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Nosocomial Pneumonia

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Nosocomial pneumonia (NP) is defined as pneumonia that develops within 48 hours or more of hospital admission and which was not developing at the time of admission. Nosocomial pneumonia, also known as hospital-acquired pneumonia (HAP), is the second most common hospital infection, while ventilator-associated pneumonia represents the most common intensive care unit (ICU) infection. Nosocomial pneumonia significantly contributes to morbidity, mortality, and escalating healthcare costs because of increases in antibiotic prescription and administration, length of ICU stay, and length of hospital stay.

Aspiration and colonization of the upper respiratory tract seem to be the major pathogenetic mechanisms for the development of NP, either in intubated or spontaneously breathing patients. The microbiology of NP depends on the timing of onset. In early-onset NP, the responsible pathogens are generally endogenous community-acquired pathogens. In late-onset NP, the responsible microbes include potentially multi-drug-resistant nosocomial organisms residing in oropharyngeal or gastric contents. Important risk factors for development of NP include coma, intubation, prolonged mechanical ventilation, repeated intubations, supine positioning, and long-term antibiotic use. The most significant preventive measures include routine hand washing and avoidance of (1) the supine position, (2) inappropriate antibiotics, and (3) overuse of H2-antagonists for stress ulcer prophylaxis. Accurate diagnosis of NP is difficult and controversial, warranting consideration for the application of invasive quantitative culture techniques over tracheal aspirates. Empiric antibiotic treatment should be prompt, starting on clinical suspicion, and based on local ICU pathogen epidemiology and antibiotic resistance patterns and on a deescalating antibiotic strategy. Innovative antibiotic strategies, such as antibiotic rotation, to help prevent the emergence of multi-drug-resistant pathogens and improve survival should be considered. **Key words:** *diagnosis*, *epidemiology*, *management*, *nosocomial pneumonia*, *pathogenesis*, *prevention*, *ventilator-associated pneumonia*

NOSOCOMIAL PNEUMONIA (NP) has been a well-known clinical entity since the beginning of twentieth century when William Osler[1] first discussed in depth the differences between community-acquired lobar pneumonias and the forms of pneumonia that occurred as complications of other diseases or postoperatively (especially following ether anesthesia) or as in so-called "terminal pneumonias." Nosocomial pneumonia has been also associated with the phrase "pneumonia is the old man's friend," the implication being that pneumonia may be the way to exit a difficult life.[2]

These days NPs are recognized as an important cause of morbidity and mortality, especially in the ICU, and are responsible for significantly increased healthcare costs and antibiotic usage.[3] Nosocomial pneumonia represents the second most common nosocomial infection after urinary tract infections and is the most common infection in an intensive care unit (ICU) setting, with an incidence between 9% and 68% and an associated mortality between 33% and 71%.[4] Nosocomial pneumonia is also responsible for more than half of the cases treated with antibiotics in the ICU.

Nosocomial pneumonia is a dynamic disease with a changing natural history, multiple etiologies, and numerous risk factors. Nosocomial pneumonias and especially its most

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common form, ventilator-associated pneumonia (VAP), remain significant problems in clinical medicine because of controversies and uncertainties in the literature concerning accurate diagnosis, effective prevention measures, and appropriate empiric antibiotic treatment. Furthermore, the emergence of multi-drug-resistant (MDR) pathogens and resistance to commonly prescribed antibiotics magnifies the problems inherent in the management of these patients. Thus, it is becoming mandatory in the management of NP to meticulously apply effective prevention measures and to use innovative antibiotic strategies, such as antibiotic rotation, to preserve the efficacy of currently used antibiotics.

During the past 2 decades, a paucity of published literature elucidates several issues concerning NP and VAP. However, more in-depth studies are needed concerning the natural history of NP, the mechanisms involved in respiratory tract colonization, effective empiric treatment strategies, and the rising rates of antibiotic resistance.

The main issues surrounding the management of NP include what methods should be used to establish an accurate diagnosis and, most importantly, the application of timely and appropriate empirical antimicrobial treatment. In this review, we discuss current concepts about NP and especially VAP: definitions, epidemiology, microbiology, diagnosis, risk factors, pathogenesis, prevention, and therapy.

DEFINITIONS

Nosocomial pneumonia or hospital-acquired pneumonia (HAP) usually affects[5] critically ill ICU patients receiving mechanical ventilation (MV), hence the term "ventilator-associated pneumonia." Nosocomial pneumonia or HAP occurs less commonly in spontaneously breathing (nonventilated) patients hospitalized out of an ICU setting on medical or surgical wards. These 2 types differ in regards to the spectrum of pathogens and severity of underlying diseases; and, not surprisingly, nonventilated patients generally have a better prognosis.[6] In both cases, pneumonia is characterized by new lung infiltrates on chest-X-ray with fever, purulent sputum, deterioration in gas exchange, and leukocytosis.

Nosocomial pneumonia or HAP is defined as pneumonia that develops within 48 hours or more of hospital admission and which was not incubating at the time of admission.[7] However, this relatively recent definition[7] excludes a significant number of patients who develop NP and VAP or ICU-acquired pneumonia (ICU-AP) within 48 hours after hospital admission as a consequence of emergency intubation, aspiration due to decreased level of consciousness and coma, or cardiopulmonary resuscitation.[6]

The American Thoracic Society (ATS) consensus statement[7] and others suggest the categorization of NP into early-onset NP (within 4 days after hospital admission or intubation) and late-onset NP (after 5 days of hospital admission or intubation). This categorization helps predict implicated pathogens and guide initial empiric antibiotics, which is known as the *epidemiological approach*.[8–12] Early-onset NP is commonly related to aspiration of endogenous community-acquired pathogens because of emergency intubation or altered mental status. Pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae, Moraxella catarrhalis*, and *Haemophilus influenzae*. On the other hand, late-onset NP is related to aspiration of oropharyngeal or gastric contents with potentially MDR nosocomial pathogens contributing to increased morbidity and mortality in these patients. Drug-resistant pathogens in late-onset NP are associated with MV more than 7 days and use of broad-spectrum antibiotics. Nosocomial pathogens include Gram-negative enterobacteria (60%), *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus* (MRSA). Categorization of pneumonia as early or late onset narrows the list of suspected pathogens and allows for prompt, accurate, and effective application of antimicrobial therapy.

The starting point for early-onset NP (ie, the time between the development of pneumonia and hospital admission, ICU admission, or

endotracheal [ET] intubation) has not been standardized. Also, the cutoff point between early-onset and late-onset NP, which is currently the 5th day of hospitalization, has yet to be firmly established.[7] Some data suggest that in patients with head injury, colonization with nosocomial drug-resistant pathogens may occur after 3 days.[9] However, other investigators have suggested the 7th day as the cutoff point between early- and late-onset NP.[12]

EPIDEMIOLOGY

Knowledge about the epidemiology of NP is limited by the different terminologies, definitions, and criteria used for diagnosing NP among innumerable studies. However, according to current definitions and the results of several epidemiological studies, NP or HAP is reported as the second most common hospital acquired infection (27%), after urinary tract infections (31%).[13,14] The third most common cause is blood stream infections (19%). Other studies[5,15] found that 80% to 86% of NPs occur in an ICU, resulting in ICU-AP or VAP. The significantly smaller number of cases that occur on medical or surgical wards, however, may subsequently require ICU care. VAP accounts for about 47% of the infections detected in ICU patients, making it the most common ICU infection.[13]

The incidence of NP ranges from 5 to 10 cases per 1000 hospital admissions in patients without risk factors; but in intubated and mechanically ventilated ICU patients, the incidence may increase 20 fold.[16] A recent consensus conference statement on ICU-AP[17] suggested that incidence ranges from 1 to more than 20 episodes per 1000 ventilator days, with an average of 7 VAP cases per 1000 ventilator days.

The incidence of NP may be also age-dependent, with about 5 NPs per 1000 inpatients aged under 35 and 15 NPs per 1000 inpatients aged above 65.[18,20] The risk for developing VAP also varies with ICU type and underlying disease, ranging from 5 cases per 1000 ventilator days in pediatric patients to 16 cases per 1000 ventilator days in patients with thermal injury or trauma.[21] The incidence is higher in surgical than in medical ICUs.[22] In cardiothoracic ICUs, the incidence is about 22%; in other surgical ICUs, it is around 14%; and in medical ICUs, it is approximately 9%.

The risk of developing VAP in the first few days after intubation and initiation of MV is approximately 1% per day of MV.[23] In the European Prevalence of Infection in Intensive Care (EPIC) study,[24] pneumonia accounted for 47% of nosocomial infections, which rose to 65% if all respiratory infections were included. Data from the National Nosocomial Infections Surveillance (NNIS)[25] show that NP accounts for 31% of all nosocomial infections in ICUs. Papia and colleagues[26] reported that, in trauma ICU patients, lower respiratory tract infections accounted for 28% of nosocomial infections.

In an ICU population, the incidence of NP increases with the length of ICU stay (1.5 times for the second week of ICU stay), the use of MV (1.6 times as compared to nonintubated patients), and the duration of MV (almost 69% of the patients on day 30 compared to 5% on day 5 of MV).[18,19,26–30] Also, the actual risk of acquiring VAP in an ICU has been estimated to be 6.5% at day 10 and 28% at day 28 of MV.[18] Risk for developing VAP was also estimated as 3% per day during the first week of MV and only 1% risk per day during the third week and beyond.[31]

Difficulties establishing the diagnosis of NP and methodological differences between studies help explain varying results and preclude precise assessment of incidence. For example, purulent tracheal secretions and pulmonary infiltrates may not correlate with the microbiological diagnosis of pneumonia when using a protected specimen brush technique. The accuracy of a clinical diagnosis of pneumonia on the basis of clinical, radiographic, and laboratory data in patients with a diagnosis confirmed by bronchoscopy was only 62%.[32,33] This may lead to an over diagnosis of NP, increased use of antibiotics, and increased costs.[34]

A valid diagnosis of NP also increases cost and length of stay. In a recent retrospective

cohort study,[35] VAP developed in only 9.3% of patients. The mean interval between intubation, ICU admission, or hospital admission and identification of VAP was respectively 3.3 ± 6.6 days, 4.5 ± 7.5 days, and 5.4 ± 7.7 days. The same study reported that 45.2% of VAP episodes developed during the first 2 days of hospitalization, 29.1% between days 3 to 6, and 25.7% after day 6. The incidence of VAP development was 63.2% within 48 hours of MV, 16.0% between 48 to 96 hours of MV, and 20.8% after 96 hours of MV. In all cases, the development of VAP significantly increases[35,36] the duration of MV by approximately 10 days (14.3 ± 15.5 days vs 4.7 ± 7.0 days), ICU length of stay by 6 days (11.7 ± 11.0 days vs 5.6 ± 6.1 days), and hospital length of stay by 11 days (25.5 ± 22.8 days vs 14.0 ± 14.6 days).[35] Attributable costs of VAP per patient during 1999 were more than $40,000, which was more than those for patients without VAP.

MORTALITY

Mortality in patients with NP ranges between 20% and 70%; while deaths are not all attributable to NP, it certainly reflects the poor health of patients developing pneumonia. In general, the lowest mortality rates occur in nonintubated, spontaneously breathing ward patients; higher mortality rates are reported for patients developing VAP in an ICU setting; and the highest rates are seen in patients with NP/VAP with acute respiratory distress syndrome (ARDS) requiring MV. Nosocomial pneumonia is associated with the highest mortality rate among nosocomial infections. In a recent cohort study,[35] hospital mortality in patients with or without VAP was not statistically different (30.5% vs 30.4%). These results are consistent with the results of another study.[37] However, subgroups of patients suffering from VAP caused by certain pathogens, including MDR *Pseudomonas aeruginosa*, MDR *Acinetobacter baumanni*, MRSA, and fungal infections, have higher mortality rates.[32,38–40] VAP mortality also increases with age, late onset infections, the complexity of comorbid medical diagnoses, and pneumonia severity. Another study showed that increased mortality in VAP was observed in medical patients compared to surgical patients.[41] Other data indicate that mortality in VAP may result from inappropriate initial antibiotic treatment, rather than VAP itself.[42–44] In sum, the relative risk of VAP-attributable mortality ranges from none to 3.6% among various studies and different patient populations.

PATHOPHYSIOLOGY AND PATHOGENESIS

Pneumonia, as defined by the consensus conference statement,[17] is distal lung airspace infection caused by microbes or microbial products. Because the lower respiratory tract is normally sterile, the presence or isolation of microbes from the lower respiratory tract is suggestive of active infection and possibly pneumonia.

The routes that bacteria can take to reach the lower respiratory tract to cause pneumonia include the following: contiguous spread, hematogenous seeding, inhalation, and aspiration.[45] Of these routes, the most frequent and most important is the aspiration of oropharyngeal and/or gastric contents. However, improper ventilator circuit manipulations can allow aerosolization of bacteria into the respiratory tract, although routine ventilator circuit changes do not seem to affect the incidence of VAP. Aspiration may occur as a result of the presence of the ET tube because it holds the vocal cords open, interferes with cough, and allows for pooling of secretions above the inflated cuff.

The stomach may serve as a bacterial reservoir for Gram-negative bacteria when the gastric pH is increased and the environment no longer bactericidal. This pH alteration results from medications used for stress ulcer prophylaxis or alkaline feeding, resulting in overgrowth of enteric bacteria. Aspirated gastric contents may thereby cause Gram-negative NP.

Another critical and easily addressed factor related to aspiration is the positioning of

patients, which affects the volume of gastric aspirates. The semi-Fowler's position (elevating the head of the bed by 30 degrees) decreases the volume of gastric juice and, thereby, the aspiration risk resulting in VAP.[46,47]

Because secretions are pooled above the ET tube cuff, aspiration may occur. Several strategies have been applied to reduce the incidence of VAP, including early tracheostomy, continuous drainage of subglottic secretions, and maintenance of an adequate cuff pressure (>25 cm H_2O to prevent cuff leak, but <30 cm H_2O to prevent tracheal injury). These strategies help prevent introduction of organisms into distal airspaces and decrease the risk of developing VAP.[48–51]

Bacterial colonization of the respiratory tract is another mechanism by which NP develops in mechanically ventilated patients. *Colonization* is defined as the equilibrium between the pulmonary host defenses and the invading capacity of pathogens. When host defenses prevent bacterial invasion but are unable to eradicate bacteria, colonization of the respiratory tract develops. Colonization of the respiratory tract is facilitated by the altered phagocytic capacity of alveolar macrophages, mucosal damage, and decreased mucocilliary clearance. Aero-digestive tract bacteria responsible for colonization may originate endogenously (ie, GI tract; upper respiratory tract: oropharynx, sinus cavities, and nares; and dental plaques) or exogenously (ie, contaminated environment: sinks, faucets, and sheets; contaminated equipment: ventilators, circuits, and radiographic equipment; enteral feeding; and direct or indirect contact with the patients). Because ET tubes develop a biofilm after several days, the use of silver-coated tubes may delay the onset and magnitude of lung colonization.[52]

After pathogens reach the lower respiratory tract, defense mechanisms attempt to eliminate the microorganisms. Whether these defense mechanisms are successful or not in preventing pneumonia depend on the bacterial burden and virulence of the invading pathogens and on the biological status of the host. Speaking to aspiration as the major pathogenic mechanism by which NP develops, early observations by Osler[1] and later by Rouby et al[53] demonstrated that pneumonia occurred predominately in dependent lung zones.

CLINICAL FEATURES, DIAGNOSIS, AND MICROBIOLOGY

Clinical features

Clinical signs of infection, such as new onset of fever, leukocytosis, and tachypnea, combined with purulent respiratory secretions, new auscultation findings, and the presence of a new radiologic opacity indicate possible pneumonia. However, the finding of a new radiologic opacity has a diagnostic accuracy for pneumonia of only 68%, especially in patients with acute lung injury.[54]

Other conditions mimicking pneumonia must be considered, including atelectasis, pulmonary edema, congestive heart failure (CHF), ARDS, neurogenic pulmonary edema, uremia, chemical pneumonitis, alveolar hemorrhage, lung contusion, pulmonary embolism (PE) with infarction, and adverse drug reaction. In light of this array of other possibilities, establishing a diagnosis of NP is controversial and problematic.[55,56]

Diagnosis

Accurate diagnosis is the most controversial and problematic issue in the literature concerning NP and VAP. Clinical criteria for establishing NP and especially VAP were first proposed in 1972 and include the appearance of new and progressive pulmonary infiltrates, fever, leukocytosis, and purulent tracheobronchial secretions.[57] Routine clinical observations (ie, new onset of high fever, auscultation findings, purulent sputum, and tracheal aspirates), laboratory results of leukocytosis, and chest radiographs (ie, new infiltrates, consolidation) are not definitive. However, clinical assessment is the starting point and the cornerstone to suspicion, diagnosis,

and initiation of therapy. Thereafter, it may be helpful to establish independent microbiological criteria with specific pathogen-sensitive results. Microbiological techniques using invasive techniques are considered as complementary tools to decrease false-positive (10%–25%) and false-negative (20%–40%) clinical judgments.[58,59]

A helpful initial endeavor is Gram staining of respiratory secretions, which can provide information within 15 minute. Samples can be obtained by different methods, including protected specimen techniques, bronchoalveolar lavage, and tracheal aspirates. Suitable samples have less than 1% of squamous epithelial cells and more than 10% of neutrophils.

A negative tracheobronchial aspirate culture has a high negative predictive value, so that a negative culture in a patient not receiving antimicrobial treatment essentially excludes VAP. Quantitative cultures of protected specimen brush (PSB) and bronchoalveolar lavage (BAL) specimens obtained through a bronchoscope have also been used to diagnose VAP. In nonintubated patients, PSB and BAL techniques have shown a high specificity for the diagnosis of NP. In mechanically ventilated patients with suspected VAP, the following observations have been made: (1) PSB and BAL are of comparable diagnostic value; (2) tracheobronchial aspirates have comparable results with PSB and BAL, but have lower specificity; and (3) all methods have false-negative and false-positive rates ranging from 10% to 30%.

In a recent review article,[6] it was concluded that quantitative culture cannot confirm a diagnosis of VAP in an individual case and that noninvasive and invasive bronchoscopic techniques have comparable reliability and are disadvantaged by the same methodological limitations. Moreover, the use of microbiological criteria to correct false-positive clinical judgments did not improve the accuracy of VAP diagnosis.

A definite diagnosis of NP and VAP can only be made by one of the following:[59] (1) open lung biopsy with histopathologic examination of lung tissue, (2) rapid cavitation of a pulmonary infiltrate in the absence of cancer and tuberculosis, (3) positive pleural fluid culture, (4) same species with same antibiogram isolated from blood and respiratory secretions without other source of bacteremia, or (5) histopathologic examination of lung tissue at autopsy. However, these criteria are based on highly invasive techniques, rare manifestations or complications of pneumonia, or death and restrict their use in routine cases. Another approach was proposed in 1979, using fiberoptic bronchoscopic techniques[60] for obtaining lower respiratory tract secretions, which are cultured quantitatively. Since then, several invasive techniques to obtain samples from the lower respiratory tract have been introduced. These techniques have been recently reviewed and are found in Table 1.[61]

To collect a proper specimen for quantitative culture and microscopic examination, the following practices have been suggested.

1. Antibiotics should not be started or changed until samples have been obtained.
2. When using bronchoscopic techniques, respiratory secretions should not be suctioned; and an anesthetic should not be injected through the working channel.
3. A return of less than 10% of instilled solution is considered inadequate for sampling.
4. When using PSB, the brush should be placed into exactly 1 mL of fluid.
5. Specimens should be transferred immediately to the laboratory.
6. When using PSB, an analysis of 10 cells per field at a magnification of 500 x represents an inadequate sample.
7. The presence of more than 1% of epithelial cells indicates an unreliable sample.

The accurate diagnosis of NP, along with identification of the responsible organism(s), can be challenging. This task becomes even more difficult in patients who are mechanically ventilated. The laboratory can enhance the accuracy of pneumonia diagnosis as well as provide the identification of an etiologic

Table 1. Techniques used for the microbiological diagnosis of NP and VAP*

A. Bronchoscopically directed techniques
1. Unprotected bronchoalveolar lavage (BAL) fluid quantitative culture ($\geq 10^5$ CFU/mL, $\leq$1% squamous epithelial cells) along with microscopic examination (detection of $\geq$5% of neutrophils or macrophages with intracellular organisms on a Wright-Giemsa stain).
2. Protected BAL fluid quantitative culture ($\geq 10^4$ CFU/mL, $\leq$1% squamous epithelial cells) along with microscopic examination
3. Protected specimen brush (PSB) quantitative culture ($\geq 10^3$ CFU/mL) along with microscopic examination.
B. Non-bronchoscopically directed (blind) diagnostic techniques
1. Blind PSB using telescopic catheters
2. Blind BAL using telescopic catheters, balloon-tipped catheters, or wire-guided catheters at wedge position
3. Blind aspiration of secretions at a wedge position using telescopic catheters

*NP indicates nosocomial pneumonia; VAP, ventilator-associated pneumonia.

organism(s). However, many challenges confront the laboratory, including the following: identifying organisms from an extensive microbiologic spectrum; distinguishing colonization from infection of predominately Gram-negative oropharyngeal flora; and providing timely results. The various diagnostic tests available for nosocomial lung infections, and, in particular, VAP include the following: blood cultures; pleural fluid; expectorated sputum; ET aspirates; and respiratory specimens obtained by more invasive techniques using bronchoscopy or transthoracic needle aspiration. Emphasis is placed on optimal specimen collection, processing of samples in the laboratory, and the evaluation of potential risks and benefits associated with the varying techniques.[62]

A recent consensus conference statement[17] suggested the following concerns in VAP diagnosis:

1. Microbiological samples are collected before initiation of antimicrobial agents.
2. Reliance on ET aspirates leads to both over-diagnosis and under-diagnosis of pneumonia.
3. Available evidence favors the use of invasive quantitative culture techniques over tracheal aspirates when establishing an indication for antimicrobial therapy.
4. Available data suggest that the accuracy of nonbronchoscopic techniques for obtaining quantitative cultures of lower respiratory tract samples is comparable to that of bronchoscopic techniques.
5. The choice depends on local resources and expertise.
6. The cost-effectiveness of invasive vs noninvasive diagnostic strategies has not been established.
7. The precision of the calibrated loop method to measure bacterial burden has yet to be compared to that of the plate dilution method.
8. The predictive value of nonquantitative BAL cultures in the diagnosis of VAP remains to be established.

Suggested criteria for the diagnosis of NP and VAP are listed in Table 2, including ATS criteria[7] and the clinical pulmonary infection score (CPIS).[63] Currently, the diagnosis of VAP and the decision to treat are based on simple clinical criteria or the CPIS, patient's clinical condition, after a vigorous search for noninfectious conditions that mimic VAP and for alternative nonpulmonary sites of infection.[64] This strategy includes a first step of evaluation

Table 2. Criteria for diagnosis of NP and VAP*

A. CDC criteria[7]		
≥3 of the following criteria		
1. Rectal temperature > 38°C or <35.5°C		
2. Blood leukocytosis > 10.10^9/L and/or left shift or leukopenia <3.10^9/L		
3. 10 Leukocytes per high-power field in Gram stain of endotracheal aspirates		
4. Positive culture from endotracheal aspirates and new progressive or persistent radiographic infiltrate		
B. Clinical Pulmonary Infection Score (CPIS)[63]		
1. Temperature °C	≥36.5 and ≤38.4	0 points
	≥38.5 and ≤38.9	1 point
	≥39.0 and ≤36.0	2 points
2. Blood leucocytosis, mm^{-3}	≥4000 and ≤11000	0 points
	<4000 and >11000	1 point
	+ band forms ≥500	1 point
3. Tracheal secretions	<14 + of tracheal secretions	0 point
	≥14 + secretions	1 point
	+ purulent sputum	1 point
4. Oxygenation: Pao_2/Fio_2, mm Hg	>240 or ARDS	0 points
	≤240 and no ARDS	2 points
5. Pulmonary radiography	No infiltrate	0 points
	Diffused, or patchy infiltrate	1 point
	Localized infiltrate	2 points
6. Culture of tracheal aspirate (semiquantitative: 0–1–2 or 3+)		
Pathogenic bacteria cultured	≤1 or no growth	0 points
	>1+	1 point
	>1 + and same pathogenic bacteria seen in Gram stain	2 points
Total points of CPIS varies from 0 to 12 points; >6 points is pneumonia		

*NP indicates nosocomial pneumonia; VAP, ventilator-associated pneumonia; and ARDS, acute respiratory distress syndrome.

of the patients' condition on the basis of classic criteria or CPIS. If there is clinical suspicion of VAP or CPIS more than 6, respiratory secretions are obtained for cultures, and antimicrobial therapy is immediately started. The second step is reevaluation after 48 to 72 hours. If VAP is confirmed either clinically or microbiologically, then antimicrobial therapy is adjusted to culture results. If clinical diagnosis is likely but not confirmed, the decision to treat or not is made on an individual basis; usually the decision is to continue antimicrobial therapy. If a nonpulmonary site of infection is confirmed, then antimicrobial therapy is adjusted to culture results and site of infection. Finally, if VAP is not likely and culture results are not significant or a noninfectious diagnosis is confirmed in the absence of sepsis or septic shock, then antibiotics are stopped.

In patients receiving MV, rapid detection of a triggering receptor expressed on myeloid cells (sTREM-1) in bronchoalveolar-lavage fluid may be useful in establishing or excluding the diagnosis of bacterial or fungal pneumonia.[65] However, this laboratory approach cannot be widely applied and it is not currently suggested.

In the Fourth International Consensus Conference statement in critical care on ICU-AP,[17] it was concluded that the diagnostic method of choice depends on local ICU expertise and method availability, keeping in mind that it is

Table 3. Common pathogens involved in VAP*

NNIS—Nosocomial Pneumonia in ICU (1986–1997)[21]	
• *P. Aeruginosa*	17.4%
• *S. aureus*	17.4%
• *Enterobacter*	11.4%
• *K. pneumoniae*	6.7%
• *H. influenzae*	4.9%
EPIC study[66]	
• *S. aureus*	31.7%
• *P. Aeruginosa*	29.8%
• *Acinetobacter*	9.9%
Ten studies between 1995 and 1997 using bronchoscopic techniques[67]	
• *S. aureus*	20.1%
• *Pseudomonas* (*aeruginosa*)	20.1%
• *Enterobacteriaceae*	19.2%
• *Acinetobacter*	11.6%
• *Haemophilus*	9.1%
• *Streptococcus pneumoniae*	1.8%
• Other Gram-negative bacilli	1.5%
• *Moraxella*	0.8%
• Fungi (mainly *Candida*)	0.7%
• Other microbes	14%

*VAP indicates ventilator-associated pneumonia; NNIS, National Nosocomial Infections Surveillance; ICU, intensive care unit; and EPIC, European Prevalence of Infection in Intensive Care.

important to obtain samples either bronchoscopically or via simple tracheal aspirates for immediate culture.

Microbiology

The etiologic agents responsible for NP, HAP, and VAP are well known (Table 3).[17] However, there is an important difference in the microbiology between early- and late-onset pneumonia. In early-onset NP, the most likely pathogens include *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Haemophilus influenzae*, and nonresistant enteric Gram-negative bacilli, such as *Escherichia coli, Klebsiella* species, *Proteus* species, *Enterobacter* species, and *Serratia marcescens.* In addition, up to half of the episodes of early-onset VAP are polymicrobial in origin. Late-onset NP is more likely to be caused by resistant Gram-negative bacteria, such as *P aeruginosa, Acinetobacter baumannii, Enterobacteriaceae, and* MRSA. *P aeruginosa* and MDR pathogens are uncommon in the absence of previous antibiotic therapy or risk factors, including prolonged MV. As many cases of late-onset pneumonia involve resistant strains, there is a higher frequency of inadequate therapy.

In a recent study, it was found that, in early-onset VAP, the most common isolated pathogen was *Staphylococcus aureus*; and in late-onset VAP, it was *Pseudomonas aeruginosa*. Gram-negative bacteria,[35] including *Pseudomonas aeruginosa*, *Enterobacter, Acinetobacter*, and enteric Gram-negative rods, are implicated in 55% to 85% of HAP cases; Gram-positive cocci, particularly *Staphylococcus aureus*, account for 20% to 30%; and 40% to 60% of cases are polymicrobial. In MV patients, *P aeruginosa* and *Acinetobacter* (eg, *Acinetobacter calcoaceticus* and *Acinetobacter baumannii*), which are often resistant to many antibiotics, account for 30% to 50% of HAP; these pathogens are uncommon in nonICU settings.

Despite the lower respiratory tract being considered sterile, approximately 50% of isolates comprise "normal" respiratory tract flora. Also, multiple organisms may be involved in more than half of cases.[68,69] Anaerobes may be copathogens in early-onset NP, but they do not appear to affect outcome adversely.[70] MRSA is more common in patients who have previously received steroids, antibiotics, or ventilation for more than 6 days (late onset) and is associated with a higher mortality rate.[39,71]

The enormous impact of antimicrobial agents on the organisms responsible for NP was first identified by Kneeland and Price,[72] who found that organisms of the normal pharyngeal flora virtually disappeared in terminal pneumonias following administration of antibiotics; they were being replaced by Gram-negative bacilli. The susceptibility of seriously ill patients to becoming colonized by exogenous organisms, even in the absence of

antimicrobial therapy, was shown by Johanson et al.[73] These authors established a relationship between colonization of the upper respiratory tract with Gram-negative bacteria in intubated patients and VAP.

NATURAL HISTORY

The natural history of NP and particularly VAP is not well understood, confounding the assessment of response to therapy. Further, it is likely true that the course of pneumonia depends on not only the pathogen involved but also the choice of antibiotics and the host's ability to respond. Thus, it is difficult to determine when a patient is not responding or even when it is possible to shorten the duration of therapy in responders to treatment. Denneson et al[74] found that there is significant improvement in clinical parameters, including fever, leukocytosis, and oxygenation, and a reduction in bacterial growth in the sputum on day 6 after starting appropriate antibiotics. Improvement occurs with resolution of fever, followed by improved oxygenation and leukocyte count and, finally, decreased bacterial colonization of the lower respiratory tract. Respiratory bacterial eradication was completely successful when the pneumonia was due to the flora associated with early-onset VAP, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, partially successful (50%) with Gram-negative flora, such as the *Enterobacteriaceae,* and not successful with *Pseudomonas* species, which persisted in cultures. In addition, secondary colonization occurred during the second week of therapy; this was generally with resistant organisms like *P aeruginosa*, *Enterobacteriaceae*, and *S aureus*. The authors[74] also observed 6 cases of secondary pneumonia; 3 involved newly acquired *P aeruginosa*. This organism emerged as a colonizer almost a week after starting antibiotic therapy for the first pneumonia, and the infection declared itself shortly after discontinuation of the first course of antibiotics.

Thus, overly long courses of antibiotics are undesirable. To facilitate discontinuation, it is necessary to define resolution of Gram-negative pneumonia by using clinical, rather than bacteriologic, parameters. Recent data[75] looked at the resolution of VAP diagnosed using clinical criteria, in an attempt to find indices predicting survival, including the CPIS. Contrary to the above study, the authors found that in survivors of VAP, oxygenation was the first to improve (7.8 days), followed by fever and leukocytosis, with progressive reduction in the CPIS score. In nonsurvivors, the CPIS score remained high and hypoxemia never resolved. A falling CPIS may, therefore, allow for shorter course therapy.[62,74] Indeed, a low or improving CPIS after 3 days of treatment has been used to identify responders that could receive short course (3 days) of antibiotic therapy.[56]

RISK FACTORS

Risk factors for developing NP include age, male gender, coma, burn injury, trauma, acute lung injury, and severity of illness; but the most important factors may be the duration of MV and prior antibiotic treatment. Antibiotics are protective against early-onset NP, but prolonged antibiotic use in hospital is a risk factor for late NP with resistant organisms.[23,30] Other studies have identified chronic cardiac or pulmonary disease, renal failure, malignancy, diabetes mellitus, head injury, tracheostomy, nasogastric tube use, paralytics and corticosteroid use, and witnessed aspiration additional risk factors.[35] Also, the risk for VAP peaks around day 5 of MV, plateaus on day 15, and then declines. Thus, in patients receiving long-term MV, the incidence of VAP is quite low.[31,76]

The most important factor for developing NP and particularly VAP is intubation and MV. The ET tube allows direct entry of bacteria into the lower respiratory tract and interferes with normal host defense mechanisms. These defense mechanisms include filtration and humidification of air in the upper airways, epiglottic and cough reflexes, and ciliary transport by the respiratory epithelium. The ET tube also becomes a reservoir

for pathogenic organisms. Feldman and colleagues[77] found that a biofilm (biomembrane colonized with bacteria) formed in the lower third of ET tubes removed from all intubated patients. Colonization and biofilm formation were noted by 12 hours after intubation and found in almost all patients after 96 hours. The same authors[77] also found that colonization occurred first in the oropharynx and stomach, then lower respiratory tract, and finally in the ET tube. This sequence is significant because contamination of the ET tube appears to originate from the lower airways, rather than through contaminated respiratory equipment or medications, and likely results from aspiration.[27] There is also evidence that instillation of normal saline during suctioning of an intubated patient contributes to nosocomial infection by flushing bacteria from the ET tube into the lower airways.[78] Although more research on this is necessary, Chulay[78] recommended avoiding instillation of normal saline while suctioning.

Understaffing of a department or an ICU has a direct effect on the rate of nosocomial infections. The incidence of NP has been documented to be inversely correlated with the number of hours of care provided to the patient.[79] This finding strongly suggests that prevention of VAP is related to the time that a nurse has at the bedside to apply effective prevention measures according to guidelines.[27] It is recommended that hospital administrators consider NP and other adverse patient outcomes when calculating anticipated savings effected by decreased staffing ratios and the use of ancillary staff members.

In the last consensus conference statement[17] on VAP, it was concluded that coma, prolonged MV through an ET tube, repeated intubations, the supine posture, and long-term antibiotic use increase the risk of ICU-AP.

PREVENTIVE MEASURES

Prevention is the most important measure in the management of VAP.[80] Prevention of NP and particularly VAP should be focused on decreasing aspiration risk and preventing colonization of the respiratory tract by altering the virulence and quantity of microorganisms in the oropharynx.[81]

General hygiene measures,[82] including hand disinfection with chlorexidine and the use of gloves, gowns, and sterile equipment, are the cornerstone for preventing nosocomial infections and should be meticulously applied in ICUs and medical wards to prevent cross-infection. Antibiotic prophylaxis in terms of selective digestive decontamination (SDD) combined with good patient and staff hygiene may also help to prevent VAP. This strategy consists of (1) topical administration of nonabsorbable antibiotics in the oropharyngeal cavity and good oral care, including frequent suctioning of oral secretions and application of oral rinses twice daily; (2) systemic administration of antibiotics during the 4 first days of MV; (3) surveillance cultures to examine and monitor SDD; and (4) optimal hand hygiene to prevent cross-infection.

The use of sucralfate, instead of ranitidine, has been found to decrease the rate of VAP. Also, modification of enteral feeding to glutamine enriched immunonutrition diets decreases the incidence of VAP. Continuous subglottic aspiration (suction) of oropharyngeal secretions has been proven to significantly protect against VAP. These special ET tubes cost $15 more than standard tubes, but preventing VAP using these tubes saves up to $1872 per patient.[83] Finally, the positioning of the patients in the semirecumbent position (30°–45°) instead of supine (0°) protects against VAP. Drakulovic and colleagues reported a significant decrease in VAP incidence from 23% to 5% by placing patients in a semirecumbent position.[84]

Critical steps in the prevention and control of nosocomial infections in the ICU are continuous application of effective infection control, including handwashing and microbiological surveillance. However, the rate of implementation of evidence-based preventive measures for VAP is low; and the barriers to implementing these measures are varied. Educating healthcare professionals and heightening their awareness are keys to success.

Table 4. Measures for the prevention of VAP*,†

1. Protection of the patient
   a. Use of gowns and gloves
   b. Adequate nutritional support
   c. Avoidance of gastric overdistention
   d. Postural changes
   e. Semirecumbent positioning (head at 45°C)
   f. Limitation of stress ulcer prophylaxis
   g. Avoidance of accidental extubation
   h. Clear oral secretions
   i. Minimized saline instillation during suctioning
2. Against microorganisms
   a. Handwashing hourly
   b. Chlorexidine oral rinse
   c. Infection control programs
   d. Avoidance of unnecessary antibiotics
   e. Selective digestive decontamination (SDD)
   f. Routine parenteral antibiotics in comatose patients
3. Against invasive devices
   a. Adequate cuff pressures
   b. Removal of nasogastric/endotracheal tubes
   c. Humidification with heat moisture exchangers
   d. Drainage of condensates from ventilator circuits
   e. Continuous subglottic drainage
   f. Oral intubation
4. Development of NP-VAP prevention protocol

*Modified from Rello and Diaz.
†NP indicates nosocomial pneumonia; VAP, ventilator-associated pneumonia.

Indeed, it is vital that all healthcare professionals participate in these programs and that these programs are customized to each ICU to ensure continuous improvement in the provision of care to critically ill intubated patients. Potential measures of control (Table 4) focus on the patient, the microorganisms, devices, and application of protocols on effective prevention measures.

A recent evidence-based systematic review[85] of preventative measures in critically ill ICU patients suggests the following measures: (1) semirecumbent positioning for all eligible patients; (2) sucralfate, instead of H2-antagonists, for stress ulcer prophylaxis in patients with low to moderate risk for gastrointestinal bleeding; (3) aspiration of subglottic secretions in patients requiring more than 3 days of MV; and (4) oscillating beds in surgical and neurological patients.

Education of critical care nurses, respiratory therapists, and physical therapists concerning VAP risk factors and prevention measures may significantly reduce VAP incidence. Zack and colleagues demonstrated a significant reduction in VAP cases from 12.6 to 5.7 per 1000 ventilator days after introducing an educational intervention program.[86]

The consensus conference statement[17] on ICU-AP concluded that the only established preventive measure is avoidance of the supine posture. Safe, inexpensive, logical, but unproven interventions include routine handwashing, avoidance of indiscriminate antibiotic use, limiting stress ulcer prophylaxis to high-risk patients, and the use of noninvasive MV whenever feasible. Finally, more data are needed concerning the benefits of postpyloric feeding, kinetic/physiotherapy, subglottic drainage, oral and digestive tract decontamination, early tracheostomy, oral versus nasotracheal tubes, and endotracheal tubes that inhibit biofilms. Prevention of NP should not only focus on identifying and reducing risk factors, but also on implementing educational programs and hospital policies, applying NP-prevention protocols and prevention strategies, enhancing compliance to existing guidelines, and using standard precaution measures.

MANAGEMENT

HAP remains a major cause of morbidity and mortality among hospitalized patients.[87,88] Although early appropriate antibiotics improve outcomes, the cause of HAP frequently is not known at the time that therapy is

initiated, mandating rationale empiric antibiotic choices. As most cases of HAP result from microaspiration of oropharyngeal secretions colonized with pathogenic bacteria, the spectrum of potential pathogens is broad. This spectrum can be narrowed by taking into account severity of illness, length of stay before the onset of pneumonia, and presence of risk factors for specific pathogens. After therapy has been initiated, follow-up of initial microbial studies and careful monitoring of the patient's course are important. Clinical improvement, even when therapy is appropriate, takes days; and, in general, therapy should not be changed for the first 2 to 3 days unless frank deterioration is noted. Patients who fail to respond or experience clinical deterioration should be reexamined carefully, and thought should be given to the possibility of a noninfectious process. Appropriate administration of antibiotics is mandatory to improve outcome and decrease morbidity, length of hospital and ICU stay, and healthcare costs. Other goals of management are to support the cardiovascular system by improving hemodynamics, tissue perfusion, and tissue oxygenation, and to prevent complications, especially sepsis and septic shock, organ dysfunction, and ventilator-induced lung injury.

Nowadays, the epidemiological[89] and deescalating[34] approach is strongly suggested by the ATS guidelines[7] in the antimicrobial management of NP, to include the following:

1. Initial antimicrobial treatment should always be empiric.
2. Empirical antimicrobial treatment should be guided by 3 criteria: severity, time of onset, and specific risk factors.
3. Selection of antimicrobial agents must be adapted to the local pattern of microbial resistance and epidemiology.
4. The diagnostic workup may offer additional data that should be interpreted in the context of the patient's condition.
5. In patients with early onset VAP without risk factors for resistant pathogens, antimicrobial therapy should cover community-endogenous pathogens and nonresistant Gram-negative *Enterobacteriaceae*.
6. In patients with late-onset VAP without risk factors, empiric antimicrobial therapy should cover potentially resistant microorganisms, including *Pseudomonas aeruginosa, Acinetobacter* species, and MRSA.
7. In patients with early- or late-onset VAP with risk factors, empiric therapy should be the same as in late-onset without risk factors, except when *Legionella* species are considered.

Keep in mind that the chance of MDR pathogens in patients with VAP is greater in those with long hospital and ICU stays, prior antibiotic therapy, multiple comorbidities, and prolonged MV. In these patients, it is mandatory to know the local microbiological pattern and the patterns of resistance to assure adequate initial treatment.

In most studies, the most common reason for treatment failure was inadequate initial empiric antibiotic coverage, mandating initial broad-spectrum antibiotic coverage. According to the ATS guidelines,[7] the antibiotics suggested for the treatment of patients with severe early-onset NP should be a second-generation or third-generation cephalosporin, a combined β-lactam/β-lactamase inhibitor, a fluoroquinolone or clindamycin plus aztreonam. In patients with severe late-onset NP, the recommended treatment includes an aminoglycoside or ciprofloxacin plus one of the following: imipenem; an antipseudomonal, broad-spectrum penicillin; an antipseudomonal, third generation cephalosporins; or aztreonam. Meropenem, piperacillin/tazobactam, or cefepime might also be administered as antipseudomonal antibiotics. A glycopeptide, such as vancomycin, should be added if MRSA is strongly suspected; linezolid or quinupristin/dalfopristin are alternatives.

Current recommendations are to start with broad-spectrum empiric antibiotics, then switch to narrow-spectrum specific therapy as guided by microbiological results.[34] This deescalating approach is likely to ensure adequate upfront coverage, yet minimize the

risk of resistance and adverse drug reactions over the treatment period. Thus, each ICU designs specific empiric treatment protocols that are likely to be effective according to local microbiology and resistance patterns and which require reevaluation after 48 to 72 hours.[64]

The standard duration of antibiotic therapy is 2 weeks according to clinical trials and guidelines. However, a recent study found that in patients receiving appropriate initial antibiotics, comparable results were found with 8 or 15 days of therapy.[90] The duration of antibiotic therapy is individualized based on the clinical response and the causative pathogen. Consensus conferences[7,91] suggest that patients infected with sensitive organisms may be treated for 7 to 10 days. Patients with multiresistant pathogens may require 14 to 21 days of treatment to prevent treatment failure or relapse. It has also been suggested, based on little data, that patients with multilobar, necrotizing, or cavitary pneumonia receive extended (2–3 weeks) treatment. Minimal data exist to indicate if therapy can be discontinued at a set time after defervescence.

Physician education about appropriate antibiotic use may minimize the risks of antibiotic resistance. Also, scheduled changes of antibiotic regimens or routine microbiological surveillance-guided changes in antibiotic policy may reduce the emergence of resistant strains. Changes in antibiotic regimens may involve antibiotic cycling, which is the changing of usual antibiotic regimens from time to time or the use of different regimens in consecutive patients. Such heterogeneous antibiotic use may improve selective pressure and the likelihood of resistance.

CONCLUSIONS

Nosocomial pneumonia and especially VAP are the most frequent infectious complications in the ICU, and they significantly contribute to morbidity and mortality. VAP is an important determinant of ICU and hospital lengths of stay and healthcare costs. Several simple preventive measures and timely initiation of appropriate antibiotics ensure better outcomes in patients with VAP. An epidemiological approach with empiric antibiotics followed by a deescalating antibiotic strategy guided by microbiological data is strongly suggested to reduce initial antibiotic treatment failures and minimize antibiotic resistance. Antibiotic rotation to prevent the emergence of MDR pathogens is also considered.

Additional studies are needed to elucidate important remaining issues concerning the pathogenesis, natural history, prevention, diagnosis, and duration of therapy of NP. Specific answers are sought concerning the attributable morbidity and mortality of NP, the cost-effectiveness of invasive versus noninvasive diagnostic strategies, and the utility of rotating antibiotics. Finally, research focused on characteristics of the local inflammatory response and structural changes that occur during NP enhances the overall understanding of NP and VAP.

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