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Clinical Challenges and Case Studies of Microorganisms in Pneumonias

The Challenge to Health Care Providers

HIGHLIGHTS OF A SYMPOSIUM

Clinical Cases in Health Care-Associated Pneumonia

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Evolution of Health Care-Associated Pneumonia Continues

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Guideline Recommendations for Diagnosis of Pneumonia

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Treatment Strategies for Community-Acquired Pneumonia

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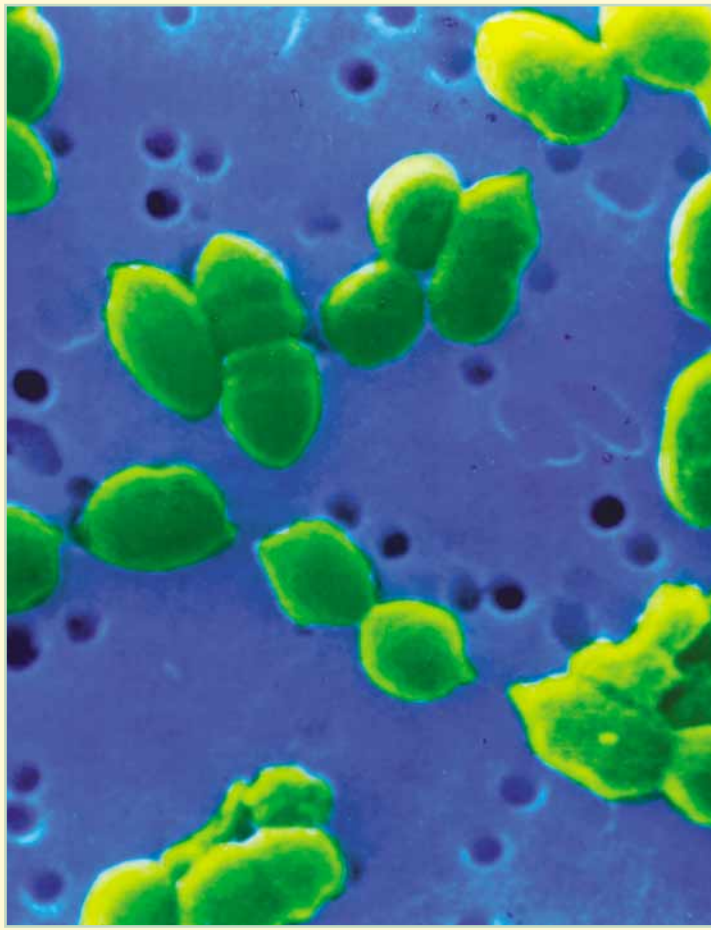

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Dr Lazarus has received speakers bureau honorarium during 2006 from sanofi-aventis.

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Dr Wunderink has received an investigator initiated grant from Eli Lilly and Company and has performed clinical research for Novartis Pharmaceuticals Corporation, who sponsored a study for which a revised manuscript has been submitted for publication. He has worked as a consultant and researcher for Inverness Medical Innovations, Inc., and has stated that he will reference their diagonostic test.

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OBJECTIVES

- Identify three common epidemiologic data references related to pneumonia and other associated infectious diseases.
- Understand key evidence-based recommendations on the diagnosis of health care-associated pneumonias.
- Assess appropriate antibiotic and nonantibotic use based upon case-based questions.

STATEMENT OF NEED

Despite a broad use of antimicrobials available to treat pneumonia, it remains the eighth leading cause of death in the United States. In 1999, the age-adjusted death rate due to influenza and pneumonia was 23.6 per 100,000 persons. Current estimates of the incidence of community-acquired pneumonia range from 4 to 5 million cases per year, with about 25% requiring hospitalization. Nosocomial pneumonia is estimated to occur in 250,000 persons per year, representing about 15% to 18% of all nosocomial infections. *Streptococcus pneumoniae* remains the most commonly identified pathogen in community-acquired pneumonia. A variety of other pathogens have been reported to cause pneumonia in the community, with their order of importance dependent on the location and population studied. These include long-recognized pathogens such as *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and influenza A, along with newer pathogens such as *Legionella* species and *Chlamydophila pneumoniae*. Other common causes in the immunocompetent patient include *Moraxella catarrhalis*, *Mycobacterium tuberculosis*, and aspiration pneumonia. The causative agent in community-acquired pneumonia remains unidentified in 30% to 50% of cases. Pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Pseudomonas aeruginosa* (MDR PA), and *Burkholderia cepacia*, are increasingly recognized causes of pneumonia. Severe acute respiratory syndrome (SARS)-associated coronavirus emerged and spread worldwide in the winter of 2002 to 2003. This virus, and its associated SARS, is another pathogen with growing importance.

TARGET AUDIENCE

Pulmonary Fellows-in-Training, Critical Care Fellows-in-Training, Physicians-Pulmonary, Critical Care, and General Medicine, Respiratory Therapists, Advance Critical Care Nurse Practitioners, and Physician Assistants.

ESTIMATED TIME OF COMPLETION: 90 MINUTES

TERM OF APPROVAL

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Introduction

Current Issues and Challenges in Pneumonia

The clinical environment of pneumonia in the United States offers a study in contrasting facts. Since the early days of the 20th century, pneumonia mortality has declined by more than fourfold, from about 180 deaths per 100,000 in 1900 to about 40 per 100,000 today.[1] However, pneumonia-associated mortality has remained largely unchanged for the past 50 to 60 years.

Pneumonia remains a leading cause of death in the United States, accounting for almost 50,000 fatalities annually. Between two and three million cases of pneumonia are diagnosed each year, leading to 500,000 hospital admissions annually. Although mortality is generally less than 1% among patients requiring only outpatient treatment, the risk of death increases by tenfold or more among patients requiring hospital admission. Intensive care unit (ICU) care is associated with a mortality risk of 30% to 40% in patients with severe pneumonia.[2]

Continual expansion of the antibiotic armamentarium has given physicians more options than ever for controlling and eradicating bacterial causes of pneumonia. Unfortunately, pneumonia-associated pathogens continue to mutate, evolve, and otherwise morph into variants that are increasingly difficult to eradicate, even with the unprecedented spectrum of antibiotic options available to physicians and their patients. According to the Centers for Disease Control and Prevention, the proportion of nosocomial (particularly ICU-related) infections involving methicillin-resistant *Staphylococcus aureus* has increased to about 50% of the total at many medical centers in the United States.

Pneumonia classifications also have begun to overlap and blur, complicating physicians' attempts to arrive at an accurate diagnosis and assess the disease severity. Many patients with pneumonia have no recent history of hospitalization, but they often have been in contact with health care providers in clinics, offices, and other settings. As a result, the distinction between community-acquired pneumonia (CAP) and nosocomial (or hospital-acquired) pneumonia (HAP) has become less rigid. This has given rise to the term health care-associated pneumonia (HCAP), which may have features of both CAP and HAP.

In some pneumonia studies, HCAP has been the predominant form of illness. From a microbiologic perspective, HCAP more closely resembles HAP or ventilator-associated pneumonia (VAP). HCAP also tends to cause more severe illness compared with CAP.[3,4]

The changing clinical environment of pneumonia has put even greater onus on clinicians to make timely diagnoses and initiate appropriate therapy as soon as possible. Clinical guidelines recommend starting therapy within 12 hours of presentation, citing data demonstrating increased morbidity and mortality risks associated with delayed therapy.[5]

The risks of delayed appropriate therapy are matched by the risks of starting a patient's treatment with inappropriate therapy. Initial inappropriate or ineffective treatment independently predicts an increased mortality risk that might be as much as fourfold or fivefold greater compared with patients who receive initial appropriate therapy.[6]

Physicians can turn to several recently promulgated and updated clinical guidelines for direction in navigating the risks, uncertainties, and conundrums related to diagnosing and treating pneumonia. Adherence to recognized clinical guidelines significantly improves outcomes of patients compared with nonadherence to guidelines.[7]

The following educational activity addresses the challenging issues surrounding recognition and management of pneumonia. In the presentations that follow, infectious disease specialists offer their knowledge and insights into current issues and standards related to bacterial pneumonia. Clinicians involved in the care of patients with pneumonia will find the information timely and readily applicable to clinical practice.

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Clinical Cases in Health Care-Associated Pneumonia

Introduction

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Pneumonia remains a leading cause of morbidity and mortality in the United States. However, early recognition and diagnosis followed by initiation of effective treatment with appropriate antibiotics can improve pneumonia outcomes. Understanding the different types of pneumonia can lead to prompt recognition of the most likely causative organisms and their potential resistance patterns. The following clinical cases illustrate differences in presentation and symptoms that can guide physicians toward a correct pneumonia diagnosis and prompt initiation of appropriate therapy.

CASE I

A 34-year-old female with a history of asthma, worsening wheeze, and nonproductive cough

Presentation and History

The patient has a 15-year history of asthma and presented for evaluation of worsening wheeze and increased nonproductive cough over a 2-week period. She had a fever for the first 3 days but no chills, chest pain, nausea, or vomiting. She returned from a 1-week vacation in Puerto Rico 60 days ago.

Current medications consist of multiple therapies for asthma and allergies. The patient has no history of hospitalization, no asthma-related emergency department visits in the past 2 years, no history of pneumonia, and no prior surgery. She is a nonsmoker and rarely drinks alcohol.

Physical/Clinical Findings

The patient has a temperature of 99.7°F, respiration of 18/min, heart rate of 87 bpm, and O_2 saturation of 97%. Cardiac exam is normal. Nasal congestion is noted. The patient is not in acute distress and appears alert. Auscultation reveals bilateral wheezing, but she has no rales. The remainder of the physical exam is normal.

Laboratory

The patient has a white blood cell count of 9900 and a neutrophil count of 78. The rest of her laboratory findings were within normal ranges.

Radiographic Findings

Chest x-rays were consistent with a diagnosis of pneumonia. The x-ray shows evidence of pneumonia in the left upper lobe (**Figure 1**).

Miscellaneous

The patient was unable to produce a sputum sample. Records from an examination in 2006 showed a normal IgE and no evidence of allergic bronchopulmonary aspergillosis.

Management and Outcome

The patient began outpatient treatment with levofloxacin. Additionally, she took prednisone for 5 days. She continued all existing medications. Patient's symptoms responded promptly, and at 2-week follow-up, her lungs were clear on auscultation and x-ray (**Figure 2**).

Chest X-Rays Before and After Treatment

Figure 1.

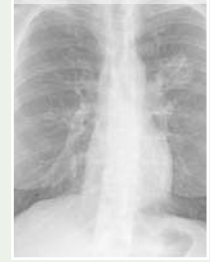
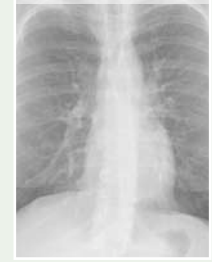


Figure 2.



Source: Angeline A. Lazarus, MBBS, FCCP

Comment

The patient had a fairly uncomplicated case of community-acquired pneumonia (CAP), except for the potential effects of comorbid asthma. With adherence to a guideline-supported approach to clinical management, the pneumonia resolved without incident.

CASE II

A 68-year-old female with a 2-day history of fever, cough, and pleuritic chest pain

Presentation and History

The patient has mild non-insulin requiring diabetes for which she is being treated. She is a nonsmoker and occasionally drinks alcohol. She had knee replacement surgery 60 days ago and spent 2 weeks at a rehabilitation facility. She had a chest x-ray for evaluation of the presenting symptoms.

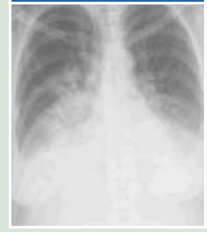
Physical/Clinical Findings

The patient has a temperature of 100.6°F, heart rate of 96 bpm, respiratory rate of 18/min, and O_2 saturation of 97%. The patient appears alert and oriented with no evidence of distress. Auscultation revealed right lower lobe rales.

Clinical Management and Follow-Up

The patient was prescribed levofloxacin (500 mg/day) for CAP and sent home. Two days later the patient presented to the emergency room with increasing cough, fever, chest pain, and dyspnea. She had a temperature of 101.8°F, heart rate of 124 bpm, respiratory rate of 24/min, O_2 saturation of 92%, and blood pressure of 110/76 mmHg. White count was 18000 with left shift, and she had a BUN of 32. The patient was admitted to the hospital for failure of outpatient therapy for CAP (**Figure 3**).

Figure 3. Admission X-Ray



Source: Angeline A. Lazarus, MBBS, FCCP

Figure 4. Gram-Positive Cocci

Source: Angeline A. Lazarus, MBBS, FCCP

Laboratory

Microbiologic assessment revealed gram-positive cocci in clusters (**Figure 4**) and *Staphylococcus aureus* growth on culture.

Treatment/Clinical Course

The patient was treated with vancomycin when sensitivity results demonstrated methicillin-resistant *S. aureus*. After a 10-day course of vancomycin, the patient improved and was discharged home.

CASE III

A 71-year-old Hungarian man with a 5-day history of fever, chills, malaise, and lightheadedness

Presentation and History

The patient presented for evaluation of the above-mentioned symptoms. His wife, a pediatrician, had given him azithromycin 4 days previously. He had a 1-day history of drenching night sweats and mild dyspnea. Symptom onset was 1 day after a trip to Arizona, which included a 12-hour layover and 8-hour stay at a Red Cross shelter because of bad weather. At the shelter, he was exposed to sick patients. Two weeks prior to the onset of his illness, the patient had a brief exposure to a sandstorm, also in Arizona. The patient has a history of hypertension, hyperlipidemia, and gastroesophageal reflux disease. He underwent excision of an acoustic neuroma in 1977, complicated by facial droop, vocal cord paralysis, and dysarthria. He also has undergone cervical vertebroplasty.

Current medications include lisinopril, simvastatin, omeprazole, and a multivitamin.

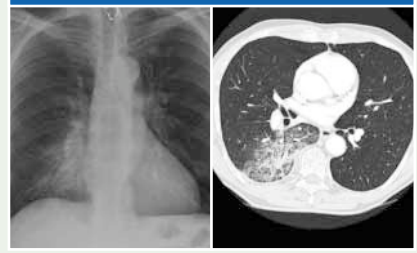
Physical Examination

The patient had a temperature of 102.4°F, heart rate of 98 bpm, respiratory rate of 18/min, and O_2 saturation of 96%. The patient was alert and oriented but appeared tired. He had no postural hypotension. Lung examination revealed decreased breath sounds in the right lower lobe with egophony and rales. The cardiac and abdominal examinations were normal.

Laboratory

The patient had a CBC of 9300 and neutrophil count of 83. Blood chemistry was normal. Blood cultures are pending. Induced sputum tested negative for acid-fast bacilli and fungi. Gram stain showed mixed flora (**Figure 5**).

Figure 5. Admission Chest X-Ray and CT Scan



Source: Angeline A. Lazarus, MBBS, FCCP

Radiographic

The patient's primary care physician requested an x-ray, as well as a chest CT, to rule out pulmonary embolism. The chest x-ray and CT findings were consistent with pneumonia.

Management and Follow-Up

The patient refused bronchoscopy and hospital admission. Treatment was initiated with levofloxacin (750 mg/day) plus clindamycin for possible aspiration pneumonia. Over the next 2 days, cough and fever decreased slightly, but the patient continued to have drenching night sweats. Tests for respiratory syncytial virus, *Legionella pneumophila*, and Influenza A and B antigen were all negative. Urine and blood cultures also were negative.

On day 3 after initial presentation, the patient returned and reported slightly reduced cough but persistence of drenching sweats and fever. His CBC had increased to 14500 and his neutrophil count to 86. Repeat chest CT revealed increased consolidation.

The patient was admitted to the hospital, and bronchoscopy was scheduled for the next day. A repeat induced-sputum analysis revealed coccidioides spheules. The patient began treatment with itraconazole and was discharged home 2 days after admission. Symptoms resolved gradually except for persistent mild cough (**Figure 6**).

Figure 6. Predischarge CT Scan

Source: Angeline A. Lazarus, MBBS, FCCP

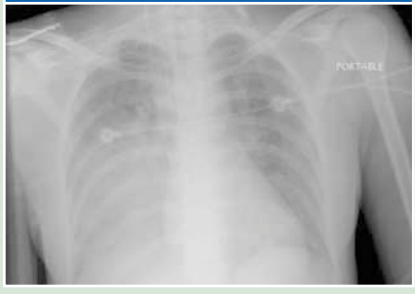
CASE IV

A 44-year-old female ophthalmologist with a 1-week history of cough and upper respiratory symptoms

Presentation and History

The patient presented to the emergency department when she developed a fever (102.5°F) and chills. Within 30 minutes, the patient complained of dizziness and became hypotensive. Her O_2 saturation was 66%. Empiric antibiotic therapy was started, and the patient was intubated and transferred to the ICU. A chest x-ray was consistent with pneumonia (**Figure 7**).

Figure 7. Administration Chest X-Ray



Source: Angeline A. Lazarus, MBBS, FCCP

The patient had a history of mild persistent asthma treated with combined ß-agonist/corticosteroid medication. She had a history of allergy to sulfa. She was a nonsmoker and had an estimated wine consumption of 2 to 3 glasses weekly. Her family history was unremarkable.

Laboratory

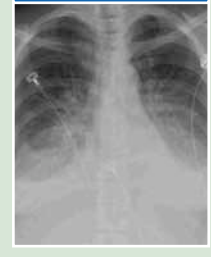
The patient had a white count of 31200 and neutrophil count of 60. Her hemoglobin was 10.9 and her hematocrit was 32. She had a pH of 7.3, O_2 of 300 on 100% oxygen, bicarb of 14, and PCo2 of 32.

Management and Follow-Up

Emergency room physicians initiated combined antibiotic therapy with vancomycin, levofloxacin, and doxycycline. In the ICU, bronchoscopy and bronchoalveolar lavage revealed gram-positive cocci in pairs. Drotrecogin-alfa was added to the patient's therapy. Subsequent analysis of BAL specimens revealed *Streptococcus pneumoniae* with sensitivity to levofloxacin.

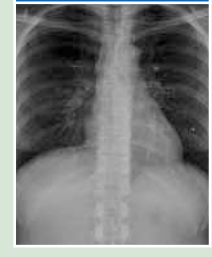
After 2 days in the ICU, the patient was extubated. She required continuous positive airway pressure (CPAP) for 4 days and then was transferred to a general unit (**Figure 8**). She was discharged home on day 9. She was ambulating well and had an O_2 saturation of 96%. **Figure 9** shows the patient's chest x-ray at her 1-month follow-up.

Figure 8. Post-ICU X-Ray



Source: Angeline A. Lazarus, MBBS, FCCP

Figure 9. Discharge X-Ray



Source: Angeline A. Lazarus, MBBS, FCCP

Evolution of Health Care-Associated Pneumonia Continues

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Introduction

Historically, pneumonia syndromes have been classified into a few discrete categories, such as hospital-acquired pneumonia (HAP), community-acquired pneumonia (CAP), and pneumonia in the immunocompromised patient. The syndromes were treated as distinct entities. However, the lines of demarcation between syndrome categories began to blur, as groups of patients that overlapped the categories emerged. A prime example is nursing home community-acquired pneumonia, which has been treated as a separate entity by some authors and investigators. Subsequently, other pneumonia syndromes emerged with features of CAP but associated with pathogens generally found in the hospital, including multidrug-resistant (MDR) pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and antibiotic-resistant gram-negative enteric pathogens. This overlap between HAP and CAP has given rise to the newer concept of health care-associated pneumonia (HCAP). Additional overlap could be seen between HCAP and pneumonia of immunocompromised patients. HIV-infected patients offered a prime example. The number of clinical circumstances included under the HCAP umbrella continued to increase, until HCAP became the predominant pneumonia syndrome, more or less by default.

Epidemiology of Health Care-Associated Pneumonia

Traditionally, pneumonia that develops outside a hospital is categorized as CAP, even among patients who have received medical care outside of a hospital. Few studies have examined the epidemiology of HCAP, but the available data suggest that health care-associated infections have characteristics that make them distinct from CAP.

A review of hospital records on 4,543 patients with culture-positive pneumonia at 59 centers showed that half the patients had CAP and more than 20% had HCAP.[1] Patients categorized as having HCAP had a mortality of 19.8%, almost double the 10% mortality among patients with CAP and slightly greater than the 18.8% mortality among patients with HAP ($P<0.0001$ for comparisons versus CAP). Patients with ventilator-associated pneumonia (VAP) had the highest mortality (29.3%).

HCAP patients more often had pathogens found in VAP than in CAP: methicillin-resistant *S. aureus*, *P. aeruginosa*, *A. baumanii*, and enterics. Some MDR pathogens were more common in patients with HCAP than in those with VAP.

A study of patients with severe, culture-proven nursing home-acquired pneumonia emphasized the role of antibiotic therapy in the development of MDR pneumonia.[2] The study focused on patients admitted to ICUs and requiring mechanical ventilation. During a 36-month period, 88 nursing home patients met criteria for inclusion. In 17 (19%) of the cases, at least one MDR pathogen was recovered from the lower respiratory tract. The frequency of MDR pathogens was 10 times greater (71% vs 7%) in patients with a recent history of antibiotic therapy compared with patients who had not been treated recently with antibiotics (**Table 1**).

The study of severe nursing home-acquired pneumonia included an evaluation of activities of daily living (ADL). Patients were assigned ADL scores based on a scale that rated a patient's ability (1 to 3) to perform certain activities, such as feeding, bathing, dressing, and toilet use. A patient with a total score of 6 is fully independent.

Among patients with no recent history of antibiotic therapy, an ADL score <12.5 was associated with absence of MDR pathogens versus 17% in those who had

Table 1. Risk Factors for MDR Pathogens

- Antimicrobial therapy in preceeding 90 days
- Current hospitalization ≥5 days
- High frequency of antibiotic resistance in community or specific hospital unit
- Presence of risk factors for HCAP
  - ≥2 days hospitalization in previous 90 days
  - Nursing home or extended care facility residence
  - Home infusion therapy or wound care
  - Chronic dialyses for >30 days
  - Family member with MDR
- Immunosuppresive disease or therapy

MDR = multidrug-resistant. **Source:** American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Available at: http://www.thoracic.org/sections/publications/statements/pages/mtpi/guide1-29.html. Accessed March 24, 2008. Reprinted with permission.

an ADL ≥12.5. In the patients with prior antibiotic therapy, MDR pathogens were isolated from 42% of patients with an ADL <12.5 and 90% of those with an ADL ≥12.5.[2]

The primary implication of the ADL findings is that a thorough history is essential to the classification and management of patients with nursing home-acquired pneumonia. The more independent a patient is, the less likely the patient is to have MDR pathogens. As a patient's inability to perform self-care increases, so does the likelihood of MDR pneumonia.

Two recent studies have provided much-needed information about the etiology of pneumonia in patients at risk for HCAP. Spanish investigators prospectively evaluated patients presenting to a hospital with pneumonia over a 4-year period.[3] The researchers found that 126 of 727 (17.3%) patients met their criteria for HCAP.

Comparison of patients with HCAP versus CAP showed that the two groups differed substantially. Patients with HCAP were significantly older (69.5 vs 63.7 years, $P<0.001$), had greater comorbidity (95.2% vs 74.7%, $P<0.001$), and were significantly more likely to be classified as high risk by the pneumonia severity index (67.5% vs 48.8%, $P<0.001$).[3]

Evaluation of individual risk factors demonstrated a higher prevalence in HCAP patients in every instance. The risk factors examined included chronic obstructive pulmonary disease, prior stroke, a history of cancer, long-term corticosteroid therapy, influenza vaccination, and recent antibiotic therapy. As previously stated, patients with HCAP also had a significantly higher pneumonia severity index score.[3]

The microbiology of HCAP and CAP also differed in the Spanish study. *Streptococcus pneumoniae* was the most commonly isolated pathogen in both HCAP patients (27.8%) and CAP patients (33.9%). However, *Hemophilus influenzae* was twice as common in HCAP (11.9% vs 6%). Aspiration was the source of pneumonia in 20.6% of HCAP patients compared with 3% of the CAP patients. Gram-negative bacteria and *S. aureus* were uncommon in both groups but occurred more often in HCAP patients. About one third more CAP patients had no identifiable pathogen than did HCAP patients (43.9% vs 32.5%).[3]

Another study published last year described characteristics of 639 culture-positive pneumonia patients who presented to a single US hospital over a 3-year period.[4] In contrast to the Spanish study, two thirds of the patients (67.4%) met criteria for HCAP. The major risk factor for HCAP was previous hospitalization (93.3%), particularly hospitalization within the past 90 days (70%). Additionally, the Spanish study excluded severely immunocompromised patients, whereas 39.2% of the HCAP patients in this study were severely immunosuppressed. Other major pneumonia risks in this population included nursing home residence (28.1%) and hemodialysis (10%).

The US study also differed microbiologically from the Spanish investigation. *S. pneumoniae* accounted for 40.9% of CAP cases but only 10.4% of HCAP patients. *S. aureus* was the single most common pathogen in HCAP patients (43.9% vs 25.5%), and *P. aeruginosa* was isolated from 35.5% of HCAP patients versus 6.7% of CAP patients. Gram-negative organisms were isolated from 19.7% of HCAP patients and from 11.6% of CAP patients.

What Is HCAP?

The previous discussion leads to an obvious question: Exactly what is HCAP? The question does not have a straightforward answer. Instead, the answer depends on issues such as the type of hospital, local definitions of HCAP, and community-defined risk factors for HCAP (**Table 2**). For example, a community hospital that receives few transfers, has no more than a modest oncology program, admits a substantial number of ambulatory nursing home patients, and has no programs in stem-cell or solid-organ transplantation will have a pneumonia population that resembles CAP. Hospitals characterized by the opposite features will probably have far more HCAP patients.

Does the designation of HCAP versus CAP, HAP, or VAP have any real clinical importance? Treatment guidelines usually divide patients into two categories related to the presence or absence of MDR pathogens. Patients who have a late onset of symptoms or risk factors for MDR pathogens receive broad-spectrum antibiotic therapy that provides coverage for MDR pathogens (**Table 3**). Patients who do not meet MDR criteria receive limited-spectrum antibiotic therapy (**Table 4**). The categorical designation (eg, HCAP versus CAP) does not have a great influence on the basic approach to therapy.

Table 2. What Is Real HCAP?

- Dependent on hospital
- Dependent on definition
- Dependent on risk factors for HCAP
- Major issue is culture negative cases
- Overestimation of aspiration

HCAP = hospital-acquired pneumonia.
Source: Richard G. Wunderink, MD, FCCP

What is clear is that giving pneumonia patients inappropriate initial empiric antibiotic therapy can have major consequences. Several studies have shown that the mortality risk associated with VAP increases substantially when a patient is started on inappropriate therapy. For example, Celis and colleagues[5] reported a 92% mortality in patients who were given inappropriate initial therapy for VAP. Similarly, Luna and colleagues[6] found that inappropriate initial treatment was associated with a mortality of 82%. Pneumonia patients frequently receive inappropriate initial antimicrobial therapy. Various studies have demonstrated rates of inappropriate therapy ranging from about 20% to more than 70%.

As a corollary, delayed initiation of appropriate antibiotic therapy also increases the mortality risk in patients with VAP. One prospective observational study examined the impact of delaying initial appropriate antibiotic therapy by

more than 24 hours.[7] Of 107 patients included in the study, 33 (30.8%) had delays in therapy of 24 hours or more after meeting diagnostic criteria for VAP. The most common reason for delayed therapy was a delay in writing orders for antibiotic therapy (25 of 33, 75.8%). The average duration of delay was 28.6 hours compared with 12.5 hours for patients whose appropriate therapy was not delayed. Patients who started appropriate treatment within 24 hours of presentation had a 12% mortality. In contrast, delaying initial appropriate therapy for 24 hours or longer more than doubled the mortality risk (28%).

Summary

HCAP is a helpful concept for categorizing, evaluating, and managing pneumonia patients. However, the definitions currently in use should be revisited and refined to make HCAP a more definitive, accurate, and clinically useful designation. Current clinical guidelines have applied HCAP too broadly, making it the predominant pneumonia category, when evidence to support this is lacking. The meaning of HCAP and its influence on clinical management will likely be a driving force behind eventual revision and updating of guidelines for CAP and VAP. Much-needed information about HCAP is starting to emerge to help distinguish the condition more clearly from other pneumonia syndromes. Until recently, HCAP has applied primarily to hospitalized patients. Whether the criteria for the HCAP designation are appropriate for nursing home patients and those discharged from emergency departments remains undetermined. The key issue that should not be overlooked in the discussion of pneumonia categories is the increasing problem posed by drug-resistant organisms. Resistance continues to increase regardless of what category is applied to a pneumonia syndrome. ■

Table 3. Empiric Treatment—MDR Risk

Potential Pathogens	Recommended Therapy
• *P. aeruginosa*	• Cefipime, ceftazidime
• *A. baumanii*	• Imipenem,meropenem
• Methicillin-resistant *S. aureus*	• Piperacillin/tazobactam
• Antibiotic-resistant (ESBL containing) Gram negative enterics	Plus
– *Klebsiella pneumoniae*	• Aminoglycoside
– *Enterobacter sp.*	• Ciprofloxacin, levofloxacin
	Plus
	• Linezolid
	• Vancomycin
• *Legionella pneumophila*	• (macrolide, quinolone)

MDR = multidrug-resistant. **Source:** American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Available at: http://www.thoracic.org/sections/publications/statements/pages/mtpi/guide1-29.html. Accessed March 24, 2008. Reprinted with permission.

Table 4. Empiric Treatment—No MDR Risk

Potential Pathogens	Recommended Therapy
• *S. pneumoniae*	• Ceftriaxone
• *H. influenzae*	• Quinolone (moxifloxacin, ciprofloxacin, levofloxacin)
• Methicillin-sensitive *S. aureus*	• Ampicillin/sulbactam
• Antibiotic-sensitive Gram negative enterics	• Ertapenem
– *E. coli*	
– *Klebsiella pneumoniae*	
– *Enterobacter sp.*	
– *Proteus sp.*	
– *Serratia marcesans*	

Source: American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. Available at: http://www.thoracic.org/sections/publications/statements/pages/mtpi/guide1-29.html. Accessed March 24, 2008. Reprinted with permission.

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Guideline Recommendations for Diagnosis of Pneumonia

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Introduction

Recognition of clinical and microbiologic features of pneumonia syndromes has led to development of clinically useful categories and definitions, such as hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP). Diagnostic testing of patients with suspected pneumonia plays a role in categorization of pneumonia syndromes, but the two principal purposes of diagnostic testing are to (1) determine whether a patient has pneumonia; and (2) determine the etiologic pathogen of the illness.[1] Timely diagnosis and determination of the pathogenic culprit are essential to rapid progression to the next step in clinical management: early, aggressive antibiotic therapy with broad-spectrum coverage. Increasingly, initiation of appropriate therapy without delay has emerged as the most prominent factor in eradicating the infectious organism, resolving symptoms, avoiding prolonged hospitalization, and reducing morbidity and mortality associated with pneumonia. Less consensus surrounds the equally important issue of when to stop antibiotic therapy.

Table 1. Diagnostic Testing

Diagnosis suspected if:

- New or progressive radiographic infiltrate
- Clinical findings suggest infection
  - New onset of fever
  - Purulent sputum
  - Leukocytosis
  - Decline in oxygenation

Source: American Thoracic Society[1]. Reprinted with permission.

Approach to Diagnosis

The American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines for management of HAP, VAP, and HCAP state that pneumonia should be suspected if a patient has new, persistent, or progressive infiltrates on x-ray. Clinical findings suggestive of infection include new onset of fever, purulent sputum, leukocytosis, and a decline in oxygenation (**Table 1**).[1] In one study of diagnostic criteria, radiographic evidence of new or persistent pulmonary infiltrates plus the presence of two of three clinical findings (fever or hypothermia, leukocytosis or leukopenia, and purulent endotracheal aspirate) proved its accuracy for diagnosing VAP.[2] That combination constitutes a fairly low diagnostic threshold but nonetheless represents an accurate approach for deciding to initiate empiric antibiotic therapy.

Enumerating the goals of diagnostic strategies, the ATS/IDSA guidelines state that the approach to diagnosis should:[1]

- Identify patients who have pulmonary infection
- Ensure collection of appropriate cultures
- Promote use of early, effective antibiotic therapy
- Identify patients who have extrapulmonary infection.

The guidelines discourage initiation of antibiotic treatment for simple colonization. Additionally, clinicians should remain mindful of the fact that routine monitoring of tracheal aspirate cultures can create misleading impressions. Moreover, the sensitivity of positive blood cultures is less than 25%. Vigilance should be maintained for organisms originated in extrapulmonary sources, even in patients with VAP. Among intubated patients, the lower respiratory tract should be sampled for culture whenever pneumonia is suspected.[1]

A comprehensive medical history and physical examination help define the severity of HAP. The chest radiograph also is helpful in defining the severity of pneumonia and its complications. Preferred views are posteroanterior and lateral if a patient is not intubated.[1]

Purulent tracheobronchitis may mimic HAP and VAP and might require antibiotic therapy. However, randomized trials are needed to determine the value of antibiotics in such patients.[1]

Clinical indications of tracheobronchitis include a fever without any other obvious cause, new or increased sputum production, and a positive tracheal aspirate culture without x-ray evidence of new pneumonia. In a study of 2,128 mechanically ventilated patients, 10.6% were diagnosed with nosocomial tracheobronchitis (NTB). The condition was diagnosed more often in surgical versus medical patients (15.3% vs 9.9%), and the most commonly isolated pathogen was *Pseudomonas aeruginosa* (~30%). Medical patients with NTB had a higher mortality (36% vs 32.1%), longer stay in the ICU (33.4 days vs 12.8 days), and a longer duration of mechanical ventilation (20 days vs 8.8 days) compared with patients who did not have NTB.[3]

Tracheal colonization is common in intubated patients and does not indicate infection in the absence of clinical findings. Additionally, tracheal colonization does not require diagnostic evaluation or therapy.[1]

For all patients with VAP, the ATS/IDSA guidelines recommend collection of blood cultures. A positive culture can indicate pneumonia or extrapulmonary infection. Thoracentesis should be performed to rule out empyema or parapneumonic effusion if a patient has a large pleural effusion or if the effusion appears toxic.[1]

Samples of lower respiratory tract secretions should be examined before changing antibiotic therapy for patients with suspected HAP or VAP. In the absence

of any clinical suspicion of HAP or VAP and nosocomial tracheobronchitis, respiratory tract cultures should not be obtained.[1]

Professional opinions vary about the best approach to sampling the lower respiratory tract. A clinical approach probably prevails throughout much of the United States, but a more aggressive bacteriologic approach tends to predominate. Investigators in a large Canadian study examined the issue by comparing two general strategies for lower respiratory tract sampling.[4]

The study involved 740 patients enrolled in 28 ICUs in Canada and the United States. Patients who had suspected VAP after 4 days in an ICU were randomized to undergo bronchoalveolar lavage (BAL) and quantitative culture of BAL fluid or endotracheal sampling and nonquantitative culture of aspirate. Patients with known colonization or infection with *Pseudomonas species* or methicillin-resistant *Staphylococcus aureus* were excluded.

Empiric antibiotic therapy was initiated in all cases until culture results were available. At that point, a protocol of targeted therapy was used to discontinue or reduce the dose or number of antibiotics, or to resume antibiotic treatment of a pre-enrollment condition if the culture was negative. The primary outcome was 28-day mortality.

The results showed no difference between the two diagnostic approaches for the primary endpoint, as the 28-day mortality was 18% to 19% in both groups. The BAL and endotracheal-aspiration groups had similar rates of targeted therapy, days alive without antibiotics, maximum organ dysfunction score, and length of stay in the ICU and hospital.

Clinical Pulmonary Infection Score (CPIS)

The CPIS offers a reasonably simplified approach to evaluation of patients with suspected pneumonia. The CPIS combines four types of information from which a diagnostic score can be derived for an individual patient (**Table 2**).[5] The score is determined by the cumulative score resulting from the combination of clinical, radiographic, physiologic, and microbiologic data. A score of 6 or higher has good correlation with the presence of pneumonia, as defined by quantitative cultures of bronchoscopic and nonbronchoscopic BAL specimens.[1]

The CPIS has been found to have a sensitivity of 77% and a specificity of 42% compared with a reference standard of histology plus immediate postmortem quantitative lung cultures.[1] The addition of gram stain of deep respiratory tract culture to the algorithm improves the sensitivity and specificity. When using a clinical strategy based on the CPIS, the decision to treat on the basis of serial clinical evaluations should be assessed again by day 3 or sooner.[1] Patients who have a CPIS score ≤6 for 3 days provides an objective criterion for selecting patients at low risk for discontinuation of empiric treatment of HAP. However, this approach still requires validation in patients with more severe forms of VAP.[1]

Routine use of the CPIS in clinical practice can help guide the decision to discontinue use of antibiotics. Reliance on individual patient scores can lead to earlier discontinuation of antibiotics, a point that cannot be overemphasized. Starting appropriate antibiotic therapy as quickly as possible leads to better pneumonia outcomes, but knowing when to stop antibiotics is equally important and often more difficult to determine.

A negative tracheal aspirate without a recent change in antibiotics has a strong negative predictive value for VAP. That negative finding should lead to a search for alternative explanations for fever.[1]

Other Strategies—Procalcitonin

Procalcitonin has been evaluated extensively as a means of differentiating sepsis from non-infectious causes of systemic inflammatory response syndrome (SIRS). However, a recent systematic review of 18 published studies demonstrated a

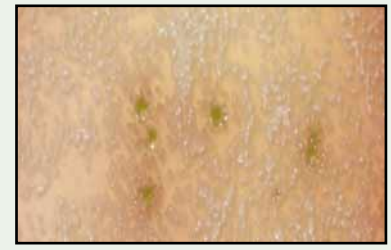
Table 2. Clinical Pulmonary Infection Score

Component	Value	Points
Temperature °C	≥36.5 and ≤38.4	0
	≥38.5 and ≤38.9	1
	≥39.0 and ≤36.0	2
Blood leukocytes per mm^3	>4000 and <11,000	0
	<4000 and >11,000	1
Tracheal secretions	Few	0
	Moderate	1
	Large	2
	Purulent	+1
Oxygenation	>240 or presence of ARDS	0
PaO_2/FiO_2 mm Hg	≤240 and absence of ARDS	2
Chest X-ray	No infiltrates	0
	Patchy or diffuse infiltrates	1
	Localized infiltrate	2

Source: Luna CM et al[5]. Reprinted with permission.

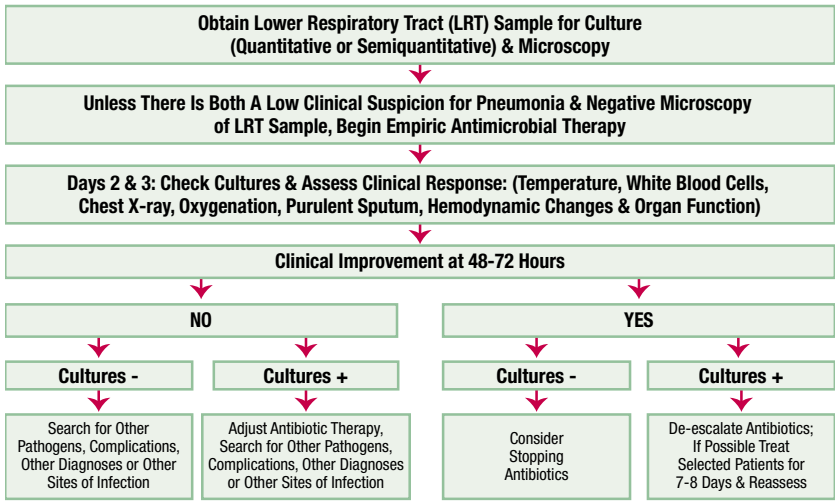
Table 3. Sputum Culture of *P. aeruginosa*

- Required for all patients before initiation or change in therapy
- Sampling techniques:
  - Tracheal aspirate
  - Broncheoalveolar lavage (BAL)
  - Protected specimen brush (PSB)
  - Decline in oxygenation



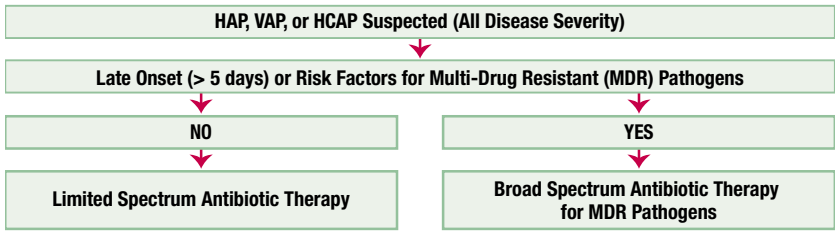
Source: Stanley B. Fiel, MD, FCCP

Table 4. HAP, VAP, or HCAP Suspected



HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; HCAP = health care-associated pneumonia.
Source: American Thoracic Society[1]. Reprinted with permission.

Table 5. Empiric Antibiotic Therapy for HAP



HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; HCAP = health care-associated pneumonia.
Source: American Thoracic Society[1]. Reprinted with permission.

mean sensitivity and specificity of 71%. The authors of the review concluded that procalcitonin does not reliably differentiate sepsis from non-infectious causes of SIRS and that the results of the review do not support widespread use of procalcitonin testing in critical care settings.[6]

Bacteriologic Strategies

The ATS/IDSA guidelines recommend qualitative cultures on endotracheal aspirates or samples collected bronchoscopically or nonbronchoscopically. Each technique has its own diagnostic threshold and methodologic limitations. The choice of technique depends on local expertise, experience, availability, and cost.[1] Bacteriologic studies are required before initiating or changing therapy for any patient. Acceptable sampling techniques include tracheal aspirate, BAL, and protected specimen brush (PSB) (**Table 3 on page 11**). Of note, studies of the impact of diagnostic strategies on antibiotic use and outcomes in patients with suspected VAP have failed to demonstrate a difference in mortality with invasive techniques (BAL or PSB) compared with quantitative or semiquantitative endotracheal culture techniques.[1]

One reasonably sized study stands out as a possible exception to the lack of difference between invasive and clinical evaluation of patients. In that study, an invasive strategy was associated with significantly lower 14-day mortality, significantly lower sepsis-related organ failure assessment scores on day 3 and day 7, significantly less antibiotic use at day 28, and significantly more antibiotic-free days.[7]

Algorithm for Clinical Management

The ATS/IDSA guidelines include a diagnostic algorithm that essentially summarizes the preceding discussion in a graphic format (**Table 4**). The algorithm is applicable to the evaluation of patients with suspected HAP, VAP, or HCAP.

The guidelines also include an algorithm for initiation of empiric antibiotic therapy for HAP, VAP, and HCAP, regardless of disease severity (**Table 5**). The algorithm can help clinicians decide whether limited-spectrum or broad-spectrum antibiotic therapy is the more appropriate approach to empiric therapy, and it can also help clinicians decide when to stop antibiotics.

Summary

Several diagnostic strategies can be employed in the evaluation of patients with suspected HAP, VAP, or HCAP. Regardless of the strategy chosen, the goals remain the same: identifying patients with pulmonary infection, appropriate culture collection, promotion of early and effective antibiotic therapy, and identification of patients with extrapulmonary infection. Invasive and noninvasive diagnostic strategies appear to offer comparable accuracy, and use of either diagnostic approach should lead to appropriate treatment and no difference in mortality. The ATS/IDSA guidelines provide a straightforward diagnostic algorithm that can help keep the chosen diagnostic strategy focused on the principal goals. ■

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Treatment Strategies for Community-Acquired Pneumonia

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Introduction

Community-acquired pneumonia (CAP) is the sixth leading cause of death in the United States. Each year, between 2 million and 3 million new cases are diagnosed, leading to 500,000 hospital admission and 45,000 deaths. Mortality risk increases with the need for and intensity of hospital care. Outpatients with CAP have a mortality risk of <1%. That rises to 10% to 14% in patients who are admitted to general hospital units. CAP patients admitted to an intensive care unit (ICU) have a mortality risk of 30% to 40%.[1] Still, the mortality of pneumonia has decreased dramatically over the past 100+ years. Pneumonia-associated mortality stood at about 180 of 100,000 persons in 1900, declining to less than 40 of 100,000 by the 1990s.[2] That good news is tempered by the recognition that pneumonia-associated mortality has changed little over the past 50 years. To redirect the long-standing mortality plateau into a new decline requires continued improvement in diagnosis and treatment of CAP. Currently, the soundest approach to management of CAP is reflected by clinical guidelines. Guideline-directed therapy clearly decreases mortality. Future decreases in mortality will require strategies to modulate the immune system.

Diagnostic and Prognostic Issues

Causative pathogens for CAP have no distinctive clinical features that would aid in diagnosis.[3] As a consequence, an ongoing need exists for improved diagnostic technology.

Streptococcus pneumoniae continues to play a dominant role in the bacteriology of CAP. Data from 26 prospective studies involving 5,961 patients in 10 countries showed that *S. pneumoniae* was the pathogen most often associated with CAP, accounting for almost 30% of the cases (**Figure 1**).

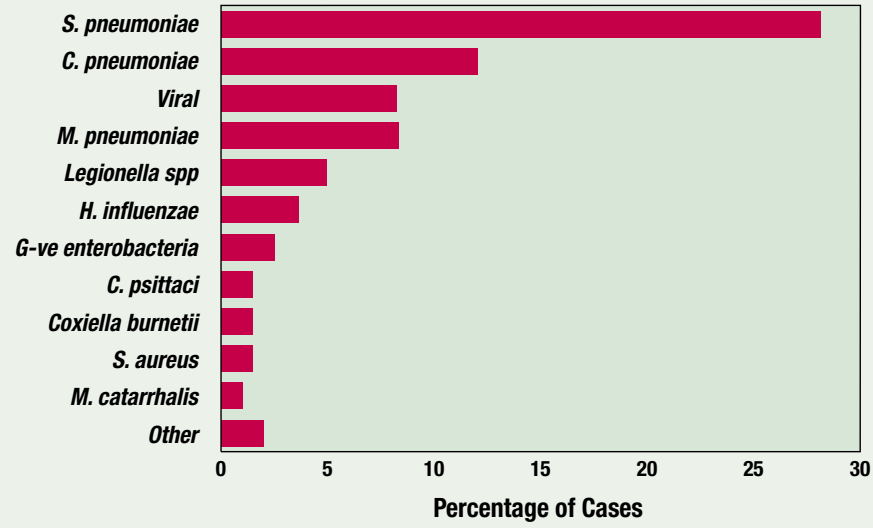
A meta-analysis of 127 study cohorts comprising 33,148 patients showed that the mortality risk associated with *S. pneumoniae* pneumonia increased from 6.4% among outpatients to 8.3% in hospitalized patients and to 18.6% in patients with *S. pneumoniae* bacteremia. Mortality then doubled to 37% in patients requiring ICU care.[4]

Several schema have been developed to risk-stratify patients, particularly strategies to identify patients with a high mortality risk. One of simplest strategies is the British CURB-65 rule, a modified version of the British Thoracic Society approach to risk stratification.[5] The CURB-65 is essentially a scale that allots one point to each of five risk factors for mortality in CAP: confusion, urea >7 mmol/L, respiratory rate ≥30/min, blood pressure (<90 mmHg systolic or ≤ 60 mmHg diastolic), and age ≥65.

By the CURB-65 rule, a score of 0 or 1 is associated with a mortality of <2%, representing patients who might be suitable for home management. A CURB-65 score of 2 is associated with an intermediate mortality risk of 9%, representing patients who warrant consideration for hospitalization. A CURB-65 score of 3 or greater indicates a mortality risk of 19%, representing patients with severe CAP that requires hospital management and possible ICU admission.

In North America, the PORT prediction rule was developed to identify low-risk patients with CAP, especially those capable of home management.[6] The PORT system assigns points for demographic variables,

Figure 1. Bacteriology of Hospitalized CAP



CAP = community-acquired pneumonia. **Source:** Woodhead M. Community-acquired pneumonia guidelines—an international comparison: A view from Europe. *Chest.* 1998;113:183S-187S. Reprinted with permission.

Table 1. Modified ATS/IDSA Criteria of Severity

Any 3 of 9 baseline (minor) clinical parameters:

- Respiratory rate (f) ≥ 30 breaths/min
- Confusion/disorientation
- Uremia (BUN level ≥ 20 mg/dL)
- Leukopenia (white blood cell count < 4000 cells/mm^3)
- Systolic blood pressure < 90 mm Hg
- Multilobar infiltrates
- PaO_2/FiO_2 ratio ≤ 250
- Thrombocytopenia (platelet count < 100,000 cells/mm^3)
- Hypothermia (core temperature < 36°C)
- Hypotension requiring aggressive fluid resuscitation

Adapted from Mandell LA et al[7]

comorbid conditions, physical observations, and laboratory and radiographic findings. A patient who presents without altered mental status and has a pulse rate <125 bpm, respiratory rate <30/min, systolic blood pressure >90 mmHg, and a temperature >35°C and <40°C has a class I (lowest) risk designation. Class II comprises patients with a cumulative risk score ≤ 70, increasing to class III for a score of 71 to 90, class IV for 91 to 130 points, and class V for a cumulative risk score >130.

Classes I and II have a mortality risk of <1% and can be potentially managed as outpatients. Class III patients have a mortality risk of 0.9% to 2.8% and may benefit from brief observation in hospital. The mortality increases to 8.5% to 9.3% for class IV, patients who require hospitalization. A cumulative score ≥130 (class V) is associated with a mortality risk of 27.0% to 31.1%, indicative of a patient who may require ICU care.[6]

CAP patients also can be risk-stratified on the basis of need for ICU care. Modified severity criteria in the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) clinical guidelines identify patients requiring mechanical ventilation and those in septic shock as being in need of ICU care.[7] Additionally, patients who have any three of nine so-called minor clinical parameters at baseline should be admitted to an ICU, according to the ATS/IDSA guidelines (**Table 1**). These recommendations should be applied with the caveat that they are recommendations based on consensus opinion; none has supporting Level I scientific evidence.

To summarize the utility of the various predictive schema, the predictive power is good and specificity is consistently high, but sensitivity is variable. The true strength of these rules lies in their negative predictive value, the ability to identify patients who do not have a high mortality risk.

Initial Antibiotic Therapy

A multivariate analysis aimed at identifying independent predictors of pneumonia-related mortality revealed ineffective initial therapy as the best mortality predictor, ahead of bacteremia, shock, and other factors.[8] Ineffective initial therapy increased the odds ratio for mortality almost fivefold among patients admitted to an ICU. Subsequently, multiple studies have confirmed the adverse prognostic impact of initial inadequate therapy.

The timeframe for initiating antibiotic therapy also has emerged as a major consideration with implications for prognosis. Much of the emphasis has evolved from studies suggesting that initiation of antibiotic therapy within 4 hours significantly reduces the risk of dying. One frequently cited study examined the relative impact of initiating therapy within 4 hours or later in 18,000 Medicare patients.[9] The data showed that starting antibiotic therapy within 4 hours (versus later) significantly reduced 30-day and in-hospital mortality, as well as the percentage of patients with a hospital length of stay exceeding 5 days (**Table 2**).

On the surface, the "4-hour rule" appears to be straightforward: A simple process of care can reduce mortality in hospitalized pneumonia patients. However, beneficial actions sometimes are accompanied by unintended consequences, as illustrated by a study published just last year.[10] Following implementation of the 4-hour rule at one Michigan hospital, the proportion of patients receiving antibiotics within 4 hours increased significantly.

However, the percentage of patients with an admission diagnosis of CAP without radiographic abnormalities also increased significantly, as did the number of blood cultures and the per-patient antibiotic use. The percentage of patients with a final diagnosis of CAP decreased significantly as compared to before the 4-hour rule, and implementation of the rule had no effect on the pneumonia severity index, CURB-65 scores, or mortality.

In the simplest terms, the study indicated that many patients received antibiotics when they did not have pneumonia. The results suggest that making an accurate diagnosis supersedes early initiation of therapy as a factor in outcome.

Combination Antibiotic Therapy Versus Monotherapy

For patients with bacteremic pneumococcal pneumonia, does treatment with an antibiotic combination improve outcomes relative to treatment with a single antibiotic? That question has been addressed in several recent studies. In one study, investigators retrospectively evaluated outcomes in 225 patients who received empiric therapy for bacteremic pneumococcal pneumonia.[11] All of the patients had a pneumonia severity index >90. Treatment was classified as single effective therapy, dual effective therapy, or more than dual effective therapy. Patients who received single effective therapy had a mortality approaching 20%, whereas dual effective therapy was associated with a mortality of less than 10%.

Combination therapy for severe CAP was evaluated prospectively in 844 adults with pneumococcal bacteremia.[12] Investigators stratified patients by illness severity, and then examined the type of therapy administered: single-agent versus dual-agent. The two approaches to antibiotic therapy produced similar outcomes in lower-risk patients. However, among the most critically ill patients, dual

antibiotic therapy reduced mortality by almost 60% compared with single-agent therapy (23.4% vs 55.3%, *P*=0.0015).

On the basis of the current understanding of antibiotic therapy for severe CAP, dual therapy, such as a third-generation cephalosporin plus a macrolide or a third-generation cephalosporin plus a fluoroquinolone, would be the most appropriate approach to treatment of critically ill patients.

Antibiotic Resistance in CAP

The impact of antibiotic resistance in CAP involves three classes of agents: beta-lactams, macrolides, and fluoroquinolones. Data are largely lacking to support the view that resistance is a major issue with beta-lactam therapy. At currently recommended doses and with availability and use of third-generation cephalosporins, beta-lactam antibiotics remain effective in most cases. However, if the minimum inhibitor concentration is ≥4 µg/L, problems with resistance may arise.

Despite widespread use, macrolides appear to maintain their bactericidal efficacy. A body of evidence has begun to emerge, suggesting that resistance is an issue when it involves the pneumococcus. Prior macrolide therapy does appear to increase resistance among pneumococci. Moreover, the degree of resistance appears to vary according to the specific macrolide agent used previously.[13]

The fluoroquinolone resistance story has multiple chapters, whose content varies according to the site of infection (community versus nosocomial or nursing home) and history of fluoroquinolone use. Our experience in Toronto indicates almost no resistance in patients with CAP and no history of fluoroquinolone therapy. When CAP patients have been treated previously with a quinolone, resistance increases but varies according to which quinolone agent was previously used. The situation with nosocomial/nursing home pneumonia and no prior quinolone therapy resembles that of CAP and a positive history for quinolone therapy. Resistance occurs most often in patients with hospital- or nursing home-associated pneumonia and prior quinolone exposure. The frequency of resistance varies greatly according to the specific quinolone agent previously received.

Clinical Guidelines for Pneumonia

In addition to the IDSA and ATS, the Canadian Infectious Disease Society and Canadian Thoracic Society have developed clinical guidelines for pneumonia, as has the British Thoracic Society. The various guidelines have recommended a similar approach to clinical management for the past 15 years or so. After diagnosing pneumonia, the clinician must decide whether treatment can occur on an outpatient basis or whether hospitalization is warranted. Hospitalized patients are further segregated according to the need for ICU care. Finally, all but the British guidelines further categorize patients on the basis of their risk for *pseudomonas*.

Using the ATS/IDSA guidelines as an example, decisions about initial antibiotic therapy depend upon pre-pneumonia health status, local rates of antibiotic resistance, and history of antibiotic therapy.[7] Most patients can be started on a macrolide, unless the local community has a high rate (>25%, although this value is entirely arbitrary) of pneumococcal resistance to macrolides. In that case, a patient can start treatment with respiratory fluoroquinolone.

Guidelines for inpatient therapy have undergone little change in recent years. According to the most recent update of the ATS/IDSA guidelines, patients with no prior antibiotic therapy can be started on a respiratory fluoroquinolone or an advanced macrolide plus a beta-lactam.[7] Patients with a recent history of antibiotic exposure can start with an advanced macrolide/beta-lactam combination or single-agent respiratory fluoroquinolone, depending upon the nature of the patients' recent antibiotic history.

Physicians may question whether clinical guidelines make a difference in outcome, and the answer is yes. In one representative study, approximately 1,200 pneumonia patients were evaluated with regard to adherence or nonadherence to clinical guidelines.[14] Patients whose treatment did not follow recommendations had a significantly higher rate of treatment failure (19.7% vs 12.9%, *P*=0.03) and a significantly higher mortality (8.9% vs 5.4%, *P*=0.008).

The Therapeutic Future for Severe CAP

Given clear evidence that pneumonia-associated mortality has remained largely unchanged for the past 50 years, new approaches to treatment are warranted. One therapeutic candidate that has been evaluated is recombinant human-activated protein C (drotrecogin-alpha).[15] In a randomized prospective, double-blind trial involving 1,690 patients with sepsis, treatment with drotrecogin-alpha was associated with a lower mortality compared with placebo. Among the patients with pneumonia as the cause for sepsis, a relative decreased risk in mortality of

Table 2. Effect of Early Administration of Antibiotics on Outcomes

Variable	All patients	Antibiotics within 4 hours	Antibiotics after 4 hours	Adjusted Odds Ratio	*P* Value
30-day mortality	12.0	11.6	12.7	0.85	.005
In-hospital mortality	7.0	6.8	7.4	0.85	.03
% of patients with length of stay >5 days	43.3	42.1	45.1	0.90	.003
30-day readmission rate	13.4	13.1	13.9	0.95	.34

Adapted from Houck PM et al[9]

28% was observed at 28 days. Survival benefit was most pronounced in severe CAP patients with *S. pneumoniae* infection and in severe CAP patients at high risk of death.

Hydrocortisone infusion as an adjunct to antibiotic therapy may also have a role. In a study involving 46 patients with severe CAP, hydrocortisone was administered as a bolus followed by continuous infusion for 7 days.[16] By day 8, patients treated with hydrocortisone had significant improvement in levels of C-reactive protein and significant improvement in oxygenation. Survival to hospital discharge was 70% in patients who received antibiotic therapy alone compared with 100% in patients who received adjunctive hydrocortisone infusion. Patients in the hydrocortisone group also had a significant reduction in the duration of mechanical ventilation compared with the placebo group. These observations need to be confirmed in larger trials before these interventions can be accepted as routine management.

Summary

S. pneumoniae remains the most important pathogen in severe CAP. Stratification of patients by illness severity aids selection of appropriate empiric therapy. Rates of bacterial resistance are increasing, and local resistance rates should be factored into the decision-making surrounding initial therapy. Guideline-directed therapy decreases the risk of treatment failure and mortality. Further decreases in pneumonia-associated mortality require therapeutic strategies that include modulation of the immune system. ■

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