Nosocomial Pneumonia

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Objectives:

1. Review the pathogenesis and risk factors for nosocomial pneumonia.
2. Discuss the bacteriology of early- and late-onset nosocomial pneumonia.
3. Discuss diagnostic methods and the controversies surrounding their use.
4. Examine antibiotic therapy regimens for nosocomial pneumonia.

Key words: antibiotic resistance; combination therapy; diagnosis; Gram-negative bacteria; nosocomial pneumonia; pathogenesis; ventilator-associated pneumonia

The incidence of nosocomial or hospital-acquired pneumonia (HAP) varies in relation to the concomitant comorbidity in a given patient population. While 10% of patients requiring ICU care after general surgery develop this infection, 20% of those intubated and up to 70% of those with ARDS will develop HAP. In critically ill, mechanically ventilated patients, the incidence of HAP is 1% per day during the first month of ventilation. However, since most patients are ventilated for short periods, up to half of all episodes of ventilator-associated pneumonia (VAP) occur within the first 4 days of ventilation (early-onset VAP). Recent data show that the risk of pneumonia is 3% per day in the first 5 days, 2% per day on days 5 to 10, and then 1% per day on days 10 to 15. The mortality rate of HAP can exceed 50% in mechanically ventilated patients, especially if the infection involves potentially resistant enteric Gram-negative organisms such as *Pseudomonas aeruginosa* and Acinetobacter organisms that are particularly common in patients who have received prior antibiotic therapy. Case-control studies in mechanically ventilated patients indicate that 50% of HAP patients die as a direct result of this infection, and not as a consequence of their underlying serious illness. One of the factors that adds to attributable mortality is the use of inadequate therapy, and this is more likely if patients are infected with antibiotic-resistant organisms.

Using the National Nosocomial Infections Surveillance system, the Centers for Disease Control and Prevention regularly collects data about nosocomial infections, and has reported the data collected between 1992 and 1997 in medical ICUs throughout the United States, involving 181,993 patients and112 medical ICUs in 97 hospitals. The most common infections by site were: urinary tract (31%), pneumonia (27%), and primary bacteremia (19%), followed by all other infections. The common sites of infection were often device-related, with 87% of bacteremias associated with central lines, 86% of pneumonias with mechanical ventilation, and 95% of urinary tract infections with urinary catheters. The most common pathogens for primary bacteremia were coagulase-negative staphylococci (36%), followed by enterococci (16%) and *Staphylococcus aureus* (13%). Central line infections were especially associated with coagulase-negative staphylococci. With nosocomial pneumonia, Gram-negative organisms predominated (64%), with *P aeruginosa* being most common (21%), followed by Enterobacter (9%), *Klebsiella pneumoniae* (8%), and Acinetobacter (6%). *S aureus* was present in 20% of nosocomial pneumonia episodes. In VAP, Pseudomonas and Acinetobacter were most common, while *Escherichia coli* was more common in nonventilated patients. Not surprisingly, the overall nosocomial infection rate correlated with average length of stay and device use. The pooled mean rate of VAP was 6.5 per 1,000 ventilator days. There was no association between device-associated infection rates and number of hospital beds, number of ICU beds, and length of stay.

Pathogenesis and Risk Factors

HAP usually develops because of impaired host defenses and the consequent inability to contain encountered bacteria. In other patients, HAP develops because bacteria in the ICU environment are sufficiently numerous or virulent to overcome either normal or impaired host defenses. Recognized risk factors for HAP include patient-related conditions, therapeutic interventions, and factors related to infection control. Patient factors predisposing to HAP include the primary critical illness

(shock, sepsis, extrapulmonary infection, respiratory failure) and underlying comorbid illness (diabetes, azotemia, COPD, CNS dysfunction, recent surgery). Therapeutic interventions that increase HAP risk include sedatives, corticosteroids, cytotoxic agents, antacids, antibiotic therapy, enteral feeding, and especially endotracheal intubation. Patients can be exposed to large numbers of bacteria via the endotracheal tube, which itself can harbor a bacterial biofilm or serve as a conduit from a colonized oropharynx. In addition, secretions pooling above the endotracheal tube cuff often contain bacteria that can be aspirated into the lung. Proper attention to cuff pressure can minimize the leaking of secretions around the endotracheal tube cuff. Even though endotracheal tubes are often contaminated with organisms, they should not be routinely changed, as reintubation itself serves as a pneumonia risk. An exception may be replacement of a nasotracheal tube with an orotracheal tube; nasal tubes promote nosocomial sinusitis, a source of pathogens for HAP. With the advent of noninvasive ventilation to manage respiratory failure, pneumonia has been less common in patients managed with this modality, compared with mechanical ventilation and endotracheal intubation.

Nosocomial sinusitis has been identified in the past as a risk factor for nosocomial pneumonia, and now an intervention study demonstrates that aggressive diagnosis and treatment of sinusitis can prevent pneumonia and mortality. In a study, 399 intubated patients, expected to be ventilated for > 7 days, were enrolled and randomized either to a group that underwent a systematic search for sinusitis when fever was present or to a control group that did not. Surprisingly, all patients were nasotracheally intubated, and all gastric tubes were nasally inserted, a practice that should be questioned given the data in this study and others before it. A total of 199 patients were in the intervention group, and whenever fever was present, the protocol required sinus CT scans at days 4 and 8 after intubation and then every 7 days. If radiographic sinusitis was present, a transnasal culture was obtained and sinusitis diagnosed if cultures showed >1,000 organisms/mL. Patients with sinusitis were treated with antibiotics and sinus lavage every 8 h. Nosocomial pneumonia was diagnosed in all patients by the finding of a new infiltrate and a positive culture from protected specimen brush sampling. The authors found that 110 of the 199 study patients had radiographic sinusitis, and a total of 80 fulfilled microbiologic and clinical criteria for sinusitis. VAP occurred in 37 of 199 of the intervention patients (23 with sinusitis, 14 without) and 51 of 200 of the control subjects ($p = 0.02$). For the 23 patients with both VAP and sinusitis, the pneumonia occurred at the same time of sinusitis or later in 16 of 23, and with the same organism in 43%. Interestingly, the mortality rate of the intervention group (36%) was significantly lower than that of the control group (46%), suggesting that aggressive diagnosis and therapy of sinusitis can have a favorable impact on patient outcome. When the data are examined for the relationship between VAP and sinusitis, VAP occurred in 29% of those with sinusitis (23 of 80) and in only 12% without sinusitis (14 of 119). Methodologic issues with the study include that nasal tubes were used, and if sinusitis was diagnosed, they were not removed. It therefore is unclear how valuable this protocol is for an ICU that does not use nasotracheal tubes.

The stomach's role in HAP pathogenesis is uncertain. Elevation of gastric pH by antacids, H_2 antagonists, or enteral feeding can lead to gastric overgrowth by enteric Gram-negative bacteria. However, the frequency with which these organisms lead to pneumonia is uncertain. Some, but not all, studies in critically ill patients show reduced HAP rates when sucralfate is used for intestinal bleeding prophylaxis instead of antacids or H_2 antagonists. Many factors influence whether gastric contents reach the lung, including increased reflux in the supine position or with enteral feeding tube placement in the stomach rather than the small bowel, gastric volume, and nasogastric tube diameter.

Infection-control risk factors for HAP include the failure to routinely use handwashing or isolation of resistant pathogens and the use of contaminated respiratory therapy equipment. Respiratory therapy equipment does not commonly bring bacteria to the lung. Even if ventilator circuits are changed as infrequently as once a week, or are never changed, HAP risk is not increased.

Bacteriology

All HAP patients are at risk for infection with a core group of organisms, including nonresistant enteric Gram-negative organisms (Enterobacter, *E coli*, Klebsiella, Proteus, and *Serratia marcescens*), *Haemophilus influenzae*, methicillin-sensitive *S au-*

reus, and *Streptococcus pneumoniae*. These organisms are particularly likely if no unusual risk factors are present, and if the pneumonia begins within the first 5 days of hospitalization (early-onset HAP) (Table 1). When risk factors are present, or if the pneumonia begins on day 5 or later (late-onset HAP), then the likely pathogens change. In addition to the core organisms, patients with witnessed aspiration are also at risk for anaerobes; those with coma, head injury, and diabetes are especially at risk for *S aureus* infection; those with a prolonged ICU stay, prior antibiotics, corticosteroids, malnutrition, or structural lung disease are at risk for *P aeruginosa* and Acinetobacter; and those who have had a prolonged ICU stay and prior antibiotics are also at risk for methicillin-resistant *S aureus* (MRSA) (Table 2). When HAP is severe, in the presence of risk factors, or if it is of late onset, resistant Gram-negative bacteria and MRSA are particularly likely (Table 3).

In the setting of severe pneumonia, drug-resistant organisms are likely, particularly if the patient has been treated with antibiotics, corticosteroids, and prolonged ventilation. These resistant organisms include Gram-negative bacteria as well as MRSA. MRSA is an increasingly common pathogen causing VAP, and is more likely in patients who have received prolonged ventilation and prior antibiotics.

Table 1—*Group 1: Patients With No Unusual Risk Factors; Mild to Moderate HAP, Onset Any Time; or Severe HAP With Early Onset*

Core pathogens
Enteric (nonpseudomonal)
Gram-negative organisms
Enterobacter spp
E coli
Klebsiella spp
Proteus spp
S marcescens
H influenzae
Methicillin-sensitive *S aureus*
S pneumoniae
Core antibiotics
Cephalosporin: second generation, nonpseudomonal third generation, or fourth generation
—or—
β-Lactam / β-lactamase inhibitor
For penicillin-allergic patients: fluoroquinolone or clindamycin + aztreonam

One group of organisms that is of unclear significance in VAP is anaerobes, and now a careful bronchoscopic study has found that these organisms almost never are involved in this infection. In this study, protected specimen brush sampling and BAL were performed in 143 patients with 185 episodes of suspected VAP, and in 25 patients with aspiration pneumonia who were ventilated. A total of 63 of 185 suspected episodes and 12 of 25 aspiration patients met microbiologic criteria for pneumonia. The organisms included common Gram-negative and Gram-positive organisms, but an anaerobic organism was isolated from only one patient in the entire group. The authors concluded from these findings that routine anaerobic therapy is not needed in ventilated patients with VAP or aspiration pneumonia.

Diagnosis and Treatment

The clinical diagnosis of HAP is made when a patient has a new or progressive lung infiltrate plus at least two of the following: fever, purulent sputum, or leukocytosis. This clinical definition is sensitive, but patients with other disease processes may be misdiagnosed as having HAP. The differential diagnosis includes congestive heart failure, atelectasis, pulmonary infarction, and inflammatory diseases (such as acute lung injury). In addition, many patients who have VAP can have coexisting infections including sinusitis, intra-abdominal infection, and central line infections.

The overdiagnosis of HAP is a particular concern in mechanically ventilated patients. Quantitative cultures of respiratory secretions, obtained bronchoscopically or with a blind catheter or brush insertion, have been used to define whether pneumonia is present. This approach is controversial because it relies on defining a microbiologic "threshold concentration" in respiratory secretions above which pneumonia is diagnosed. Early forms of pneumonia may go undiagnosed with this approach, and there are technical problems involved in collecting samples and interpreting results, especially in patients who are concurrently receiving antibiotics. The impact of these procedures on the outcome of patients with VAP has been addressed by a number of studies. In these studies, bronchoscopy has not always had a benefit, but if a benefit was present, it was seen in populations that often received inadequate antibiotic therapy due to a high frequency of

drug-resistant organisms. Although bronchoscopy has been reported to lead to fewer patients getting antibiotics and to less antibiotic resistance than management by clinical tools, not all studies have found this. In fact, in one study, similar benefits were seen when the clinical pulmonary infection score was used to decide whether to continue empiric antibiotic therapy after observing the patient's clinical course for 3 days during therapy. If quantitative cultures are not collected, the etiologic pathogen can still be identified in intubated patients (along with other colonizing but not infecting organisms), by collecting tracheal aspirates for culture. The role of expectorated or suctioned sputum cultures in nonintubated patients is controversial.

One thing that has become clear in studies of VAP is that initial antibiotic therapy must be accurate in order to assure the best possible outcome. If therapy is not accurate (and invasive methods may delay the initiation of therapy, and maybe even appropriate therapy), then outcome is poor, even if microbiologic data become available and explain why the initial therapy was incorrect. Thus, initial therapy is usually empiric and based upon the suspected etiologic pathogens (Tables 1-3). Many patients can be treated with a single broad-spectrum agent, but certain resistant organisms require combination therapy. Monotherapy can be used for non-ICU HAP, in patients without special risk factors, and in the ICU patient with early-onset infection and no special risk factors. Combination therapy is superior to monotherapy for bacteremic *P aeruginosa* infection and should be used in this setting. For nonbacteremic *P aeruginosa* infection, combination therapy is often used to prevent the emergence of resistance during therapy, but the optimal combination regimen is not defined, and the addition of an aminoglycoside to a β-lactam agent may have little benefit. However, current practice is to use combination therapy for patients with severe,

Table 2—*Mild-Moderate HAP; With Risk Factors; Onset Anytime*

Core Pathogens Plus:	**Core Antibiotics Plus:**
Anaerobes (witnessed aspiration, recent thoracoabdominal surgery)	Clindamycin or β-lactam/β-lactamase inhibitor (alone)
S aureus (coma, head trauma, diabetes, renal failure)	+/– Vancomycin (until MRSA is ruled out)
Legionella (high-dose corticosteroids)	Erythromycin +/– rifampin
Prolonged ICU stay, prior antibiotics, corticosteroid therapy, structural lung disease	Treat as severe pneumonia (Group 3)*

*See Table 3 for Group 3 recommendations

Table 3—*Group 3: Patients With Severe HAP: Either Early Onset With Risk Factors, or Late Onset*

Core Pathogens Plus:	**Aminoglycoside or Ciprofloxacin Plus One of the Following:**
P aeruginosa	Antipseudomonal penicillin
Acinetobacter spp	β-Lactam/β-lactamase inhibitor Ceftazidime or cefoperazone Fourth-generation cephalosporin (cefepime) Imipenem, meropenem Azotreonam
Consider MRSA	+/– Vancomycin or alternatives (linezolid, quinupristin, dalforpristin)

late-onset HAP, or those with severe, early-onset HAP in the presence of certain risk factors, in an effort to prevent resistance; more data supporting the efficacy of this approach are needed. Combination can involve an antipseudomonal β-lactam, with either an aminoglycoside or ciprofloxacin, but the latter may be preferable because of its excellent penetration into respiratory secretions and because of the limited efficacy and enhanced renal toxicity associated with aminoglycosides. Stepdown to monotherapy may be appropriate if *P aeruginosa* or another highly resistant pathogen is not isolated from the tracheal aspirate of an intubated patient. Agents that can be used as monotherapy for severe pneumonia not caused by a drug-resistant organism include ciprofloxacin (400 mg q8h), imipenem (1 g q8h), meropenem, cefepime, and piperacillin/tazobactam. If patients have risk factors for MRSA (above), it may be necessary to add coverage for this organism, pending the results of tracheal aspirate cultures. This is especially true if the tracheal aspirate Gram stain shows Gram-positive organisms. Therapy for MRSA can center on vancomycin or one of its alternatives, such as linezolid or quinupristin/dalforpristin.

In two recent studies, piperacillin/tazobactam was an effective monotherapy for HAP. In the first study, piperacillin/tazobactam (3 g of piperacillin and 375 mg of tazobactam q4h) was compared with ceftazidime; patients in each arm of the study were also given tobramycin, which could be discontinued after respiratory culture results were known. A total of 300 patients were enrolled, with 136 clinically evaluable. The piperacillin/tazobactam group had a significantly higher clinical success rate (74% vs 50%), higher frequency of eradication of baseline pathogens (66% vs 38%), and lower mortality rate (7.7% vs 17%) than the ceftazidime group. The patients generally did not have severe illness (only 20% had severe illness), and the need to use antibiotics every 4 h is somewhat limiting. However, in a second study, a dose of 4.5 g of piperacillin/tazobactam was given three times daily, and approximately 50% of the study group was composed of patients receiving mechanical ventilation. The mean APACHE (acute physiology and chronic health evaluation) II score in this study was 14.7. Piperacillin/tazobactam was compared with imipenem, and it was associated with significantly more success and fewer failures, greater success against *P aeruginosa* (90% vs 50%), and fewer episodes of *P aeruginosa* resistance during therapy, even when used as a monotherapy regimen. These data suggest that piperacillin/tazobactam can be used in patients receiving mechanical ventilation as monotherapy for severe HAP, adding it to a list that includes a number of other agents.

Prevention

Attention to pneumonia risk factors and infection control efforts are the most effective preventive strategies. A specially adapted endotracheal tube that allows for the suction of subglottic secretions pooled above the endotracheal tube cuff has been shown to prevent some episodes of HAP. Prophylactic antibiotics, either as an aerosol or as part of a selective digestive decontamination strategy, do not reduce mortality rates, and their use raises concerns about the emergence of resistant pathogens. Such uses of antibiotics are experimental and prophylactic antibiotics should not be used in routine clinical practice.

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In a randomized, controlled, and blinded study, 76 patients were managed with an endotracheal tube that allowed for the continuous aspiration of subglottic secretions, while 77 were managed with conventional endotracheal tubes. The use of continuous aspiration was associated with a significant ($p < 0.03$) reduction in the incidence of nosocomial pneumonia and a reduction in the number of infections due to Gram-positive cocci and H influenzae*, but no difference in the number of infections caused by* P aeruginosa *or other resistant Gram-negative organisms. When pneumonia developed, it occurred later in the continuous aspiration patients than in control patients. The simplicity of this method for pneumonia prevention is very appealing, and contrasts with other more complex and less effective methods, as pointed out in the accompanying editorial.*

Notes