents.[20] They additionally demonstrate a high rate of concomitant resistance to fluoroquinolones, making carbapenems the recommended first-line agents for ESBL-producing strains.[19,20]

P aeruginosa is the most common multidrug-resistant gram-negative bacillus causing HAP/VAP[1,16] and is the most frequent VAP isolate in patients on mechanical ventilation for more than 4 days.[7] Risk factors are similar to those of MRSA. Resistance is acquired via the formation of multiple efflux pumps that force antibiotics back out of the cell. *Pseudomonas* also develops increased resistance to many different types of beta-lactam antimicrobials. Patients with pneumonia caused by multidrug-resistant *P aeruginosa* are at increased risk of severe sepsis and death.[21] Specifically, infection with non–lactose-fermenting gram-negative bacilli, of which *Pseudomonas* is the most common, has been suggested to be an independent predictor of death and recurrence.[22]

A baumannii represents an emerging pathogen in the care of critically ill patients with pneumonia. The rates of infection among injured military personnel in the Middle East are high.[23] Moreover, epidemiologic studies examining the military health system indicate that outbreaks stem from contamination of hospital equipment rather than inoculation of wounds from the environment.[23,24] *Acinetobacter* spp are aerobic, non–lactose-fermenting gram-negative bacilli frequently found in soil and fresh water.[16] While normally of low virulence, those strains recovered in injured and hospitalized patients have intrinsic resistance to many antibiotics, and cause nosocomial infections that may spread rapidly among hospitalized patients.[16,24] Mechanisms of antimicrobial resistance of *Acinetobacter* spp are threefold, and several mechanisms may be at work in any given strain.[24,25] Due to its ability to rapidly acquire resistance to many drugs, prior antibiotic exposure is a significant risk factor for resistance.[26]

PREVENTION
Patient Risk Modification

Preoperative risk factors to help stratify and modify risk in patients have been widely applied in cardiac prediction models.[27] Several substantial studies have attempted to create a similar pulmonary risk index.[28–31] The National Surgical Quality Improvement Program (NSQIP) and the Patient Safety in Surgery (PSS) study are national collaborative efforts that have sought to decrease complications among surgical patients. Using data from the NSQIP and PSS, Johnson developed the Respiratory Risk Index, which may be more broadly applicable.[32] This index is a scoring system that categorizes patients as low, medium, or high risk for postoperative respiratory failure, based on such factors as emergency and complex surgeries, American Society of Anesthesiologists (ASA) status, and patient comorbidities (eg, COPD, ascites, renal failure). While these studies focus on respiratory failure in general, they likely correlate with risk factors for HAP specifically.

Targeting modifiable risk factors can decrease rates of postoperative pneumonia. Current smoking increases the risk for postoperative pulmonary complications threefold[33–37] even in patients without chronic lung disease. Paradoxically, patients who stop smoking immediately before surgery appear to be at a higher risk of pulmonary complications than those who are still smoking and those who have quit for a longer period of time.[34,36] While this finding is unexplained and somewhat paradoxical, patients who smoke and will undergo elective surgery should be encouraged to stop smoking at least 8 weeks before surgery whenever possible. In patients with COPD and asthma, as well as congestive heart failure, it is important to optimize their treatment preoperatively. For patients with asthma and COPD, preoperative steroids and

measurement of peak inspiratory flow may dictate when a patient is in his or her personal best condition. This should be the goal for elective preoperative therapy.

Postoperative pain control is essential to decrease pulmonary complications. Neuraxial anesthesia may have a 20% absolute reduction in risk of pulmonary complications.[38] Procedure site and its relation to postoperative pain also have a significant impact on respiratory complications. There is an inverse relationship between pulmonary complications and distance of the incision from the diaphragm,[39] making postoperative pain control a significant modifiable risk factor.

Minimizing Aspiration Risk

As previously described, aspiration of oropharyngeal and gastric secretions contributes greatly to nosocomial pneumonia. Hospitalized patients frequently have nasogastric and nasoenteric tubes placed for various reasons, such as for decompression of the digestive tract or facilitation of enteral feedings. Patients with nasogastric tubes in place demonstrate increased rates of pharyngeal aspiration, regardless of the size of the tube.[40] The role of percutaneous endoscopic gastrostomy versus nasogastric tube feedings has been debated with no clear evidence-based conclusion about whether one is better than the other.[41,42] Realistically, the elimination the use of nasogastric tubes in hospitalized patients is impossible. The clinician must carefully evaluate the need for enteral access and perhaps consider solutions that eliminate nasal tubes for patients who require long-term enteral access.

Patient positioning can also have a significant impact on rates of pneumonia. Among 86 patients randomized to the semirecumbent position (45°) versus supine position (0°), patients in the supine position had significantly higher rates of pneumonia.[13] Similarly, Metheny[10] demonstrated that patients who had more frequent aspiration events were more likely to have been maintained with their head of bed at less than 30°. Current guidelines for prevention of VAP recommend semirecumbent positioning for all patients without contraindications to doing so.[1,28,43] Diligence is required in this endeavor, as the goal of 45% head-of-bed elevation is not reached as much 85% of the time.[44]

Decontamination of Digestive Tract

Organisms colonizing the upper aerodigestive tract in hospitalized patients are frequently associated with HAP. Elimination of these colonizing organisms may significantly impact the rates of HAP. The majority of the research into this area has focused on its effect on nosocomial infections and colonization with drug-resistant bacteria.[15,45] Poor oral hygiene contributes significantly to the incidence of VAP in intubated patients. Nurses must understand their important role in improving oral hygiene and its effect on rates of pneumonia. Education and diligence with current patient care standards can be a powerful starting point for decreasing rates of VAP. An education program focusing on the role of oral hygiene in prevention of VAP was accompanied by a reported 50% decrease in institutional VAP rates.[46] Good oral hygiene alone will not eliminate VAP, however. For this reason, there is interest in the effects of eliminating colonizing organisms from the oropharynx with the use of antimicrobial solutions. A large prospective, randomized, double-blind, placebo-controlled trial of more than 900 patients using a chlorhexidine oral rinse and nasal gel to decrease rates of nosocomial infections in cardiac surgery patients found a significantly lower rate of lower respiratory tract infections in the treatment group.[47] While this study focuses purely on cardiac surgery patients, the large sample size makes the results very compelling. In a recent meta-analysis, the use of chlorhexidine resulted in a 59% relative risk reduction for VAP in surgical patients.[48] However, the findings of this study were limited by significant heterogeneity among the trials examined.

Aspiration of gastric contents has also been felt to contribute to nosocomial pneumonia. Selective decontamination of the digestive tract (SDD) involves, in addition to topical antimicrobials, an oral antibiotic regimen and possibly a brief course of systemic antibiotics. A meta-analysis published in 1994 included 2270 patients in randomized trials and attempted to assess the impact of SDD on mortality and rates of respiratory tract infections.[49] While investigators found a significant decrease in the rate of nosocomial pneumonia in the treatment group, specifically due to gram-negative bacteria, this study found no difference in overall mortality between the two groups. Additionally, the study noted several trials demonstrating trends toward increased colonization with drug-resistant organisms in the treatment group.

More recently, de Jonge and colleagues[45] re-examined the effect of SDD on colonization with drug-resistant organisms. They found no difference in ICU or hospital mortality between control patients and those randomized to SDD. The rate of acquired colonization of gram-negative bacteria was 16% in the treatment group versus 26% in the control group. While this study did not demonstrate a negative impact of SDD with respect to antibiotic resistance, concern for this outcome remains. Current clinical practice guidelines recommend that topical antibiotics not be used alone. There is insufficient data regarding the cost-effectiveness of intravenous antibiotics or regarding their impact on antibiotic resistance to make any recommendations about their use for SDD.[43]

Finally, an important contributor to upper digestive tract colonization in critically ill patients is stress ulcer prophylaxis. Many ICU patients are at increased risk of upper gastrointestinal bleeding secondary to stress ulceration, with an associated increase in morbidity and mortality.[50,51] For this reason, these patients are frequently treated with such medications as histamine blockers and proton pump inhibitors to curb their risk of bleeding. The normal acidic environment of the stomach renders it essentially sterile. Today's antacid medications are able to decrease gastric acid secretion by approximately 80%. This alteration in the acid content of gastric secretions is likely to promote rather than inhibit bacterial colonization. The question of whether or not agents that increase gastric pH and control stress ulcer bleeding are associated with increased rates of nosocomial pneumonia when compared with agents that reduce bleeding but do not affect pH has been the subject of much debate and some study. Decreased rates of nosocomial pneumonia have been shown in patients treated with sucralfate as compared with antacid medications or ranitidine.[33,52] However, these decreased rates of pneumonia may come at the cost of increased gastrointestinal bleeding.[52] As it stands, patients felt to be at high risk for stress ulceration (eg, patients with head trauma, burns, prolonged mechanical ventilation, coagulopathy) should continue to be treated with medications that increase gastric pH. Consideration should be given to limiting the use of these medications in patients not truly at high risk for bleeding.[28,43]

Endotracheal Tube and Ventilator Management

The endotracheal tube and ventilator circuit present another area commonly targeted for risk reduction. Specifically, the endotracheal tube is a foreign body that forms a direct conduit from the heavily colonized oropharynx to the normally sterile trachea. The presence of an endotracheal tube allows biofilm formation and promotes entrapment and adherence of bacteria to the biofilm, where antibiotics do not penetrate well. Some investigators have suggested the use of specialized endotracheal tubes that resist the formation of biofilm, or the use of mucous shaving devices to remove biofilm from the interior of the tube.[53] Currently, the cost associated with implementing these measures has limited their use.

The route of endotracheal intubation has also been considered as a risk factor for VAP. Many investigators have suspected nasotracheal intubation to be associated with increased rates of nosocomial maxillary sinusitis. Results of studies examining this topic are not conclusive.[54–56] Of 399 nasotracheally intubated patients, those who underwent weekly screening and treatment where indicated for sinusitis, had a significantly decreased rate of VAP as compared with patients who were not screened for sinusitis (relative risk, 0.61; 95% CI, 0.4–0.93).[54] Whether or not such aggressive screening for sinusitis is cost-effective is not clear, but clinicians should maintain an appropriate index of suspicion for sinusitis, and investigate further when indicated.

The elimination of secretions pooling on the endotracheal tube cuff has been successful in clinical trials by reducing tracheal contamination.[57,58] A study randomizing cardiac surgery patients to traditional endotracheal tubes versus those with a subglottic suction port did not demonstrate a significant decrease in VAP. However, the time to VAP occurrence was 5.6 days in the treatment group, versus 2.9 days in the control group ($P = .006$).[57] This delay to onset of VAP has been echoed in a recent meta-analysis.[59] The additional cost for treatment is approximately $14 per tube. An endotracheal tube with a subglottic drainage port, as well as a polyurethane cuff, has also shown promising results. The high-volume, low-pressure cuff is designed to have fewer longitudinal channels that allow secretions to run down below the cuff, and may be associated with a more than 50% risk reduction for VAP.[58] Based on the above results, current evidence-based prevention guidelines advocate the use of subglottic secretion drainage.[2,28,43]

The method of endotracheal tube suctioning has not been shown to influence the rates of VAP.[60–64] Closed suctioning systems are thought to have several advantages:

Positive pressure in the ventilator circuit is maintained.
Exogenous contamination of the endotracheal tube is prevented.
The need for barrier precautions on performance of suctioning is eliminated.
The surrounding environment is left uncontaminated.

Studies looking at this topic are heterogeneous and inconclusive.[61–63] Current guidelines describe these techniques as equivalent for patient care, with a slight cost savings associated with the reusable closed suction techniques.[43]

Management of the ventilator circuit has been examined as a method to prevent VAP. Frequent changing of the ventilator circuit, while attractive theoretically, has not been shown to decrease rates of VAP.[65–67] Circuit changes should occur only when tubing is visibly soiled and, of course, between patients.[28,43,68]

Similarly, the method of humidification of the ventilator circuit has been targeted for risk reduction. Previous studies indicate that heat- and moisture-exchange filters may be associated with decreased rates of colonization of ventilator circuits when compared with heated humidifiers.[69] These results have led some to recommend the use of heated moisture exchangers to decrease the risk of VAP.[43] Recently, two large randomized studies compared rates of VAP for heated humidification systems versus those for heat- and moisture-exchange filters.[70,71] The studies found no difference between the groups in rates of pneumonia, rates of mortality, or length of mechanical ventilation. The current guidelines from the American Thoracic Society do not recommend the use of heated moisture exchange filters for VAP prevention.[1]

Sedation and Ventilator Weaning

Risk of VAP is associated with length of mechanical ventilation.[1] Mechanically ventilated patients are frequently given sedative infusions both for their comfort and to

prevent self-injury. However, these medications depress levels of consciousness and respiration. Patients randomized to receive daily interruptions of their sedative medications spend fewer days on mechanical ventilation and fewer days in the ICU than those receiving traditional care.[72] Daily wake-ups are also associated with a decreased incidence of VAP as compared with control patients, whose sedation was interrupted only at the discretion of the clinician.[73] Efforts to improve the efficiency of ventilator weaning have also met with success. Patients randomized to a ventilator management protocol, including a daily spontaneous breathing trial, have been shown to spend fewer days on the ventilator.[74]

In a recent study by Girard and colleagues,[75] these efforts were implemented in a paired fashion. Patients were randomized to receive a daily spontaneous awakening trial followed by a spontaneous breathing trial, versus usual care with a daily spontaneous breathing trial. Study patients were found to have increased ventilator-free days, decreased ICU length of stay, and decreased mortality. The above studies have indicated that implementation of protocols designed to minimize mechanical ventilation can lead to decreased rates of VAP.

Pulmonary Hygiene

Pulmonary hygiene, or the ability to cough and clear secretions, plays an important role in the development of HAP. Surgical patients, in particular, suffer from an impaired ability to cough and deep breathe secondary to incisional pain leading to splinting. Thoracic and abdominal procedures are associated with the highest risk of pneumonia.[76] The use of incentive spirometry to improve patients' ability to cough and deep breathe is encouraged to decrease the risk of HAP. A recent Cochrane Review examined the use of incentive spirometry as a preventative measure in patients' status post–coronary artery bypass grafting with a single study demonstrating a nonsignificant reduction in pneumonia.[77] That being said, current guidelines still recommend the use of either incentive spirometry or cough and deep breathing exercises as a preventative measure.[2,39]

DIAGNOSIS
Clinical Evaluation

The method of establishing the diagnosis of HAP remains controversial and no method has emerged as the gold standard. A multitude of possible explanations exist for new-onset fevers and leukocytosis. Attempting to establish the diagnosis of pneumonia on radiological studies alone is similarly unreliable. For these reasons, clinical guidelines are available to aid in decision making about who does and does not have pneumonia. The Centers for Disease Control and Prevention and the National Healthcare Safety Network have developed criteria for the diagnosis of nosocomial pneumonia, taking into account clinical factors, such as fever and leukocytosis, as well as radiological criteria, including persistent new findings on chest radiograph (**Box 1**).[78] Physicians have used these types of clinical features to formulate the diagnosis of pneumonia for years. However, many investigators have questioned the reliability of the physician's clinical impression. Autopsy studies have shown that relying on a clinical diagnosis of pneumonia is unsatisfactory,[79,80] Many clinical circumstances make it difficult to determine the likelihood of pneumonia, and antibiotics are frequently used when pneumonia is not present. These results call into question the physician's ability to diagnose pneumonia based solely on clinical findings. The Clinical Pulmonary Infection Score (CPIS) was developed to help quantify clinical findings and minimize either the initiation of antibiotic therapy or to influence its duration. CPIS represents a "weighted

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Box 1
Centers for Disease Control and Prevention criteria for nosocomial pneumonia (adult)

Radiology

　Two or more serial chest radiographs[a] with at least one of the following:

　　New or progressive and persistent infiltrate

　　Consolidation

　　Cavitation

Signs/symptoms/laboratory

　At least one of the following:

　　Fever (>38°C or >100.4°F) with no other recognized cause

　　Leukopenia (<4000 white blood cell count per microliter [WBC/μL] or leukocytosis (>12,000 WBC/μL)

　　For adults 70 years old or older, mental status changes with no other recognized cause

And at least two of the following:

　New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements

　New-onset or worsening cough, or dyspnea, or tachycardia

　Rales or bronchial breath sounds

　Worsening gas exchange (Pao$_2$/fraction of inspired oxygen [Fio$_2$] ≤240), increased oxygen requirements, or increased ventilation demand

[a] In patients with no underlying pulmonary or cardiac disease, one definitive radiograph is acceptable.

From Centers for Disease Control and Prevention. Available at: www.cdc.gov/ncidod/hop/nnis/members/pneumonia/final/pneumoniacriteriav1. Accessed May 1, 2008.

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approach'' to the clinical diagnosis.[81] This scoring system includes both clinical and radiological factors that increase the likelihood of the presence of pneumonia. Point values are assigned to each criteria and a sum is calculated. Traditionally, a threshold score of more than six has been used to diagnose pneumonia (**Table 1**).[82]

The clinical utility of this scoring system has been evaluated extensively. In a review of 40 specimens obtained from bronchoalveolar lavage (BAL), Pugin[82] compared the findings to clinical data. In this study, the CPIS correlated with BAL results in 80% of cases. In cases where the CPIS was more than six, 93% had bacteriologic evidence on pneumonia based on BAL. On the other hand, of cases where the CPIS was six or less, no patient satisfied the microbiologic criteria for pneumonia. These results indicate that the CPIS may be good predictor of the presence of pneumonia in mechanically ventilated patients.

On the other hand, some investigators suggest that the CPIS, while being very sensitive, lacks specificity and leads to unnecessary antimicrobial treatment. In a study of 201 patients who underwent an invasive diagnosis of pneumonia, patients with VAP had the same CPIS as patients without VAP. The CPIS strategy agreed with bronchoscopy findings in 65% of patients. In patients without VAP on BAL, 53% would have received antibiotics based on their CPIS. The CPIS strategy in these patients would have led to 840 days of empiric antibiotic treatment as compared with 424 days when the invasive strategy was used.[83]

Table 1			
Modified Clinical Pulmonary Infection Score			
	Points		
Measurement	**0**	**1**	**2**
Temperature (°C)	36.5–38.4	38.5–38.9	≤36.4 or ≥39
Peripheral white blood cell count	4000–11,000	<4000 or >11,000 (>50% bands: add 1 extra point)	
Tracheal secretions	None	Nonpurulent	Purulent
Chest radiograph	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Progression of infiltrate from prior radiographs	None		Progression (acute respiratory distress syndrome or congestive heart failure thought unlikely)
Culture of endotracheal tube suction	No growth/light growth	Heavy growth (Some bacteria on gram stain: add 1 extra point)	
Oxygenation (Pa_{O_2}/ fraction of inspired oxygen [F_{IO_2}])	>240 or acute respiratory distress syndrome		≤240 and no acute respiratory distress syndrome

Adapted from Swoboda SM, Dixon T, Lipsett PA. Can the clinical pulmonary infection score impact ICU antibiotic days? Surg Infect (Larchmt) 2006;7:331–9; with permission.

While most studies indicate that clinical evaluation is extremely sensitive in identifying VAP, the specificity is quite low. Clinical diagnosis combined with short-course antibiotic therapy may be reasonable.[84] In a 2000 study, Singh[85] examined short-course empiric therapy for patients in the ICU with suspected VAP. Patients with a new pulmonary infiltrate and a CPIS of six or less were randomized to receive a standard 10 to 21 days of antimicrobial therapy versus 3 days of empiric ciprofloxacin. The CPIS was re-evaluated after 3 days and, if it remained six or less, patients in the experimental group had therapy discontinued. The rate of antimicrobial resistance or superinfection was significantly higher in patients receiving standard therapy. The duration of antimicrobial therapy was significantly lower in the experimental group, with no difference in mortality. This study suggested that patients with suspected VAP could be safely treated with an initial short course of antimicrobial therapy, followed by re-evaluation of their clinical status. However, while this strategy helps limit overall antibiotic exposure, patients will continue to be exposed patients to unnecessary antibiotics. Clinical guidelines can aid physicians in the diagnosis of suspected HAP, but clinical judgment remains somewhat unreliable.

BACTERIOLOGIC EVALUATION

The bacteriologic diagnosis of pneumonia involves sampling the lower airways to obtain quantitative cultures. Blind tracheobronchial aspiration (TBAS) is a noninvasive technique accomplished by inserting a flexible catheter into the distal trachea via

the endotracheal tube. Suction samples are obtained and sent for quantitative culture. The typical threshold for diagnosis of pneumonia is growth of more than 10^5 colony forming units per milliliter (cfu/mL). This technique has the advantage of being relatively noninvasive and offers a distinct bacterial load to establish the diagnosis of pneumonia. However, the blind nature of the technique prevents directed sampling of specific lung segments known to have an infiltrate on radiograph, possibly increasing the false-negative rate. Additionally, contamination of the suction catheter is difficult to prevent as it traverses the endotracheal tube and more proximal airways, possibly increasing the false-positive rate.

More invasive techniques involve bronchoscopically guided sampling of the lower airways. BAL allows sampling of specific lung segments suspected to be involved with pneumonia. The bronchoscope is advanced and wedged in a distal airway. The airway is then irrigated with approximately 50 mL of sterile saline, which is retrieved after several seconds. This process is repeated and the samples are pooled. Bacterial growth of more than 10^4 cfu/mL is consistent with pneumonia.[1,86] The advantage of this technique is that it allows the clinician to perform directed sampling of the airway, ideally limiting the false-negative rate. It also provides a bacteriologic cut-off for the diagnosis of VAP. Unfortunately, the technique is highly operator dependent. Contamination of the bronchoscope and other technical problems can compromise the results. Some investigators have also questioned the accepted diagnostic cut-off of 10^4 cfu/mL, suggesting that the use of 10^5 cfu/mL provides fewer false positives and reduces the use of inappropriate antibiotic therapy.[87] Finally, BAL is an invasive procedure with possible complications. Use of the bronchoscope can cause alterations in oxygenation and ventilation that may be poorly tolerated by some patients. Additionally, bronchoscopy can be associated with such complications as bleeding, airway inflammation, and pneumothorax.

The final invasive microbiologic diagnostic technique is use of the protected specimen brush (PSB). The telescoping catheter brush is advanced blindly or through a bronchoscope directed in the suspected distal airway. Serial dilutions of the specimen are performed. A diagnostic cutoff of more than 10^3 cfu/mL is typically accepted as being consistent with HAP.[1,87] This technique has similar advantages and disadvantages to those of BAL. If bronchoscopy is used, PSB does offer the advantage that the specimen brush is protected from contamination with upper airway secretions, as it is not advanced until properly positioned in the distal airway. There is a concern that the risk of bleeding or pneumothorax as a complication may be higher with PSB, and thus patients with thrombocytopenia may be at slightly greater risk with this technique.

Many studies have looked at the utility of various quantitative culture techniques. Heyland[88] found that patients undergoing invasive testing with BAL or PSB were ultimately treated with fewer broad-spectrum antibiotics and fewer antimicrobials overall. Timsit[89] found that direct examination of BAL fluid had an overall sensitivity and specificity of 93.6% and 91.5% for the diagnosis of VAP, focusing on the intracellular organism count as a guide to diagnosis. He found that for patients who had empiric therapy started based on the results of BAL fluid examination, only 12% received incorrect empiric therapy. With early appropriate antibiotic therapy being an important predictor of mortality, a technique that facilitates early guidance of therapy may be very clinically useful.

Ruiz[90] compared invasive and noninvasive quantitative cultures in a randomized trial looking at PSB versus TBAS. This study showed no difference in ICU length of stay, length of mechanical ventilation, 30-day mortality, or attributable mortality between the two study groups. The cost was $29 per patient for PSB versus $368 per

patient for TBAS. The only independent factor found to influence growth in culture was the presence of antimicrobial treatment at the time of sampling.

More recently, the Canadian Critical Care Trials group demonstrated similar findings in looking at BAL compared with TBAS.[91] They randomized 740 patients on mechanical ventilation for more than 4 days with a clinical suspicion of pneumonia to BAL with quantitative culture versus TBAS with qualitative culture. This study controlled for the time of initiation of empiric antibiotic therapy, which was after completion of the diagnostic study in both groups. The choice of empiric therapy was also considered. Investigators found no difference in 28-day mortality between patients undergoing BAL as compared with those undergoing TBAS. Additionally, there were no differences in the secondary outcomes of hospital and ICU length of stay, duration of mechanical ventilation, or ICU and hospital mortality.

These results are somewhat in contradistinction to the large randomized trial completed by Fagon and colleagues.[92] This study of 413 patients randomized to invasive versus noninvasive diagnosis of VAP found decreased 14-day mortality and improved organ function scores in patients undergoing invasive diagnosis. These patients also were subject to fewer days of antibiotic therapy and fewer numbers of antibiotics, and identification of pathogenic processes that required intervention, such as intra-abdominal infection. The hazard ratio for death at 28 days for patients who underwent noninvasive diagnosis and management was 1.54 (95% CI, 1.10–2.16).

Many authorities continue to recommend invasive techniques even though such techniques have yet to demonstrate that they reduce mortality rates. In patients with a high incidence of systemic inflammatory response syndrome, clinical criteria alone are associated with a high false-positive rate. These patients are frequently given antibiotic therapy based on clinical findings. With further evaluation of these patients by BAL, pneumonia can be frequently ruled out and antibiotics discontinued.[93] In another study, Croce[94] demonstrated that TBAS and gram stain provide inadequate data on which to base empiric treatment because of a poor correlation between findings on gram stain of BAL fluid versus results of quantitative culture. In this study, the best diagnostic yield was seen when clinical suspicion was used to prompt further testing by invasive techniques.

The utility of invasive culture techniques may not be found in the primary diagnosis of VAP. Shorr[95] evaluated four randomized trials of diagnostic techniques and found that invasive strategies do not ultimately affect mortality related to VAP. This is likely because empiric antibiotic choices must be made before knowing the results of quantitative cultures. However, invasive cultures may play an important role in decreasing antibiotic use, an effect that may have an indirect impact on mortality.

TREATMENT
Empiric Therapy

The most important factor influencing the mortality of HAP is prompt and adequate empiric treatment. Multiple studies have demonstrated that delays in appropriate antibiotic therapy are associated with increased mortality.[1,15,96,97] In a study looking at inadequate empiric therapy for VAP in trauma patients, Mueller[97] found that mortality, ICU length of stay, and duration of mechanical ventilation all increased with the number of episodes of inadequate empiric therapy. Treatment should be instituted immediately after specimen collection and should be directed against likely specific pathogens. The choice of empiric therapy should account for patient risk factors, such as length of hospital stay, duration of mechanical ventilation, previous culture results, previous antibiotic exposure, and immunosuppression. Specifically, the number

of days spent on mechanical ventilation and prior antibiotic administration have both been demonstrated to be independent risk factors for HAP secondary to multidrug-resistant pathogens.[98] Local community- and hospital-resistance patterns should also be considered. In general, common hospital-acquired pathogens include MRSA, *P aeruginosa, Klebsiella*, and *Acinetobacter* sp.[16,87,99]

Vancomycin has become the most commonly used agent to treat MRSA in hospitalized patients. Pulmonary infections with MRSA present a particular problem because vancomycin has poor penetration of lung tissue. Higher plasma levels are required to achieve therapeutic concentrations in the lung, leading to potentially increased toxicity. Such difficulties in dosing also lead to increased recurrence rates after treatment with vancomycin.[22] An additional consideration is concern for emergence of vancomycin resistance. Recent studies have demonstrated a trend of increasing mean inhibitory concentration toward vancomycin (>2 μg/mL), indicating decreasing susceptibility.[100,101] Based on these trends, it is unclear if vancomycin remains the drug of choice for treating MRSA pneumonia. To ensure adequate antibiotic coverage at the start of treatment, alternative therapies have emerged for treatment of MRSA in the face of increasing concern for vancomycin resistance.[101–103] When compared with pneumonia caused by methicillin-sensitive *S aureus*, MRSA is associated with a prolonged ICU length of stay and increased hospital costs, despite appropriate initial therapy.[104]

Due to the incidence of resistance discussed previously, acinetobacter pneumonias may be particularly difficult to treat. Carbapenem agents are the initial drug of choice for *Acinetobacter* spp, if susceptibility is retained.[24] Beta-lactamase inhibitors, such as sulbactam, may also be considered, as these agents have intrinsic activity against *Acinetobacter.*[1] In as many as 50% of cases, acinetobacter isolates may be resistant to all antimicrobials except the polymyxins.[105,106] There is some evidence that treatment with intravenous or inhaled polymyxin E (Colistin) may be a safe and effective treatment for patients with pneumonia secondary to this highly resistant organism.[105,107]

The question of whether or not to cover potentially multidrug-resistant gram-negative pathogens, such as *P aeruginosa,* with two antimicrobials remains unanswered.[15,108] There has been considerable debate regarding combination therapy for nosocomial pneumonia, particularly when concern exists for potentially drug-resistant pathogens.[109,110] Those in support of combination therapy argue that synergy between agents with different mechanisms improves response to treatment and decreases the risk of developing antibiotic resistance.[109] In addition, with two drugs the probability that one of the drugs will cover the pathogen initially is increased. Others argue, however, that monotherapy is effective in most cases, and combination therapy results in unnecessary antibiotic exposure. In addition to placing patients at risk for antibiotic toxicity, this approach can also lead to antibiotic resistance.[110] In a study of trauma patients, Croce[111] found that patients treated with a combination of a third-generation cephalosporin and gentamicin actually had increased rates of treatment failure and superinfection compared with those treated with the cephalosporin alone.

In general, for patients who receive appropriate initial therapy, there is no proven benefit related specifically to combination therapy. However, recent investigations suggest that patients treated with initial combination therapy are more likely to receive appropriate empiric therapy, with an associated improved mortality.[112–114] In addition, pneumonia secondary to non–lactose-fermenting gram-negative bacilli is associated with increased rates of recurrence and mortality.[22,115] In a recent study by Heyland,[113] patients with suspected VAP were randomized to empiric monotherapy versus

combination therapy. There was no improvement in mortality with combination therapy. However, the percentage of patients receiving effective empiric therapy was significantly higher in the combination-therapy group. In addition, for patients with one or more multidrug-resistant organism identified on enrollment cultures, empiric therapy was adequate only 19% of the time, versus 84% of the time for patients receiving combination therapy. For these reasons, current treatment guidelines recommend double coverage for multidrug-resistant gram-negative bacilli in patients critically ill with suspected pneumonia.[1,15]

De-Escalation of Treatment

Prolonged treatment with broad-spectrum antibiotics contributes to development of drug-resistant organisms.[15,116,117] While narrowing the spectrum of coverage based on culture results may not improve treatment of specific infections in individual patients, it can benefit the hospital as a whole by limiting development of bacterial resistance.[15] De-escalation of therapy is accomplished by changing to antibiotics with a narrower spectrum, by eliminating unnecessary antibiotics from the treatment regimen, or by changing to oral therapy as tolerated. Several recent studies have examined the use of de-escalation therapy for VAP. Up to 68% of ICU patients will have the spectrum of antibiotic therapy narrowed based on culture results.[9,118,119] However, patients with VAP secondary to multidrug-resistant pathogens have a significantly decreased rate of de-escalation therapy. In a recent observational study looking at empiric broad-spectrum therapy ICU patients with VAP, de-escalation was accomplished for only 23% of patients with multidrug-resistant pathogens, versus 68% of cases due to other pathogens. De-escalation was not associated with decreased response rates.[118] Gianstou and colleagues[120] examined outcomes in patients who undergo de-escalation of therapy after diagnosis with BAL or tracheal aspiration with quantitative culture. Patients who received adequate empiric therapy and underwent de-escalation had decreased 15- and 28-day mortality, and decreased ICU and hospital length of stay. De-escalation rates were significantly higher for patients undergoing diagnosis with BAL (66.1%) as compared with tracheal aspiration (21%). Again, while BAL has not been proven to be the gold standard for diagnosis of VAP, it may be helpful in guiding treatment.

Duration of Therapy

Recommendations for duration of antimicrobial therapy for nosocomial pneumonia have evolved significantly in recent years. As described previously, the study by Singh and colleagues[85] suggested that a shortened course of therapy may be acceptable for many patients if they demonstrate clinical improvement. As clinicians saw the results of short course of therapy in this unblinded study, the duration of antibiotic therapy given in the control group decreased significantly over the study period, resulting in an early termination of the study. These results gave an early indication that antibiotic duration could be safely limited in many patients.

The most significant impact on this topic likely came with Chastre's 2003 study[115] randomizing patients with VAP to 8 versus 15 days of antimicrobial therapy. Death from any cause was similar between the two groups (18.8% for 8 days versus 17.2% for 15 days, risk difference 1.6 [95% CI, -3.7–6.9]). Additionally, there was no difference in overall recurrence rate (28.9% versus 26.0%; risk difference, 2.9 [95% CI, -3.2–0.1]) for VAP. However, for patients with pneumonia caused specifically by non–lactose-fermenting gram-negative bacilli, the recurrence rate after 8 days of therapy was significantly higher. In a retrospective evaluation of the same study population, pneumonia secondary to non–lactose-fermenting gram-negative bacilli and

MRSA were both independently associated with recurrence.[22] While concern for recurrence is significant when treating drug-resistant infections, the results of these studies indicated that many patients could be safely and effectively treated with shortened courses of antibiotics.

The question remains: What is the shortest course of antimicrobial therapy appropriate for nosocomial pneumonia? Repeat BAL has been used as a method of assessing response to therapy and allowing for shorter duration of antibiotic therapy. Discontinuation of appropriate therapy after 4 days in patients with decreased bacterial growth on repeat BAL has shown a decrease in antibiotic duration and total antibiotic days, with no effect on mortality, length of stay, ventilator-free days, relapse rate, or rate of superinfection.[86] These data indicate that further shortening of antibiotic courses may be safely accomplished in appropriate patients.

In 2005, the American Thoracic Society published comprehensive guidelines for the management of HAP and VAP in adults.[1] Timing of onset of pneumonia and patient risk factors are important considerations. For patients with early-onset pneumonia and no additional risk factors, initial therapy should be limited in spectrum (**Table 2**).[1,6,12,14,15,86,121,122] Choices include:

Third-generation cephalosporins
Fluoroquinolones
Penicillins with gram-negative coverage but no antipseudomonal activity
Carbapenems with gram-negative coverage but no antipseudomonal activity

For patients with late-onset pneumonia, or risk factors for multidrug-resistant bacteria, initial therapy should include combination therapy targeted at non–lactose-fermenting gram-negative bacilli. Potential therapies include antipseudomonal beta-lactam agents, such as cefepime, piperacillin/tazobactam, or meropenem; plus an aminoglycoside or antipseudomonal fluoroquinolone, such as ciprofloxacin. Additionally, the patient requires coverage for possible MRSA pneumonia with vancomycin or linezolid. Antibiotic spectrum may then be adjusted based on culture results. However, recent data suggest evolving resistance of MRSA to both vancomycin and linezolid, based on increasing mean inhibitory concentration to these agents,[100,101] a problem that will have a significant impact on the future treatment of HAP.

OUTCOMES

HAP has a significant impact both medically and economically. Specifically, ICU patients with VAP experience longer ICU and hospital lengths of stay, cost more to treat, and have higher mortality rates than other patients.[4,5,7] In their evaluation of 127 episodes of VAP at a single institution, Warren and colleagues[3] cited increased costs of almost $50,000 per episode of VAP. Perhaps more importantly, VAP in this study was associated with an overall mortality of 32%, versus 11% in patients who did not have VAP.

These daunting statistics give urgency to the ongoing efforts to help hospitals and health care providers decrease the impact of HAP. Successful strategies focus on the implementation of evidence-based treatment guidelines, VAP-prevention bundles, and staff education initiatives.[107,121–124] Hospital authorities can decrease mortality rates through the use of treatment guidelines for nosocomial pneumonia that focus on early empiric therapy targeting organisms and sensitivities known to be prevalent at their institution.[98]

VAP-bundles are collections of educational materials, guidelines, and tools such as checklists that help clinicians deliver best-practice to every patient every time. The role of VAP-prevention bundles is also important to ensure all patients receive therapy known

Table 2
Causative organisms and empiric treatment

Infection	Causative Organisms	EmpiricTherapy
Hospital acquired		
Early onset; no risk factors for multidrug-resistant organisms	*H influenzae; Spneumoniae;* MSSA; gram-negative bacilli or *Enterobacteraciae* (*Klebsiella, E Coli, Serratia*); anaerobes; *Legionella*	Ceftriaxone 1 g IV every 24 h or moxifloxacin 400 mg IV PO every 24 h
Late onset; risk factors for multidrug-resistant organisms	Above organisms and *P aeruginosa;* MRSA	Piperacillin/tazobactam 4.5 g IV every 6 h (3.375 g if not *Pseudomonas*), or cefepime 1 g IV every 8 h, or ciprofloxacin 400 g IV every 8 h plus clindamycin 600 g IV every 8 h
Ventilator associated		
Early onset (<5 d)	*S pneumoniae; H influenzae;* MSSA; *Enterobacteraciae*	Ceftriaxone 1 g IV every 24 h or moxifloxacin 400 mg IV/PO every 24 h
Late onset (≥5 d)	Enteric gram negative organisms; *Enterobacteraciae; P aeruginosa;* MRSA; *Acinetobacter* spp	Piperacillin/tazobactam 4.5 g IV every 6 h with or without aminoglycoside, or ciprofloxacin 400 mg IV every 12 h with or without aminoglycosid, or cefepime 1 g IV every 8 h with or without aminoglycoside; plus vancomycin 15 mg/kg IV every 12 h, or linezolid 600 mg IV every 12 h
Immunocompromised	*Legionella;* fungal	Azithromycin 500 mg IV every 24 h, fluconazole 200 mg IV every 24 h

Abbreviations: IV, intravenously; MSSA, methicillin-sensitive *Staphyloccous aureus*; PO, by mouth.

to be effective. Key components of these bundles include directives for semirecumbent positioning, continuous suction of subglottic secretions, appropriate provider hand hygiene, and care of ventilator circuits. Implementation of a VAP bundle alone did not decrease VAP rates from greater than the National Nosocomial Infections Surveillance System 90th percentile.[123] However, when this was combined with an auditing program providing weekly staff feedback, the rate decreased to the 25th percentile. Staff education sessions highlighting VAP risk factors and prevention strategies can help increase staff compliance with the VAP bundle[124] by showing practitioners the impact of the disease and how their actions can help improve outcomes.

In summary, HAP represents a significant problem in the United States and worldwide. An understanding of the pathophysiology and local microbiology of the disease is a critical factor in prevention, diagnosis, and treatment. Prompt and effective

antibiotic therapy is necessary to ensure adequate treatment. Evidence-based practice guidelines and education programs can help decrease both the medical and economic impact of nosocomial pneumonia.

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