Nosocomial Pneumonia: More Than Just Ventilator-Associated

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We reviewed literature published from 1995 through 2000 on developments in ventilator-associated pneumonia. There is no gold standard with which to compare the accuracy of various invasive procedures performed for diagnosis. Moreover, leaders in the field are calling for an outcomes-based analysis to assess the utility of invasive procedures. Two things are clear: 1) adequate empiric therapy is beneficial, and 2) changes in therapy based on recovery of pathogens by invasive means do not affect outcome. Clinicians are urged to review local antimicrobial resistance patterns and to initiate empiric therapy on the basis of those data.

Introduction

In the past three decades, the Centers for Disease Control and Prevention has gathered data on the incidence of hospital-acquired pneumonia and other infections. National Nosocomial Infections surveillance now tracks the incidence of nosocomial pneumonia in representative hospitals [1]. Respiratory tract infections, although not the most common nosocomial infections, cause the greatest morbidity and mortality [2]. Ventilator-associated pneumonia (VAP) rates of 13 cases/1000 ventilator-days are the mean in surgical intensive care units. The mortality attributed to hospital-acquired pneumonia ranges from 7% in nonintubated patients to 27% in patients with VAP. Up to 60% of all bone marrow transplant recipients who develop pneumonia will not survive. The estimated cost of caring for the nearly 250,000 to 300,000 patients with nosocomial pneumonia exceeds $1.5 billion.

Thus, there are several important reasons to study nosocomial pneumonia. Patient risk factors might be modified, prognosis for individual patients can be provided, pathophysiologic mechanisms can be better understood, and preventive measures can be identified.

Just as not all fever and pulmonary infiltrates equate with pneumonia, not all cases of nosocomial pneumonia are VAP. However, in an era of ever-increasing dependence on technologically dependent medical care, better than 90% of nosocomial pneumonia occurring in the intensive care unit (ICU) setting is VAP [3].

Recent studies on nosocomial pneumonia have focused on patient outcome [4,5••,6•]. Where previous studies debated the merits or inadequacies of diagnostic assays, management strategies, or preventive maneuvers, current studies emphasize the impact of the intervention on patient survival.

Definitions

Nosocomial pneumonia has been narrowly defined as pneumonia acquired 48 or more hours after admission to the hospital. Although most episodes of nosocomial pneumonia are associated with ventilator assistance, the term is not synonymous with VAP; however, it does encompass both early- and late-onset VAP. Broadly defined, nosocomial pneumonia includes pneumonia acquired in health care institutions. Both hospital-acquired and nursing home–acquired pneumonia should be included in this term because the microbial flora of both sites differ substantially from that of the community.

Ventilator-Associated Pneumonias

Diagnostic methods

The diagnosis of VAP is difficult at best. Usually considered on the basis of clinical and radiologic features, it is rarely confirmed by histopathologic exam. Recovery of recognized pathogens is fraught with uncertainty and leaves much to be desired. Several excellent reviews have been published on the utility of bronchoscopically directed and blind sampling of the lower respiratory tract by protected specimen brush or bronchoalveolar lavage methods [7,8•,9,10], but bronchoscopy is neither benign nor inexpensive and is not universally available. Recent bronchoscopic studies are highlighted in Table 1. Quantitative culture of pathogens obtained by directed bronchoalveolar lavage [11], protected specimen brush [12], or even by blinded sampling [13] in patients with VAP has not affected outcome. Consequently, empiric regimens of therapy have been forwarded by recognized experts in the field [14,15]. Suffice it to say, none of the invasive techniques have been shown to favorably affect patient outcome.

Table 1. Utility of bronchoscopic or blind sampling compared with endotracheal aspiration of sputum specimens

	Methods				
			Blind, %‡		
Test characteristic	PSB, %*	BAL, %†	PSB	BBS	Endotracheal aspirate, %
Median sensitivity	67	73	75	83	82
Median specificity	95	80	85	100	60
Positive predictive value	75	65			

Data from Grossman and Fein [7], Flanagan [8•], deJaeger *et al.* [10], Campbell [13].
*PSB with quantitative culture of 103 colony-forming units [CFU]/mL.
†BAL with quantitative culture of 104 CFU/mL.
‡Blind PSB with quantitative culture of 103 CFU/mL; BBS with quantitative culture of 104 CFU/mL.
BAL—bronchoalveolar lavage; BBS—blind bronchial sampling; PSB—protected specimen brush.

Establishment of the exact cause of any one patient's pneumonic process is a Sisyphean task. There is no gold standard for comparison, and reproducibility of pathogen recovery is less than perfect. Moreover, the impact on outcome has been negligible for patients requiring a change in antibiotic therapy to provide adequate activity against recovered isolates [4]. Perhaps the most influential and clinically useful information to come from bronchoscopic retrieval of respiratory secretions is the lack of an etiologic pathogen. Heyland *et al.* [5••] demonstrated that, as such, negative quantitative cultures lead to a substantial reduction in antibiotic usage. Several authors [16,17••,18] have demonstrated no difference in mortality when antibiotic therapy was altered according to recovery of pathogens by these invasive techniques.

Survival was greatest among patients who received adequate empiric therapy [16,18]. Recently, Fagon *et al.* [6•] reported that outcome of patients with VAP managed by bronchoscopically obtained specimens (by protected specimen brush or bronchoalveolar lavage with quantitative cultures) was improved compared with a clinically managed group. This randomized, multicenter, uncontrolled trial found a statistically significant difference in mortality at 14 days, but not at 28 days, in favor of the bronchoscopically managed group. Other differences between the groups that could have contributed to increased mortality among the clinically managed patients included the greater percentage of patients with positive cultures (85.6% vs 44.1%) and polymicrobial pneumonia (45.5% vs 12.3%) compared with the bronchoscopically managed group. Perhaps the most significant result of this study was to confirm the earlier work by Heyland *et al.* [5••] showing that bronchoscopic intervention can reduce the use of antibiotics by identifying patients without pneumonia.

Microbiologic studies of bronchoalveolar lavage or protected specimen brush specimens by Gram stain enhanced the diagnostic accuracy for VAP but did not affect selection of empiric therapy [19]. Cytologic evaluation of specimens for inflammatory cells and bronchial cells was useful for identifying protected specimen brush specimens that were inadequate for culture [20].

Niederman [21,22] summarized the utility of bronchoscopic intervention and quantitative cultures in the management of nosocomial pneumonia as follows: serial recovery of pathogens, especially at high concentrations, identifies patients at high risk for death; and the impact of repeated quantitative cultures is uncertain and does not affect the survival rate of patients who do not respond to initial therapy.

In my opinion, this is exactly right. No differences in survival have been noted (with the exception of the study by Fagon *et al.* [6•]) when invasive specimen recovery is performed. Perhaps the most compelling reason to perform quantitative cultures is to identify patients in whom antibiotic therapy can be reduced or omitted altogether. This in itself is not an insignificant outcome.

How then should we approach the treatment of nosocomial pneumonia? Because neither the clinical nor the radiologic criteria for diagnosis are absolute, and the utility of bronchoscopic or blind specimen retrieval does not affect mortality, this is no easy task.

The answer, I believe, lies in the knowledge and understanding of the clinical and epidemiologic setting in which the episode of nosocomial pneumonia has occurred. Just as patients with early-onset VAP are recognized as being at risk for infection with pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* organisms typically found in the community, nursing home residents must be recognized as being at risk for acquiring hospital-associated flora. Both groups develop nosocomial pneumonia, but therapy for each may be decidedly different. Clinicians must be familiar with the antibiotic susceptibility profiles of their institutional and community microbial flora. Even within a single institution, the pattern of antimicrobial resistance varies. In our hospital, a large tertiary-care, teaching Veterans Affairs hospital, the pattern of pathogens and their antibiotic susceptibility profiles significantly differs between the medical and surgical ICUs.

Table 2. Common etiologic pathogens recovered from patients with nosocomial pneumonia

	Frequency, %	Clinical setting
Gram-positive cocci		
Methicillin-resistant *Staphylococcus aureus*	17.9–21.1	Late VAP, HAP, NHAP
Methicillin-sensitive *S. aureus*	10.8–17.9	Early VAP, NHAP
Streptococcus pneumoniae	1.1–3.2	Early VAP, NHAP
Vancomycin-resistant enterococci	0.8–1.9	Late VAP, HAP
Gram-negative bacilli		
Pseudomonas aeruginosa	18.0–38.0	Late VAP, HAP
Acinetobacter species	2.6–5.4	Late VAP, HAP
Enterobacteriaceae		Late VAP, HAP, NHAP
Escherischia coli	1.6–7.4	
Klebsiella species	1.7–6.5	
Serratia species	2.2–3.8	
Enterobacter species	3.3–10.3	
Haemophilus species	2.7–7.4	Early VAP, NHAP
Moraxella species	0.3–1.3	Early VAP, NHAP
Fungi		
Candida species	3.8–12.2	Late VAP, HAP

Adapted from Ibrahim *et al.* [3] and Fagon *et al.* [6].
HAP—hospital-acquired pneumonia; NHAP—nursing home–acquired pneumonia; VAP—ventilator-associated pneumonia.

The pathogens

Our hospital, like most large teaching facilities, has seen its share of multidrug-resistant organisms. Methicillin-resistant *Staphylococcus aureus* is an endemic pathogen with a prevalence of 60% to 70%. Vancomycin has become an empiric consideration for every patient with nosocomial pneumonia. Only when Gram stain or culture of sputum confirm its absence do we discontinue vancomycin treatment.

The literature reports only a handful of patients who have *S. aureus* with intermediate susceptibility to vancomycin [23]. We have had recent experience with just such an isolate. Combination therapy with cefazolin plus vancomycin cleared the patient's bacteremia [24]. Fortunately, the patient's isolate did not spread horizontally, and this infection has not recurred.

Vancomycin-resistant enterococci were initially isolated from our hemodialysis patients in 1994; at that time, few effective options were available for therapy. Recently, linezolid and quinupristin-dalfopristin have limited the morbidity associated with these pathogens. Before the availability of these newer agents, our patients with vancomycin-resistant enterococci pneumonia recovered by use of aerosolized vancomycin to eradicate the pathogen.

Aerobic gram-negative bacilli with extended-spectrum β-lactamase production are uncommon in our hospital, primarily because we have followed a restrictive pattern of use of third-generation cephalosporin and extended-spectrum β-lactamase penicillin since 1981. Because we share a common housestaff and faculty with our university affiliate, isolates that have broader resistance patterns do migrate to our facility. Consequently, we have had to use aerosolized colistin to eradicate a case of *Pseudomonas aeruginosa* nosocomial pneumonia [25].

Fortunately, these occurrences are rare; nonetheless, they affect the overall antibiotic-resistance selection pressure the hospital experiences. We are fortunate, again, not to have major problems with nosocomial acquisition of *Legionella pneumophila* or with *Aspergillus* species. In part this is due to perhaps a less susceptible population—we do not offer organ transplantation. In addition, there has been limited construction within and around the patient care areas of our facility. I have experience with an outbreak of *Aspergillus* pneumonia in transplant recipients with known risk factors [26]. These pathogens enter the differential diagnosis with each episode of nosocomial pneumonia in hospitals where these risk factors are present.

Nonfermentative aerobic gram-negative bacilli, such as *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia,* are all pathogens of opportunity. Most patients infected by these isolates have been hospitalized for several weeks, are usually ventilator-dependent, and have received antecedent antibiotics. Clinicians need to keep a high index of suspicion for the recovery of these pathogens, as well as *Candida* species, in this setting. Common pathogens are identified in Table 2.

Prevention

Hospitalized patients at risk for VAP include postoperative patients, those with pre-existing pulmonary or central nervous system disease, trauma patients, transplant recipients, or immunosuppressed individuals [27•]. Although we cannot control these illnesses and events, once a patient requires ventilatory support, some practices can reduce the occurrence of VAP. First, strict attention must be paid to handwashing. As mundane as it sounds, handwashing is the

Table 3. Antibiotic therapy for infection with selected pulmonary pathogens

Clinical settings and pathogens	Empiric antibiotics
Severe HAP /late-onset VAP/NHAP	
Pseudomonas aeruginosa, Acinetobacter species, methicillin-resistant *Staphylococcus aureus, Legionella pneumophila*	Carbapenems plus aminoglycosides, vancomycin, azithromycin, or new fluoroquinolones
Moderate HAP/early VAP/NHAP	
Enterobacter species, *Klebsiella* species, *Proteus* species, *Serratia marcescens, Haemophilus influenzae, Streptococcus pneumoniae,* methicillin-sensitive *S. aureus*	Ceftriaxone, fluoroquinolones, beta-lactam/beta-lactamase inhibitor; penicillin-allergic patients: aztreonam and clindamycin

Adapted from American Thoracic Society [14] and Mandell and Campbell [15].
HAP—hospital-acquired pneumonia; NHAP—nursing home–acquired pneumonia; VAP—ventilator-associated pneumonia.

key to preventing acquisition of nosocomial pathogens. Several years earlier, my colleagues and I performed a prospective observational study of handwashing practices in a respiratory care unit in which all the patients were ventilator-dependent. Although attending physicians and the nurses in the unit achieved 90% to 100% compliance with pre- and postexam handwashing, house officers, medical students, respiratory therapists, and radiology technicians all had 40% to 60% compliance. Handwashing is a simple, effective practice to reduce nosocomial transmission in patients at risk for VAP [28,29].

Gastrointestinal approaches to preventing VAP have included use of selective decontamination with oral or topical antimicrobials. While meta-analysis has shown that selective decontamination has significantly reduced the rate of VAP and mortality, concern for potential emergence of antibiotic-resistant bacteria has led most US and Canadian hospitals to abandon the practice [30]. Use of H_2 blockade compared with sucralfate has been thoroughly investigated [31–33]. The most recent collaborative trial, conducted in Canada, suggests that sucralfate is no longer preferable to H_2 blockers because it is associated with increased risk for gastrointestinal bleeding and does not reduce the rate of VAP [34].

Beneficial ventilator management maneuvers include less frequent changes of ventilator circuitry, oral compared with nasal intubation, subglottic secretion drainage, and semirecumbent compared with supine positioning of the patients [35••]. Of lesser importance are the use of kinetic measures (*ie*, rocking beds) and use of heat and moisture exchanges, which are preferred over heat and humidifiers.

A thematic approach to treatment

Clinicians can meet the challenges of treating patients with VAP by maintaining a current knowledge base of their hospital's epidemiologic profile. Because each clinical scenario brings its own set of potential pathogens to which patients have increased susceptibility, each area of the hospital may have unique resident microbial flora [36•,37].

Emerging antibiotic resistance is more common in recent years because of our greater dependence on technologically advanced life support. Failure to recognize when antibiotic therapy is unnecessary or can be altered leads to further resistance. Periodic rotation of antibiotics within intensive care units [38] has been advocated for reducing antibiotic selection pressure. Clinicians should consult with their infectious diseases colleagues and infection control practitioners.

Because the goal of therapy is to cure the patient, adherence to a single approach for all patients as set by clinical guidelines or paradigms may not be in the patient's best interest. Recognition of at-risk patients and pathogens is, like politics, local. At Barnes-Jewish Hospital in St. Louis, Missouri, Ibrahim *et al*. [3] found a greater proportion of *P. aeruginosa* pneumonia among patients who developed infection more than 96 hours after admission to the ICU. Earlier in this paper, I commented on the likely pathogens in my institution. I suggest that clinicians be open to novel routes of antibiotic administration [39]. Aerosolized aminoglycosides, vancomycin, imipenem, and colistin have all been used successfully in our patients. These data are uncontrolled and anecdotal, but I remain convinced that these patients would not have survived otherwise.

It is, I think, wiser to prove that an antibiotic was not needed and withdraw that therapy than to discover that it was needed and add it without benefit of survival. I will decline to recommend specific antibiotics for specific isolates. Such decisions must be made for each patient at the local level.

Antibiotics used to treat nosocomial pneumonia are listed in Table 3.

Nursing Home–Acquired Pneumonia

With the aging of the general population of the United States, persons older than 85 years of age are the fastest-growing segment of the population. It is estimated that by 2030, 20% of the population will be over 65 years of age, and the number of those 85 years or older will increase from 3.5 million to more than 9 million. However, such growth in an aged population will increase the demand for long-term care. Elderly persons in the community are healthier and have fewer episodes of pneumonia than those who reside in long-term care facilities [40].

Persons residing in long-term care facilities are more likely to have comorbid conditions that place them at increased risk for development of pneumonia. Among these are the loss of daily living independence, poor nutritional status, inability to handle oral-pharyngeal secretions, neurologic impairment, and use of antipsychotic and hypnotic sedative medications [41].

Aspiration of oral-pharyngeal pathogens is central to the pathogenesis of nursing home–acquired pneumonia.

Older adults who reside in nursing homes usually cannot live independently, requiring variable amounts of assistance with the activities of daily life. Four major areas of impairment lead to nursing home placement, and all contribute to the pathogenesis of nursing home–acquired pneumonia. First is impaired physical functioning. Whether due to comorbid conditions (*eg*, congestive heart failure, diabetes, or renal disease) or to specific neuromuscular problems that compromise chest-wall physiology or impair glottic closure, such deficits increase the risk of pneumonia.

Second is malnutrition, often undiagnosed; patients may not have lost weight but may be hypoalbuminemic or hypocholesterolemic, both risk factors for death in nursing home residents [42].

Depression is an often overlooked factor in the decline of an elderly patient. Medications used to treat behavioral changes due to depression may sedate patients, thereby increasing opportunities for aspiration of oral-pharyngeal secretions and foods.

Finally, dementia, with a frequency of 11% among persons aged 65 years or older, is a common problem. Alzheimer's disease affects 4% of the nursing home population; the remaining patients have other neurocognitive disorders, commonly stroke or Parkinson disease, and senile dementia due to brain atrophy. Patients with dementia are all too often heavily sedated and prone to aspirate.

Among at-risk persons, residence in an institutional setting compounds the risk of acquiring pneumonia; however, physiologic changes occur in all individuals as they become older. Such changes are subtle and frequently are overlooked.

Defense deficits

All elderly patients, regardless of whether they can be independent, have acquired local pulmonary deficits and immunologic perturbations that facilitate progression of pneumonia after aspiration. With aging, lung elasticity is reduced, forced expiratory volume decreases, compliance increases, and vital capacity decreases [43]. Diminished ciliary clearance, along with increased risk of aspiration due to neuromuscular or gastrointestinal functional changes, precedes and increases the risk for pneumonia. Lack of intracostal muscle mass diminishes cough. Reduction in gas exchange function due to loss of alveolar surface area occurs even in healthy elderly persons. This reduction is compounded by comorbid loss in cardiac output and by smoking [43].

Immunologic surveillance also declines in elderly persons: reduced primary T-cell proliferation, decreased production of cytokines, and diminished B-cell interaction reduce antibody response to both native pathogen and packaged vaccine antigens [44]. Inadequate nutrition leads to anergy and lymphopenia. Protein-calorie malnutrition is common among nursing home residents, as are deficiencies of such micronutrients as vitamin C, zinc, and selenium, all of which impair wound healing and predispose to pneumonia [45]. Clues to protein energy malnutrition include alopecia, glossitis, dependent edema, skin desquamation, and dry, de-pigmented hair.

The pathogens

The relative incidence of nursing home–acquired pneumonia is 10-fold greater than the incidence of pneumonia among a comparable group of persons from the community 75 years of age or older, and is approximately 365 per 1000 population [40]. To be sure, institutionalized patients are at greater risk for acquisition of epidemic respiratory tract infections. Outbreaks of influenza and respiratory syncytial virus [46], infection with *Chlamydia pneumoniae* [47], and multidrug-resistant *S. pneumoniae* infection [48] have been reported. Nonetheless, most cases of nursing home–acquired pneumonia are sporadic, not epidemic, and most are caused by *S. pneumoniae*. However, aerobic gram-negative bacilli cause 20% of all respiratory infections, compared with 4% in community-dwelling elderly persons [40].

Therapy for nursing home–acquired pneumonia is often initiated without benefit of clinical investigation or radiologic confirmation. Few data are available to establish the role of atypical pathogens (*eg*, *L. pneumophila, Mycoplasma pneumoniae,* or *C. pneumoniae*) or anaerobic pathogens in nursing home–acquired pneumonia [40]. Dependence on recovery of pathogens from blood culture is biased to select for *S. pneumoniae* and *S. aureus.* Tuberculosis rates are four to five times greater than those among elderly patients living in the community. Consequently, tuberculosis must be included in the differential diagnosis of nursing home–acquired pneumonia, especially among patients who do not respond to empiric therapy.

Mortality rates of 5% to 40% per episode of nursing home–acquired pneumonia have been reported [40,41]. Pneumonia is the leading cause of death among nursing home residents, and causes one third to one half of all nursing home resident deaths [41]. Bacteremic patients have a 50% mortality rate. Critical to survival is the level of functional independence. According to Muder [40], 60% of persons with multiple dependence die within a year and fewer than 25% survive 2 years.

Management of nursing home–acquired pneumonia is difficult at best. Often, physicians are removed from the site, ancillary staff may provide direct care, and evaluation may be inadequate. Compounding such care may be the need to deal

Table 4. Risk factors for nursing home–acquired pneumonia

Reduced independence in activities of daily living
Age-related immune senescence
Aspiration/difficulty with oral pharyngeal secretions
Immobility
Cognitive impairment
Sedation
Malnutrition
Depression

Data from Muder [40], Medina-Walpole and Katz [41], Sarkisian and Lachs [42], Chan and Welsh [43], Miller [44], and Morley and Silver [45].

with a demented, delirious, and combative patient. Under such circumstances, the use of empiric antibiotics is the norm. Patients may be unable to cooperate or to produce sputum for Gram stain and culture. Living wills or powers of attorney for health care may limit intervention for a diagnostic evaluation. Little wonder, then, that the mortality rate among patients with nursing home–acquired pneumonia reaches 40%.

Prevention

Many variables that contribute to acquisition of pneumonia among elderly and institutionalized patients are not amenable to change. No one can stop the march of time, but we can prevent aspiration by limiting use of nasogastric tubes for feeding. We can also reduce the risk for acquisition of gram-negative bacilli by limiting use of antimicrobials, H_2 blockers, and antacids. We can enhance pulmonary toilet by frequent suctioning of oral-pharyngeal secretions and by feeding patients while they are sitting upright. These are but a few measures that will reduce the risk of acquiring pneumonia. Table 4 summarizes risk factors for nursing home–acquired pneumonia [49,50]. Finally, we must and can vaccinate all elderly persons for pneumococcal disease and influenza. It is still astounding that 10,000 to 40,000 deaths per year result from pneumonia and influenza [39] in the community and in the nursing home. A more concerted effort is needed to achieve universal immunization. We should vaccinate patients, and all health care workers should receive influenza vaccine annually.

Conclusions

The utility of bronchoscopically directed or blind specimen recovery in the management of VAP lies in the identification of patients for whom antibiotic therapy can be discontinued. Adequate empiric therapy is associated with better survival. Change in antibiotic therapy based on recovery of pathogens does not lead to better survival. Antimicrobial resistance patterns are local; consequently, therapy chosen for empiric use should provide adequate activity against endemic microbial flora.

Prevention of VAP is incompletely understood, but there are maneuvers with evidence-based support that should be incorporated into clinical practice. For non-ventilator-dependent patients, nosocomial pneumonia is related more to difficulty with oral-pharyngeal secretions than to other comorbid conditions. Nursing home residents are at increased risk for aspiration and subsequent development of pneumonia than are independently living elderly patients. Neuromuscular disease, malnutrition, dementia, and depression all contribute to nursing home–acquired pneumonia in a complex interaction.

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