Community-Acquired Pneumonia: Current Principles of Evaluation and Therapy

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DR. LIANG: Introduction

Community-acquired pneumonia (CAP) is a common disease in the United States—3.3 to 4 million cases occur annually.[1,2] As such, CAP exacts a tremendous social cost: with an incidence of 12 cases per 1000 population per year, CAP accounts for an annual cost of patient care and lost wages of more than $20 billion,[3] 64 million days of restricted activity, 39 million days of bed confinement, and 10 million days of work loss.[4] In addition, CAP is the sixth leading cause of death in the United States—77,000 patients with the disease die annually.[5] The elderly are particularly affected, and this patient population accounts for approximately 90% of all deaths associated with CAP.[6,7]

Further, CAP is estimated to account for at least 10 million visits to physicians annually.[8,9] Up to 20% of patients with CAP require inpatient hospitalization, representing 600,000 to 1 million hospital admissions.[10] This figure is significant because patients with CAP who require care in the intensive care unit have a mortality rate of up to 50%.[11–13] Also, inpatients who are older than age 85 years and who have comorbid disease, impaired motor response, vital sign abnormalities, and high creatinine levels are at higher risk of mortality.[14]

Etiologic pathogen. As indicated in this case study, the etiologic pathogen generally considered responsible for most cases of CAP is *Streptococcus pneumoniae*.[3,15] Other less common pathogens include *Haemophilus influenzae* and *Chlamydia pneumoniae*, as well as oral anaerobes, *Staphylococcus aureus*, *Legionella pneumophila*, *Moraxella catarrhalis*, and Hantavirus.[16] However, in 30% to 60% of CAP patients, no identifiable pathogen is identified.[17] Thus, diagnosis and treatment is often based primarily upon clinical factors, none of which appears definitive in identifying the causal agent.[18] Initiation of prompt and appropriate treatment is important, however, because early treatment of CAP has been shown to be associated with improved outcomes.[19,20] Hospitalists have also been reported to obtain better outcomes as well as reduced costs in treating CAP patients.[21]

Guidelines for evaluation and treatment. Because of the profound reliance upon clinical factors, competing guidelines have been introduced for the evaluation and treatment of patients with possible CAP. As noted in this case study, the American Thoracic Society (ATS) (New York, NY)[22] and the Infectious Diseases Society of America (IDSA) (Alexandria, VA)[23] have promulgated practice parameters for CAP diagnosis and treatment. However, it should be noted that CAP guidelines have also been promulgated by other groups, such as the Canadian Infectious Disease Society (Ottawa, Ontario, Canada),[24] the British Thoracic Society (London, England),[25] a combined group of Italian specialist societies,[26] the South African Pulmonology Society (Vlaeberg, South Africa),[27] and a group from the Netherlands.[28]

American Thoracic Society guidelines. A comparison of the ATS and IDSA guidelines illustrates the differing philosophies of diagnosis and treatment in an area where no definitive method is established.[29,30] As indicated in this case study, the ATS guidelines focus upon empirical treatment of CAP because of the difficulties associated with identifying the specific etiologic agent. This approach is supported by several factors, including 1) the clinical presentation of patients with CAP who are infected with the same etiologic agent varies, 2) chest films may not show reliable etiologic clues,[31] 3) distinguishing bronchitis from CAP is difficult, and 4) the failure rate is high for attempting to identify the pathogen through culture. This latter concern is particularly important; even with the use of sputum culture, serologic tests,

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and bronchoscopy, a pathogen is identified in only approximately 50% of cases.[32] Further, CAP is diagnosed correctly by sputum gram stain alone in fewer than one third of patients,[33] and the error rate in interpretation has been reported to be greater than 30%, even for infectious disease and pulmonary specialists.[34]

Infectious Diseases Society of America guidelines. IDSA guidelines for CAP, which are more recent than the ATS guidelines, attempt to integrate etiology and presentation of patients with CAP and provide algorithms that promote continued efforts to identify the CAP pathogen. These guidelines are designed to make the choice of antibiotic treatment more rational in order to maximize the possibility of cure while minimizing the chance of pathogen resistance. Radiologic studies are an integral part of the IDSA guidelines, as well as Gram stain, other tests, and a determination of the presence of risk factors that indicate whether the patient should be hospitalized. Assessment of the risk of mortality is also an important part of the guidelines.

Comparison of guidelines. Fundamentally, ATS and IDSA guidelines differ on the basis of the role of CAP etiology. ATS guidelines approach the CAP patient with the perspective that etiologic tests such as sputum Gram stain and culture have only a low yield, which obviates the need for such tests, whereas the IDSA guidelines perceive these tests as assisting in guiding treatment for each patient as well as providing important information about the community's CAP patterns, including *S. pneumoniae*-resistant strains. IDSA provides current information on emerging CAP strains on its website at *www.idsociety.org* for both adult and pediatric patients.[35] In addition, efforts to integrate IDSA and ATS guidelines are in progress in order to provide a single set of recommendations for the treatment of CAP.[16] As well, modifications to the ATS guidelines for CAP have been proposed to reflect additional information regarding the antimicrobial resistance patterns of CAP agents (including *S. pneumoniae*),[36,37] refined risk factors indicating the need for hospitalization,[38] and the introduction of new antibiotic agents.[39] It should be noted that the incidence of penicillin-resistant *S. pneumoniae* varies significantly, and, although there is no doubt of the increased incidence of such strains,[40] variation between countries, between communities, and even within communities is apparent from the results of studies from around the world.[41–46]

Summary. Overall, CAP is a very common and highly important disease. Current diagnosis and treatment modalities focus on clinical assessments even while attempting to identify the etiologic agent. Continued efforts to integrate guidelines through evidence-based practice should assist in making antibiotic treatment rational for the CAP patient. However, physicians should avail themselves of information through the Internet regarding emerging strains and monitor the available literature for updates of practice guidelines that reflect the most current approaches to treating the CAP patient.

CASE ONE PRESENTATION

Initial Presentation

A 51-year-old college professor presents to her primary care physician with a chief complaint of persistent cough and fever.

History

The patient's cough began 3 weeks before presentation, at the same time her 16-year-old daughter was recovering from a "chest cold." Her daughter's chest cold fully resolved in 10 days without antibiotics. As the daughter was improving, the patient herself began to note a nonproductive cough, a temperature of 100.5°F, and hoarseness. The patient assumed that she had a viral infection, so she took a nonprescription cough suppressant and ibuprofen. She continued to cough and felt generally unwell. After 2 weeks of these symptoms, she began taking cefaclor from a several-months-old prescription for another family member; this drug did not relieve her symptoms.

In the physician's office, the patient complains of a paroxysmal cough that it is now keeping her awake at night. She denies sputum production, wheezing, or hemoptysis. She says that her temperature has never exceeded 101.2°F during this course. She admits chills, but not sweats. She has also noted more shortness of breath than usual when taking her customary 1-mile walk. Vocal hoarseness has progressed to the point of hindering her teaching. She recalls that several of her students have been stricken with a similar respiratory illness, and that a few have mentioned taking antibiotics. She has never been exposed to tuberculosis, and she had a negative tuberculin skin test approximately 5 years ago. She has never smoked tobacco. She drinks alcohol only at social occasions and never has more than two drinks. She lives at home with her husband and teenage children, all of whom are well except for her daughter's recent illness. The patient has not recently traveled; she enjoys gardening and has no pets. The patient has not had the pneumococcal vaccine but receives the influenza vaccine annually, and she received vaccination 1 month before presentation. She takes no medications except for those previously mentioned.

Physical Examination

Physical examination reveals a well-nourished woman

who appears acutely ill and is hoarse. She is alert and oriented. During the evaluation, she suffers paroxysms of nonproductive cough, making it occasionally difficult for her to complete sentences. Her temperature is 101.1°F; blood pressure, 116/78 mm Hg; pulse, 132 bpm; and respiratory rate, 30 breaths/minute.

No skin rash and no sinus tenderness are evident. The conjunctivae are clear, and the oropharynx has no lesions, erythema, or exudate. The neck is supple, and no lymphadenopathy is palpable. No cardiac murmurs are noted.

Lung examination reveals a few crackles in the right midlung zone but no wheezes or rhonchi. There is no dullness to chest percussion, no egophany, and no vocal fremitus. The abdomen is soft and nontender, with active bowel sounds and no hepatosplenomegaly or masses. The genitourinary examination is unremarkable. There is no joint swelling or tenderness. The neurologic examination reveals no focal deficits.

QUESTION

- **What is the recommended approach to the initial evaluation of suspected pneumonia?**

DISCUSSION

General Principles

Cost-containment efforts have compelled physicians to consider the potential contribution of each proposed diagnostic study to the treatment plan of a patient with CAP. Also, depending on collection technique and operator skill, microbiologic and serologic studies can lack sensitivity and specificity. These concerns form the basis for the minimalist diagnostic approach offered by the ATS.[17] In the ATS guidelines, the use of expectorated sputum studies and serologic testing are downplayed, and more aggressive testing is reserved for epidemiologic interest or for patients who are not responding to initial therapy.

Although the economic mandate to reduce testing certainly tempts a physician to offer empiric antibiotic therapy on the basis of history and physical examination findings obtained in the office setting, IDSA contends that this approach should be resisted for several important reasons.[23] First, antibiotics are not entirely benign medications and can have severe adverse effects (eg, hypersensitivity, antibiotic-associated colitis) or can interact with other medications (eg, causing prolongation of the QT interval). More importantly, use of antibiotics for inappropriate indications or with an inappropriately broad spectrum of activity contributes to the development of antibiotic-resistant microbes, limiting treatment choices for the patient and the general population. Finally, therapy based on pure empiricism eliminates the epidemiologic tracking of organisms of public health significance, such as Legionella, drug-resistant pneumococci, Hantavirus, and influenza virus. Therefore, the first step in pneumonia management, according to IDSA guidelines, is confirmation of the diagnosis and of an etiologic agent.

Diagnostic Testing

The correct etiologic diagnosis can be established by a number of modalities (**Table 1**). The chest radiograph remains the cornerstone in the initial diagnostic evaluation of CAP and is recommended by IDSA in both the inpatient and outpatient settings.[23] Another commonly used tool, although controversial, is the sputum Gram stain and culture.

Sputum Gram stain and culture. The sputum Gram stain is thought to represent lower respiratory secretions when more than 25 leukocytes and less than 10 epithelial cells are seen in a low-powered microscopic field.[47] When such a Gram stain also shows a predominant organism, there is a greater than 90% chance of selecting an appropriate empiric antibiotic therapy.[33] This "low-tech," inexpensive, rapid method is recommended for all CAP patients by the IDSA. However, this recommendation is disputed by the ATS on the basis of variation of test accuracy. The accuracy of the sputum Gram stain is highly dependent on proper collection of a deep-cough specimen before the initiation of antimicrobial therapy and prompt delivery to the microbiology laboratory.[23]

Sputum may be difficult to obtain from debilitated patients because of a weak cough, obtundation, or dehydration. In these situations, inhaled nebulized saline may help mobilize secretions for collection. Nasotracheal suctioning can sample the lower respiratory tract directly, but this approach risks oropharyngeal contamination. The clinical history and chest radiograph may dictate the use of other stains, such as the acid-fast stain for mycobacteria, the modified acid-fast stain for *Nocardia*, or the toluidine blue and Gomori methenamine silver stains for *Pneumocystis carinii*. Direct fluorescent antibody staining of sputum, bronchoalveolar lavage fluid, or pleural fluid may identify *Legionella* species as a pathogen.

The sputum culture remains a controversial tool because of poor collection technique and delayed delivery to the laboratory, antibiotic use prior to collection, and oral contamination;[48] the sensitivity of sputum culture is estimated at 50%.[23] Nevertheless, sputum culture is still recommended as a pretreatment specimen with rapid transport to the laboratory to help tailor therapy. The sputum culture may prove particularly helpful when

potentially resistant bacterial pathogens are identified. When indicated by history or chest radiograph, expectorated morning sputum is the preferred specimen for mycobacterial stain and culture. Preantibiotic cultures of blood and pleural fluid, if present, can also yield an etiologic agent and should be obtained.

Serologic testing. Serologic testing for pathogens such as *Legionella* species, *Mycoplasma* species, and *C. pneumoniae* is typically performed only in the setting of a high clinical suspicion, and delays of several days for results frequently render these tests more valuable to the epidemiologist than to the clinician. Serologic testing should be performed in the setting of a typical clinical syndrome or in the setting of a deteriorating patient with no microbiologic diagnosis, and should include sera drawn in both the acute and convalescent phases for comparison. A positive immunoglobulin M (IgM) titer or a fourfold increase in the immunoglobulin G (IgG) titer is suggestive of recent infection with these organisms.

Urinary assay. A sensitive urinary assay has been developed for the detection of *L. pneumophila* antigen.[49] The test is highly specific, but because the urinary antigen persists for up to 1 year after infection, urinary assay cannot differentiate between past and current infections. A urinary assay for the detection of *Histoplasma capsulatum* antigen is also available.[50] This highly specific assay can be a useful diagnostic adjunct to traditional fungal complement fixation and immunodiffusion test batteries.

FINDINGS ON OUTPATIENT TESTING

A chest radiograph shows a patchy infiltrate partially obscuring the right heart border. The cardiac silhouette is of normal size, and no pleural effusions are noted. Complete blood count (CBC) shows a mild leukocytosis and leukocyte count of 14,000/mm^3. Basic blood chemistries are normal, and pulse oximetry is 87% without supplemental oxygen. Based on the patient's outpatient test results and the fact that she has tachypnea and hypoxemia, her physician decides to hospitalize her for initial treatment.

QUESTION

- **Was the decision to hospitalize this patient appropriate?**

DISCUSSION

Choosing the Site of Care: The Patient Outcomes and Research Team System and Risk Stratification

The complex interplay between host and microbe makes the decision regarding site of care for pneumonia

Table 1. Diagnostic Testing for Community-Acquired Pneumonia in Outpatient and Inpatient Settings

Treatment Setting	Test
Outpatients and inpatients	Chest radiograph
	Sputum Gram stain
	Sputum bacterial culture (optional for outpatients)
All inpatients	Complete blood count with differential
	Complete metabolic profile
	Arterial blood gases
	Blood cultures (two cultures before antibiotics)
Inpatients with appropriate clinical setting	HIV serology
	Legionella serology/urinary antigen/ sputum direct fluorescent antibody
	Mycoplasma serology
	Chlamydia serology
	Fungal serology, *Histoplasma* urinary antigen
	Respiratory specimen for mycobacterial, fungal, *Pneumocystis* stains/cultures
	Thoracentesis
	Nasopharyngeal swab for viral direct fluorescent antibodies
Deteriorating patient without microbiologic diagnosis	Bronchoscopy with bronchoalveolar lavage, protected catheter, transbronchial biopsy
	Thoracoscopic or open-lung biopsy
	Transthoracic aspirate*
	Legionella testing†
	Mycoplasma serology†
	Chlamydia serology†
	Fungal serology, *Histoplasma* urinary antigen
	Evaluations for heart failure, pulmonary embolus, neoplasm, connective tissue diseases

*Under radiographic guidance, performed by skilled operators.

†If not previously performed in a patient who is failing therapy, or as convalescent IgG serology in which the initial test was unrevealing and the diagnosis remains unclear.

Adapted with permission from Bartlett JG, Breiman RF, Mandell LA, File TM Jr: Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America:. *Clin Infect Dis* 1998;26:811–838.

Table 2. Pneumonia Prediction System of the Patient Outcomes Research Team

Risk Factor	Point Value
A) Age, sex, and residence	
Male	Age, yr
Female	(Age, yr)–10
Nursing home	10
B) Underlying chronic disease	
Cancer	30
Hepatic disease	20
Cardiac disease	10
Renal disease	10
Stroke/transient ischemic attack	10
C) Vital signs and mental status	
Temperature < 95° or > 104° F	15
Systolic blood pressure < 90 mm Hg	20
Pulse ≥ 125/bpm	10
Respiratory rate ≥ 30 breaths/min	20
Disorientation	20
D) Initial testing	
Pleural effusion	10
Sodium < 130 mmol/L	20
Glucose ≥ 250 mg/dL	10
Blood urea nitrogen ≥ 30 mg/dL	20
Hematocrit < 30%	10
Arterial pH < 7.35	30
Pa_{O_2} < 60 mm Hg or $_{O_2}$ saturation < 90%	10

Risk Class	Point Total	Mortality, %
I	Age < 50 yr and no B or C risks	0.1
II	≤ 70	0.6
III	71–90	2.8
IV	91–130	8.2
V	> 130	29.2

Adapted with permission from Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243–250.

challenging. Several recent studies have attempted to stratify risk on the basis of objective clinical findings. Most useful among these studies is the schema of Fine et al,[38] who report the findings of the multicenter Patient Outcomes and Research Team (PORT).

Studying a large cohort of patients with pneumonia, the PORT investigators first established a list of underlying host factors, physical examination findings, laboratory values, and radiographic features disproportionately associated with morbidity and mortality. These factors were prioritized in a point system, with patients assigned to one of five risk classes (classes I through V) on the basis of total risk score (**Table 2**). This system was then validated in a retrospective analysis of 38,039 patients. Patients in classes I through III had less than 3% mortality, and less than 6% of these patients required admission to an intensive care unit. Fewer than 10% of patients in classes I and II who were treated as outpatients eventually required hospitalization. Patients in classes IV and V experienced a steep increase in mortality (8% and 29%, respectively). Based on this information, Fine et al[38] recommend that patients in risk classes IV and V should be routinely hospitalized, and patients in risk classes I and II should be routinely treated as outpatients. Patients in risk class III can either be treated as outpatients or briefly admitted. According to the PORT scoring system, the patient in case one has a total risk score of 81 points, placing her in risk class III. (This risk class corresponds to an overall mortality of 2.8% in the validation cohort.)

Practically applied, the PORT system requires a small set of readily available laboratory tests (arterial blood gases, a basic metabolic profile, and a CBC), chest radiography, and a thorough history and physical examination. The PORT system enables the clinician to approximate the likelihood of a patient thriving in the outpatient treatment setting.

Acknowledging the myriad factors that are not quantifiable by any risk stratification system, Fine et al[38] point out that outpatient oral therapy presumes the ability to ingest and absorb medication, adhere to a regimen, and return for follow-up visits. These researchers also note that any such set of guidelines is subject to considerable modification by individual patient scenarios and clinical judgment and require large prospective clinical trials to fully validate.

QUESTION

- **What further evaluation is indicated in the hospital setting?**

DISCUSSION

Inpatient Evaluation

Once a patient is admitted to the hospital, IDSA guidelines again stress the need to identify a pathogen. Ultimately, the confirmation of a pathogen requires either strong serologic evidence or isolation of the pathogen from respiratory secretions, blood, or a normally sterile body fluid. Although few studies have rigorously

investigated the value of diagnostic testing in pneumonia, at least one study[33] has documented faster resolution of fever with a proven microbiologic etiology, and another study has linked incorrect antibiotic therapy to poor outcome.[51] In addition, emerging bacterial resistance to antimicrobial agents and newer, more costly therapies provide indirect evidence that empiricism is costly both in terms of selection of resistant organisms and drug cost.

INITIAL TREATMENT AND CLINICAL COURSE

The patient is admitted to the hospital. Sputum Gram stain reveals numerous leukocytes and mixed flora, and the patient is started on empiric intravenous ceftriaxone and oral azithromycin to cover both typical and atypical pathogens, as suggested by IDSA guidelines. Cultures of blood and sputum, obtained before initiation of antibiotics, are sterile. The patient's fever gradually disappears over 2 days. Physical examination of the lungs shows clearing, and by hospital day three, oxygenation improves enough to allow discontinuation of supplemental oxygen.

QUESTION

- **What are current recommended approaches to empiric antimicrobial therapy of CAP?**

DISCUSSION

Empiric Antimicrobial Therapy

The choices for empiric antimicrobial therapy of pneumonia outlined in the IDSA guidelines (**Tables 3** and **4**) have been driven by two factors: emerging pathogens and emerging resistance to traditional antimicrobial selections. Although typical pathogens (eg, *S. pneumoniae, H. influenzae, M. catarrhalis, Klebsiella pneumoniae*) remain prevalent, the role of atypical pathogens (eg, *C. pneumoniae, Mycoplasma pneumoniae, L. pneumophila*) in CAP has been increasingly recognized. Macrolides, newer quinolones, and tetracyclines have been selected as empiric therapy in the outpatient setting for their good activity against both atypical and typical pathogens. Also, emerging multidrug resistance among pneumococci has made the newer quinolones (ie, levofloxacin, trovafloxacin, grepafloxacin, sparfloxacin), to which these isolates remain largely susceptible, an attractive therapy. In the hospital, the use of ceftriaxone or cefotaxime (which have the best in vitro pneumococcal activity among cephalosporins) with or without a macrolide (for atypical pathogens) is recommended for nonsevere pneumonias. Newer quinolones, which have good activity against both typical and atypical pathogens, provide another option. This latter recommendation has been controversial because of a perceived dearth of published clinical experience.

In recent years, there has been an explosion in the development of well-absorbed oral antibiotics with favorable pharmacokinetic profiles. Most notable among these are the newer fluoroquinolones and macrolides, several of which are indicated for once-daily dosing. Although oral therapy may have significant social,[52] economic, and medical benefits, there are few studies that directly compare the safety and efficacy of intravenous (IV) and oral therapy in the hospital setting.[53] Also, IV therapy is a criterion for hospitalization in many resource utilization systems. Consequently, few physicians choose oral antibiotics for initial therapy of pneumonia in hospitalized patients.

QUESTION

- **When can this patient safely be switched from IV to oral antibiotic therapy?**

DISCUSSION

Intravenous-to-Oral Switch Therapy

More data exist to support the use of IV-to-oral "switch" therapy than for oral therapy alone. Several studies address this approach in a controlled, randomized fashion; these studies have been recently reviewed.[54] A common sense approach, based on the work of Halm et al,[55] suggests that IV therapy may be converted to oral administration under the following circumstances:

- The patient is improving clinically, which is defined as body temperature ≤ 101°F, pulse ≤ 100 bpm, systolic blood pressure ≥ 90 mm Hg, respiratory rate ≤ 24 breaths/minute, and oxygen saturation ≥ 90%
- The patient is able to ingest and absorb oral antibiotics
- The patient has adequate social supports to note and report any change in clinical status
- The patient is capable of keeping outpatient follow-up visits

Halm and colleagues[55] suggest that most patients will meet these criteria in a median of 3 hospital days, although some variability is seen in daily practice.

SEROLOGY FINDINGS AND SWITCH TO ORAL THERAPY

Serologic testing is positive for *C. pneumoniae* IgM, allowing definitive therapy. The patient is discharged on doxycycline. After a total of 14 days of systemic antimicrobial therapy, she is completely recovered and asymptomatic.

Table 3. IDSA Guidelines for Empiric Antibiotic Therapy for Community-Acquired Pneumonia

Setting	Treatment Options
Outpatient	
Without modifying factors	Macrolides, newer fluoroquinolones, doxycycline
Suspected drug-resistant pneumococci	Newer fluoroquinolones
Aspiration	Amoxicillin/clavulanate
Adult ≤ 40 yr	Doxycycline
Inpatient	
On regular ward	Ceftriaxone or cefotaxime or a β-lactam/β-lactamase inhibitor combination ± macrolide; or a newer fluoroquinolone alone or azithromycin alone
Intensive care unit	Ceftriaxone or cefotaxime or a β-lactam/β-lactamase inhibitor combination plus erythromycin, azithromycin, or a newer fluoroquinolone
Lung with structural disease	Antipseudomonal penicillin/cephalosporin or carbapenem plus aminoglycoside
Penicillin allergy	Newer fluoroquinolone with or without clindamycin
Aspiration	Fluoroquinolone plus clindamycin or metronidazole or a β-lactam/β-lactamase inhibitor combination alone

IDSA = Infectious Diseases Society of America.

Adapted with permission from Bartlett JG, Breiman RF, Mandell LA, File TM Jr: Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis* 1998;26:811–838.

CASE TWO PRESENTATION

Initial Presentation

A 23-year-old graduate student presents to the college infirmary complaining of cough, fever, and shaking chills. The patient felt fine until 3 days before presentation, when he began to cough and feel generally unwell. His cough was productive of moderate amounts of yellow sputum without blood. In the 12 hours before presenting to the infirmary, the patient noted a fever of 102°F and experienced severe, teeth-chattering chills unrelieved by ibuprofen. A friend witnessed these symptoms and convinced the patient to come to the infirmary. The patient also admits to being "a little short of breath."

History

The patient has essentially no medical or surgical history. He has no medication allergies and is currently not taking any medication. He has not traveled recently, nor has he had contact with sick individuals. He has never been exposed to tuberculosis and had a negative tuberculin skin test earlier this year as part of a routine physical examination. He has no risks for HIV infection. He has never had influenza or pneumococcal vaccine.

Physical Examination

The patient is an acutely ill–appearing young man in mild respiratory distress. His temperature is 104°F; pulse, 132 bpm; blood pressure, 102/60 mm Hg; and respiratory rate, 30 breaths/minute. The skin is mildly diaphoretic. The neck is supple, and there is no palpable lymphadenopathy. The heart rhythm is tachycardic but regular and without murmur. Lung examination is remarkable for crackles in both bases with egophany in the right lower field, but no dullness to percussion. The abdomen is benign and without hepatosplenomegaly. No peripheral edema and no focal neurologic deficits are noted.

Outpatient Testing

Pulse oxygen saturation is 88% without supplemental oxygen. A chest radiograph reveals alveolar infiltrates in both lower lobes, with a small right pleural effusion.

Hospital Admission and Clinical Course

The patient is admitted to the hospital. After the collection of a sputum specimen and blood cultures, he is started on high-dose IV erythromycin (1 g/6 hr) and IV ceftriaxone (1 g/24 hr). Initial laboratory testing reveals a leukocyte count of 18,000/mm^3 with a neutrophil predominance in the differential count. Hemoglobin is 13.1 g/dL, and platelet count is 425,000/mm^3. Blood chemistries show mild elevations (less than two times normal) of aspartate aminotransferase and alkaline phosphatase. Arterial blood gases are remarkable for a Po_2 of 56 mm Hg, a Pco_2 of 24 mm Hg, and a pH of 7.39. The sputum Gram stain, unfortunately obtained several hours after the initiation of antibiotic therapy, reveals many polymorphonuclear leukocytes with few epithelial cells, but no organisms are seen.

Approximately 24 hours after admission, the patient

suffers a cardiovascular collapse and deepening hypoxemia, requiring mechanical ventilation and IV pressors for blood pressure support. A repeat chest radiograph shows new infiltrates in the right middle lobe and left upper lobes in addition to worsening infiltrates in the previously noted sites. The leukocyte count has increased to 23,000/mm^3. A sputum culture (obtained after the initiation of antibiotic therapy) and two blood cultures (obtained before the initiation of antibiotic therapy) are negative at 24 hours.

QUESTION

- **What is the rationale for giving high-dose erythromycin?**

DISCUSSION

Therapeutic Options for Legionella Infections

This patient has a rapidly progressive multilobe pneumonia with evolving sepsis syndrome, and infection with *Legionella* species clearly must be considered in the etiologic differential diagnosis. The negative sputum Gram stain and early negative cultures support the diagnosis. Given this scenario, it is appropriate to reassess the therapeutic options now available for Legionnaire's disease.

Erythromycin has long held the position as drug of choice in *Legionella* infections, based on clinical successes and a paucity of available alternatives. However, high-dose erythromycin has several clinically significant drawbacks, including venous and gastrointestinal intolerance, reversible ototoxicity, and the large fluid volume required for each dose. The newer macrolide, azithromycin, and several newer fluoroquinolones, including ciprofloxacin, ofloxacin, and levofloxacin, all have excellent in vitro activity against *Legionella* species and favorable pharmacokinetic and side effect profiles. In addition, fluoroquinolones and azithromycin possess excellent intracellular penetration that improves killing of intracellular organisms.[56] However, clinical data to support the use of these newer agents for severe disease are scant and largely based on animal models.[23] Despite this, IDSA guidelines and some clinicians now consider azithromycin, the previously mentioned fluoroquinolones, and doxycycline to be preferred to erythromycin in the treatment of legionellosis. However, erythromycin will likely remain an important part of the armamentarium against this pathogen until further clinical experience with these newer agents emerges.

In the treatment of severe pneumonia, the clinician also must be mindful of pneumococci, *Staphylococcus aureus*, and gram-negative organisms in the microbiologic differential diagnosis. This consideration is reflected in IDSA guidelines by the addition of a third-generation cephalosporin or a β-lactam/β-lactamase combination to the atypical coverage offered by a macrolide or fluoroquinolone.

Table 4. IDSA Guidelines for Antimicrobial Therapy for Selected Pathogens in Community-Acquired Pneumonia

Pathogen	Treatment Options*†‡
Streptococcus pneumoniae	
MIC < 0.1 µg/mL	**Penicillin, amoxicillin,** cephalosporins, macrolides, clindamycin, fluoroquinolones, doxycycline
MIC 0.1–1.0 µg/mL	**Penicillin G high-dose, ceftriaxone, cefotaxime, amoxicillin, fluoroquinolones,** clindamycin, doxycycline, oral cephalosporins
MIC > 2.0 µg/mL	Based on susceptibility profile; fluoroquinolones, vancomycin
Empiric	Based on community resistance patterns; fluoroquinolones, penicillin, others as listed above
Legionella species	**Macrolides ± rifampin, fluoroquinolones,** doxycycline ± rifampin
Chlamydia pneumoniae	Doxycycline, macrolides, fluoroquinolones
Mycoplasma pneumoniae	Doxycycline, macrolides, fluoroquinolones

NOTE: The treatment options in bold are preferred agents.

IDSA = Infectious Diseases Society of America; MIC = minimal inhibitory concentration.

*Cephalosporins: cefazolin, cefuroxime, cefotaxime, ceftriaxone (parenteral); cefpodoxime, cefprozil, cefuroxime (oral).

†Macrolides: erythromycin, clarithromycin, azithromycin.

‡Fluoroquinolones: levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, (ciprofloxacin, ofloxacin, levofloxacin for Legionella species).

Adapted with permission from Bartlett JG, Breiman RF, Mandell LA, File TM Jr: Community-acquired pneumonia in adults: guidelines for management. The Infectious Diseases Society of America. *Clin Infect Dis* 1998;26:811–838.

SWITCH OF ANTIBIOTICS AND FURTHER TESTING

The patient is continued on ceftriaxone but is switched from erythromycin to IV azithromycin (500 mg/day) because of concern for intracellular

penetration, with an ongoing working diagnosis of legionellosis. The patient's clinical status is unimproved at 48 hours, and he remains intubated with increasing doses of pressors; his cultures remain negative. A urine specimen is sent for *Legionella* antigen assay; this test is also negative.

QUESTION

- **What is the next step in evaluating the CAP patient who is not responding to empiric therapy?**

DISCUSSION

Consideration of Reasons for Treatment Failure

When the patient's clinical status worsens despite appropriate therapeutic measures, the clinician must consider several possible reasons for treatment failure.[23]

First, the clinical diagnosis of infection must be questioned. Multiple noninfectious entities, such as neoplasms; pulmonary edema, embolus, or hemorrhage; connective tissue diseases; and drug toxicity can produce fever and the radiographic appearance of pneumonia. If the diagnosis of infection seems clear, the clinician must consider the complex interplay of microorganism, antibiotic, and host in the treatment regimen. For example, failure to respond to antibacterial agents may indicate the presence of an atypical pathogen, such as fungi, mycobacteria, *Nocardia*, viruses, or *P. carinii*. The presence of a secondary superinfection also must be considered.

Treatment failure may also occur when a drug-resistant pathogen, such as a drug-resistant pneumococcus, is present. The clinician must consider whether the correct therapeutic agent has been selected and whether systemic levels of drug are inadequate because of adverse medication adherence, poor absorption, or drug interaction. Finally, failure to respond may be indicative of deficits of local or systemic immunity, anatomic derangements (eg, bronchiectasis, emphysema), obstruction, or empyema.

Additional Testing

Making a microbiologic diagnosis in the nonresponding patient who defies diagnosis by standard culture techniques may require significant effort and cost and more invasive testing.

Laboratory tests. Serologic and urinary antigen testing, as previously described, may provide important information, albeit with a delay of 1 or several days in most centers. Tuberculin skin testing may provide a clue to mycobacterial disease. Nasopharyngeal swabs for direct fluorescent antibody testing may yield evidence of viral respiratory antigens. When these procedures fail to yield a microbiologic diagnosis, more invasive diagnostic techniques may be indicated.

Transtracheal aspiration and fiberoptic bronchoscopy. The value of transtracheal aspiration depends on the operator's skill because this procedure can have dangerous complications. Now performed only rarely, transtracheal aspiration has been largely supplanted by fiberoptic bronchoscopy (FOB) in the diagnosis of pneumonia.[57] FOB allows the use of several diagnostic techniques. Bronchoalveolar lavage with saline can obtain deep respiratory specimens for a broad range of stains and cultures. Transbronchial biopsy of infiltrated lung parenchyma can reveal alveolar or interstitial pneumonitis, viral inclusion bodies, and invading fungal or mycobacterial organisms. Quantitative culture with a protected brush catheter is used to distinguish between tracheobronchial colonizers and pneumonic pathogens.[58] When secretions cultured from a brushed specimen contain 103 CFU / mL of a bacterial pathogen, lower respiratory infection should be suspected.

Thoracoscopic or open-lung biopsy. A more substantial amount of lung tissue may be obtained for culture and histologic examination by thoracoscopic or open-lung biopsy. These more invasive procedures usually are reserved for the unimproved, critically ill patient with a pneumonia that defies diagnosis by less invasive techniques.

Molecular techniques. Powerful molecular techniques, although expensive and not available in every center, are increasingly being applied to the diagnosis of pneumonia. DNA probes have been used for the detection of *Legionella* species, *M. pneumoniae*, and *Mycobacterium tuberculosis* in sputum.[59] These probes have excellent sensitivity and specificity but may produce false-positive results. The polymerase chain reaction has been shown to be a sensitive tool for the early detection of *M. tuberculosis* in sputum specimens. Because of the potential for an early and accurate microbiologic diagnosis, these techniques will likely play a greater role in future diagnostic algorithms.

BLOOD CULTURE FINDINGS AND THERAPY CHANGE

On hospital day three, both blood cultures from the day of admission are found to have growth of gram-positive cocci in pairs and chains. The following day, *S. pneumoniae* is identified. Susceptibility studies show the isolate is highly resistant to penicillin, cephalosporins, and macrolides. At this point, the patient's therapy is changed to vancomycin. The patient recovers after a total hospitalization of 15 days, 10 of these days in the intensive care unit, and an additional week of oral levofloxacin following discharge.

(from page 54)

QUESTION

- **How could this patient have been managed differently?**

DISCUSSION

Pitfalls in Pneumonia Management

In case two, failure to respond to a macrolide/β-lactam combination in a patient with a rapidly progressive syndrome consistent with overwhelming infection should have raised the possibility of a drug-resistant bacterial pathogen. In addition, the clinicians placed much emphasis on the negative Gram stain, which was collected late and possibly rendered unrevealing by prior antibiotic therapy, illustrating the importance of proper technique and timing in the use of this tool. Pneumococci can produce a rapidly progressive pneumonia outside the typical syndrome of lobar pneumonia with a single rigor and rust-colored sputum. Given emerging multiple drug resistance, a cogent argument can be made for empiric addition of vancomycin at 48 hours of nonresponse, rather than awaiting definitive microbiologic confirmation in a critically ill patient. If a pathogen that is susceptible to clinically effective agents other than vancomycin can be identified, vancomycin can later be deleted from the regimen.

QUESTION

- **How have drug-resistant pathogens affected the management of CAP?**

DISCUSSION

Drug-Resistant Bacteria: A Mounting Challenge

During the past decade, there has been an explosive, worldwide increase in antimicrobial resistance among bacteria. Among pneumonic pathogens, *S. pneumoniae* is the most striking example. *S. pneumoniae* is the most common etiology of pneumonia, with 14 to 46 cases per 1000 person-years in the elderly population in the United States; pneumococcal pneumonia is associated with an estimated 30% mortality when left untreated.[60] Although pneumococci have traditionally been exquisitely susceptible to penicillin, many communities in the United States and worldwide have noted endemic strains of the organism possessing intermediate or high resistance to penicillin. The Centers for Disease Control and Prevention (Atlanta, GA) report that 35% of pneumococcal isolates exhibit penicillin resistance in some areas of the country, although considerable geographic variation exists.[61] Even more concerning is the fact that many of the highly penicillin-resistant strains are also resistant to multiple cephalosporins, erythromycin, and trimethoprim-sulfamethoxazole. Fortunately, many multiresistant strains remain susceptible to the newer fluoroquinolone agents, including levofloxacin, sparfloxacin, grepafloxacin, and trovafloxacin; however, resistance among pneumococci to these agents has already begun to emerge.[62] Of note, intermediate resistance to penicillins is easily overcome with the high levels of drug attainable with high-dose penicillin or with ceftriaxone or cefotaxime. Imipenem may also be effective for some strains. No strains with resistance to vancomycin have been isolated.

Local patterns of antimicrobial resistance as well as the emerging side effect profiles of these newer drugs may have a significant impact on the selection of antimicrobials. Together, these factors provide a powerful argument for culture confirmation of the bacterial agents of pneumonia. These factors also provide sound reason in favor of pneumococcal vaccination, which can prevent disease with resistant and susceptible strains alike.

Simultaneous with the increase in pneumococcal resistance has been the emergence of resistance among other gram-positive pathogens, such as enterococci and staphylococci. Many experts now feel that nonmedical uses of antimicrobial agents (eg, in animal feeds) have played an important role in the development and spread of resistant microbes.[63] However, investigators and clinicians also stress that inappropriate initiation of broad-spectrum antibiotics for nonbacterial syndromes, failure to collect cultures at all, and failure to appropriately narrow therapy to fit culture isolates have exerted selective pressure favoring resistant pathogens.[64]

CONCLUSION

Clinical Outcomes in Pneumonia

Despite resistant pathogens and difficulties in diagnosis, patients with pneumonia have generally favorable clinical outcomes. In a recent study of the PORT cohort, Fine et al[65] report that patients hospitalized with pneumonia survived to 30 days in 92% of cases and returned to usual employment in 82% of cases, despite having residual symptoms in 86% of cases. Regardless, medical management of the patient with pneumonia at the turn of the millennium seems dominated by two sharply conflicting outcome goals—containment of cost and containment of antimicrobial resistance. Retrospective studies have shown no difference in outcomes in pneumonia patients with and without a microbiologic diagnosis.[66,67] The value of tools such as Gram stain and culture of expectorated sputum and serologic testing for various pathogens has been questioned by many authors,[23] and these tests provide easy targets for those seeking to reduce costs in medical care.

The real cases described above are good examples

of how the sputum Gram stain and culture can be insensitive when poorly collected or when an atypical pathogen is present. They highlight that information from such studies is more likely to be clinically relevant when positive (eg, a predominant organism on Gram stain or in culture). Case two further emphasizes the utility of blood cultures in the patient with severe pneumonia, even when growth is atypically late. Likewise, more sensitive molecular techniques, almost certain to become more prominent in the diagnostic algorithm of many clinicians out of frustration with currently available tests, are equally certain to be expensive. Despite these shortcomings, the IDSA guidelines make a cogent argument for attempting to make a microbiologic diagnosis with the available tools, however flawed.

Costs Related to Diagnosis and Treatment

The publication of the most recent ATS guidelines and the newer IDSA guidelines gives rise to this question: Can medicine afford the unbridled empiricism that has characterized antibiotic prescribing since the arrival of these agents? The costs of treatment failures and additional erosion of the effectiveness of the available antimicrobial pharmacopeia, although far more difficult to measure, are no less tangible than the cost of a Gram stain. Is the potential savings of additional hospital/intensive care unit days, at this point not well-documented because of a lack of good prospective studies, worth the smaller expense of a Gram stain? Is prevention of morbidity and mortality as a result of resistance in virulent pathogens, such as pneumococci or *S. aureus*, worth the cost of a sputum culture or a molecular probe? Although answers to these questions are outcomes research opportunities not yet seized, the lack of success in containing resistant enterococci and pneumococci worldwide suggests that additional attempts to focus therapy are worth the cost. It also appears from preliminary data that adequate therapy based on a Gram stain may hasten resolution of fever and lack of adequate therapy can lead to worse outcomes.[33,51]

Although syndrome overlap frequently precludes assumptions that might be used to construct cost-reducing diagnostic algorithms, the prudent clinician can often minimize cost by focusing on important historical and clinical features. Some of the additional cost incurred in a more extensive evaluation might also be defrayed by cost savings from oral and IV-to-oral switch therapies, with studies stratified by systems such as the PORT prediction system. These therapies offer potential improved outcomes in terms of patient satisfaction and minimization in productivity loss; quantitation of these improvements forms another area of opportunity for study.

Impact of Newer Guidelines

The potential impact of the PORT prediction rule and IDSA guidelines is significant for managed care and health systems. Considerable cost savings can be realized both in the identification of a low-risk group of patients who can be safely treated in the outpatient setting with oral antibiotics, and the use of clinical algorithms that encourage switching from IV to oral therapy when appropriate. For example, Chan et al[68] predicted a cost savings of £176,000 (UK) if 800 patients were treated with oral therapy for a single year. Cunha[69] showed that combined cost of drug plus administration was reduced tenfold when an oral antibiotic was used in place of an IV formulation. Ramirez and colleagues[70] estimated a savings of $104,524 in treating 74 patients with IV-to-oral switch therapy, with only a single readmission.

The cost-effectiveness of diagnostic testing to establish an etiologic diagnosis is somewhat more difficult to evaluate. Although at first glance an increase in direct costs is suggested from testing, it is possible that the more targeted therapy offered by a specific microbiologic diagnosis may offer long-term cost savings in the form of more rapid clinical improvement, decreased length of hospital stay, fewer treatment failures, fewer complications, and the use of less-expensive antibiotics. Even more ephemeral, but no less important, is the theoretical discouragement of bacterial resistance by targeted therapy. The true economic impact of these factors awaits further analysis. In any case, it is likely that the PORT data and guidelines such as those published by the IDSA and ATS will be used by managed care organizations and health systems to construct clinical algorithms for the management of CAP, to which physicians may be held accountable. Clearly, CAP still commands our attention and demands further rigorous study to optimize treatment outcomes. **HP**

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