Overview of Lower Respiratory Tract Infections: Diagnosis and Treatment

Joseph R. Dalovisio, MD

Head, Section on Infectious Diseases, Department of Internal Medicine, Ochsner Clinic Foundation, New Orleans, LA

Because the diagnosis and treatment of community-acquired pneumonia (CAP) continue to present decision-making challenges, a number of professional organizations have developed treatment guidelines to provide parameters for diagnosis and treatment. The Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) both recently updated their guidelines for the treatment of CAP to take into account the changes that have occurred in antimicrobial susceptibility and the availability of newer antimicrobial agents. Both the IDSA and ATS guidelines stratify treatment according to where the patient is treated, but the ATS guidelines further characterize patients according to the presence or absence of cardiopulmonary disease or other modifying factors. For outpatients with CAP, doxycycline, a macrolide, or a newer fluoroquinolone with enhanced activity against *Streptococcus pneumoniae* are the IDSA-preferred agents for empiric treatment. The ATS recommends monotherapy with a macrolide or doxycycline in patients without modifying factors, or combination therapy with a β–lactam plus a macrolide, or monotherapy with an antipneumococcal fluoroquinolone in patients with modifying factors. For empiric therapy of CAP in hospitalized patients, the IDSA recommendations are as follows: an extended-spectrum cephalosporin plus a macrolide, a β–lactam/β–lactamase inhibitor plus a macrolide, or a fluoroquinolone with extended activity against *S. pneumoniae*. For hospitalized patients without modifying factors, the ATS recommends monotherapy with azithromycin or an antipneumococcal fluoroquinolone. For hospitalized patients with modifying factors, combination therapy with a β–lactam plus a macrolide, doxycycline, or monotherapy with a respiratory fluoroquinolone are recommended. Given the increasing resistance of *S. pneumoniae* to macrolides and doxycycline, a respiratory fluoroquinolone may represent the best choice of therapy.

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Pneumonia is the sixth most common cause of death in the United States and a significant cause of death worldwide (1). In recent years, a number of new advances have occurred with regard to pneumonia diagnosis and treatment, including identification of new pathogens such as *Chlamydia pneumoniae*, hantavirus, and others, and the development of newer therapeutic agents such as fluoroquinolones, macrolides, streptogramins, oxazolidinones, and β–actam antibiotics (2). Additionally, new diagnostic tools such as nucleic acid amplification techniques and antigen detection methods provide hope that the speed and accuracy of diagnosis and the effectiveness of therapy will improve. Despite these advances, respiratory tract infections remain problematic both in diagnostic and therapeutic decision-making arenas.

Pneumonia is suspected in patients who have fever and cough coupled with an abnormal chest x-ray. Unfortunately, this combination of findings also may be attributable to noninfectious causes such as pulmonary thromboembolic disease, congestive heart failure, pulmonary hypersensitivity reactions, and other etiologies. In addition to the difficulty of differentiating pneumonia from noninfectious causes of fever, cough, and pulmonary infiltrates, defining the microbial etiology of pneumonia is problematic. With meningitis, bacterial endocarditis, or urinary tract infections, a positive culture of the appropriate clinical specimen strongly predicts its microbial cause. Microbial diagnosis of pneumonia etiology, however, is complicated by the problems of upper airway contamination of specimens. In addition to these difficulties,

antibiotic resistance of usual respiratory tract pathogens such as ***Streptococcus pneumoniae***, ***Haemophilus influenzae***, and ***Moraxella catarrhalis*** continues to increase (3-5).

GUIDELINES FOR THE MANAGMENT OF COMMUNNITY-ACQUIRED PNEUMONIA

Because of the challenges of both diagnosing and treating pneumonia, a number of professional organizations have developed treatment guidelines to give physicians parameters for diagnosis and disease management. In 1993, the American Thoracic Society (ATS), British Thoracic Society, and Canadian Infectious Disease Society all published guidelines on treatment of community-acquired pneumonia (CAP) (6-8). In 1998, the Infectious Diseases Society of America (IDSA) published its CAP management guidelines (9). In the year 2000, IDSA, Canadian Infectious Disease and Thoracic Societies, and the Drug–Resistant ***Streptococcus pneumoniae*** Therapeutic Working Group (DRSPWG) published new or revised guidelines for treatment of CAP (2,10,11). In 2001, the ATS published their revised guidelines for CAP (12). The newest guidelines take into account the changes that have occurred in antimicrobial susceptibility and the availability of newer antimicrobial agents. These newer guidelines should help to shape the future of CAP diagnosis and treatment.

DIAGNOSIS

The patient's history helps identify certain risk factors and conditions associated with specific pathogens (2). For instance, in a patient with a history of alcoholism, one would suspect ***S. pneumoniae***, ***Klebsiella pneumoniae***, or perhaps anaerobic bacteria as the cause of pneumonia. Depending on the stage, human immunodeficiency virus (HIV) infection would increase concern about infection caused by ***S. pneumonia***, ***Mycobacterium tuberculosis***, ***Pneumocystis carinii***, and other opportunistic pathogens. Other associations between medical conditions and certain pathogens have been identified (Table 1) (2).

The IDSA guidelines emphasize the use of chest radiography to diagnose pneumonia and to differentiate patients with acute febrile bronchitis from those with pneumonia. In addition to helping

Table 1. Epidemiological conditions related to specific pathogens in patients with selected community-acquired pneumonia. Adapted with permission of the University of Chicago Press from Bartlett, et al. Clin Infect Dis 2000; 31:347-382. (2)

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae* and anaerobes
COPD and/or smoking	*S pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Legionella* spp
Nursing home residency	*S pneumoniae*, gram-negative bacilli, *H influenzae*, *Staphylococcus aureus*, anaerobes, and *Chlamydia pneumoniae*
Poor dental hygiene	Anaerobes
Epidemic Legionnaires' disease	*Legionella* spp
Exposure to bats or soil enriched with bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
HIV infection (early stage)	*S. pneumoniae*, *H influenzae*, and *Mycobacterium tuberculosis*
HIV infection (late stage)	Above plus *Pneumocystis carinii*, *Cryptococcus*, and *Histoplasma* spp
Travel to southwestern US	*Coccidioides* spp
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Influenza active in community	Influenza, *S. pneumoniae*, *S. aureus*, *Streptococcus pyogenes*, and *H. influenzae*
Suspected large-volume aspiration	Anaerobes (chemical pneumonitis, obstruction)
Structural disease of lung	*Pseudomonas aeruginosa*, *Burkholderia* (*Pseudomonas*) *cepacia*, and *S. aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis*, and *S. pneumoniae*
Airway obstruction	Anaerobes, *S. pneumoniae*, *H. influenzae*, and *S. aureus*

COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus.

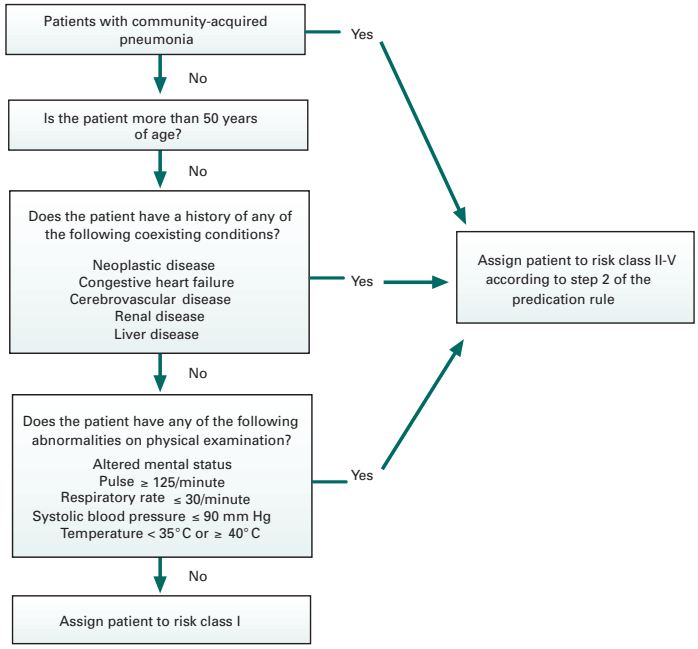

Figure 1. Pneumonia Patient Outcomes Research Team (PORT) Clinical Prediction Rule for patients with CAP. Adapted with the permission of the Massachusetts Medical Society from Fine, et al. N Engl J Med 1997; 336:243-250. (13)

diagnose pneumonia, the chest x-ray can detect and assess lung disease, assess severity and extent of pneumonia, and provide a baseline from which to assess clinical response. The physical examination cannot confirm a diagnosis of pneumonia. However, it helps to ascertain the severity of illness and assess the venue for treatment (i.e., inpatient vs. outpatient).

The decision to treat the patient as an inpatient or an outpatient remains one of the most important decisions made by the clinician, because it affects both cost of treatment and clinical outcome. The Pneumonia Patient Outcomes Research Team (PORT) study provided a clinical prediction rule that correlates well with short-term mortality for patients with CAP (13). Although the clinical prediction rule was not created to be a triage tool, its ability to predict mortality can help determine a treatment venue (Figure 1; Tables 2,3). The use of the PORT clinical prediction rule as a triage tool for patients with CAP has been endorsed by the IDSA (2) and the Canadian Infectious Disease and Thoracic Societies (11).

ETIOLOGY

Perhaps the most obvious difference between the ATS guidelines published in 1993 and revised in 2001 and the IDSA guidelines published in 1998 and 2000 has been in the intensity with which

Table 2. Point scoring system for assignment to pneumonia risk classes II, III, IV, and V. Adapted with the permission of the Massachusetts Medical Society from Fine, et al. N Engl J Med 1997; 336:243-250. (13)

Characteristic Demographic Factor	Points Assigned*
Age	
Men	Age (y) n
Women	Age (y) –10
Nursing home resident	+10
Coexisting illnesses†	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Pleural effusion	+10

Characteristic	Points Assigned*
Physical examination findings	
Altered mental status‡	+20
Respiratory rate ≥ 30/min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 35°C or ≥ 40°C	+15
Pulse ≥ 125/min	+10
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea nitrogen ≥ 30 mg/dL (11 mmol/liter)	+20
Sodium < 130 mmol/liter	+20
Glucose ≥ 250 mg/dL (14 mmol/liter)	+10
Hematocrit < 30%	+10
Partial pressure of arterial oxygen < 60 mm Hg§	+10

* A total point score for a given patient is obtained by summing the patient's age in years (age minus 10 for women) and the points for each applicable characteristic.
† Neoplastic disease is defined as any cancer except basal- or squamous-cell cancer of the skin that was active at the time of presentation or diagnosed within 1 year of presentation. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.
‡ Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.
§ An oxygen saturation of less than 90% on pulse oximetry or intubation before admission was also considered abnormal.

Table 3. Assignment of pneumonia risk class. Data from Fine, et al. N Engl J Med 1997; 336:243-250. (13)

Risk class (number of points)*	
I	(see Figure 1)
II	(≤70)
III	(71-90)
IV	(91-130)
V	(>130)

* Inclusion in risk class I was determined by the absence of all predictors identified of the prediction rule, Figure 1. Inclusion in risk classes II, III, IV, and V was determined by a patient's total risk score, which was computed according to the scoring system shown above.

Table 4. Recommendations for expectorated sputum collection, transport, and processing. Adapted with permission of the University of Chicago Press from Bartlett, et al. Clin Infect Dis 2000; 31:347-382. (2)

- Specimen should
  - Be obtained by deep cough
  - Have gross purulence
  - Be obtained before treatment with antimicrobial agents
  - Be obtained in the presence of a health care provider
  - Be immediately transported to the laboratory for prompt processing
- A purulent portion should be selected for Gram's staining and culture
  - Quellung staining should be done when available
- Cytological screening should be done under low-power magnification (x100) to determine the cellular composition
  - Cytological assessment is not necessary for screening specimens for detection of respiratory viruses, ***Legionella*** species, or mycobacteria
- Culture should be performed with use of standard techniques
- Results should be reported with semiquantitative assessment

specific microbial diagnosis is pursued and the degree of empiricism recommended in treatment. The IDSA guidelines cite three reasons for establishing a specific etiologic diagnosis of CAP (2). The first is to improve care of the individual patient. Identifying specific etiologic agents facilitates selection of optimal, pathogen-directed, antibiotic therapy and accurate disease staging. By targeting antibiotic selection, one limits consequences of injudicious use such as increased expense, antibiotic resistance induction, and adverse effects. In addition, switching from an empiric broad-spectrum intravenous regimen to a narrower-spectrum oral one is easier if an etiology is known. Frequently, narrower-spectrum antibiotics are less expensive than broad-spectrum antibiotics. The second reason to establish an etiology is to gather enhanced epidemiologic information that can improve care for other patients by advancing the general body of knowledge. Enhanced epidemiologic information helps identify emerging pathogens, drug-resistant pathogens, and trends. It also helps limit antibiotic overuse. The third reason concerns diagnostic costs. Although the 1993 ATS guidelines (8) state that diagnostic tests are expensive and not a good value, the average cost of diagnostic studies is less than 1% of the hospital charges for a patient with CAP (2).

MICROBIOLOGIC STUDIES

For patients with CAP who are not ill enough to be hospitalized, the utility of microbiologic studies is unclear. However, in hospitalized patients with CAP, both the IDSA and ATS recommend that at least two blood cultures be done before initiating antibiotics (2,12). The IDSA also encourages the use of sputum Gram's stain. The IDSA guidelines emphasize, however, that specimens should be obtained by deep cough and should be grossly purulent if they are to be used in clinical decision-making (Table 4). The specimen should also be obtained before treatment with antibiotics, in the presence of the health care provider, and should be transported immediately to the lab for processing. Cytologic screening should be done under low-power magnification to determine the quality of the sputum before a bacteriologic assessment is made (acceptable specimens have >25 polymorphonuclear cells and <10 squamous epithelial cells). In addition to these studies, the IDSA and ATS guidelines recommend a complete blood count, chemistry panel, liver function tests, oxygen saturation, and HIV antibody screening (in patients aged 15-54 years) as part of the initial diagnostic evaluation.

SEROLOGIC STUDIES

Serologic studies for diagnosis of CAP are generally not helpful because most tests lack specificity and have a slow turnaround time. No single serologic test is available to rapidly diagnose ***Mycoplasma pneumoniae***, ***C. pneumoniae***, or Legionnaire's disease. In contrast, however, there are some useful antigen detection tests available. The urine ***Legionella*** antigen test should be performed in cases of suspected Legionnaire's disease (i.e., if the patient is older than 40 years of age, immunocompromised, or unresponsive to β-lactam antibiotic therapy) or if the patient presents during an outbreak of Legionnaire's disease. This urine antigen test is used to test for ***Legionella*** serogroup 1, which accounts for approximately 70% of reported Legionella pneumonia cases in the United States. The urine antigen test has a sensitivity of between 50% and 60% and a specificity of greater than 95%. Pneumococcal urinary antigen tests have been approved by the United States Food and Drug Administration (FDA).

Table 5. Pathogen-directed antimicrobial therapy for community-acquired pneumonia. Adapted with permission of the University of Chicago Press from Bartlett, et al. Clin Infect Dis 2000; 31:347-382. (2)

Organism	Preferred antimicrobial	Alternative antimicrobial
Streptococcus pneumoniae Penicillin-susceptible*	Penicillin G; amoxicillin	Cephalosporins (cefazolin, cefuroxime, cefotaxime, ceftriaxone, or cefepime); oral cephalosporins (cefpodoxime, cefprozil, or cefuroxime); imipenem or meropenem; macrolides†; clindamycin; fluoroquinolone‡; doxycycline; ampicillin ± sulbactam or piperacillin ± tazobactam)
Penicillin-resistant§	Agents based on in vitro susceptibility tests, including cefotaxime and ceftriaxone; fluoroquinolone‡; vancomycin	—
Haemophilus influenzae	Cephalosporin (2nd or 3rd generation); doxycycline; β-lactam/β-lactamase inhibitor; azithromycin; TMP-SMX	Fluoroquinolone‡; clarithromycin
Moraxella catarrhalis	Cephalosporin (2nd or 3rd generation); TMP-SMX; macrolide; β-lactam/ β-lactamase inhibitor	Fluoroquinolone‡
Anaerobe	β-Lactam/β-lactamase inhibitor; clindamycin	Imipenem
Staphylococcus aureus/ Methicillin-susceptible Methicillin-resistant	Nafcillin-oxacillin ± rifampin or gentamicin/ Vancomycin ± rifampin or gentamicin	Cefazolin or cefuroxime; vancomycin; clindamycin; TMP-SMX Linezolid
Enterobacteriaceae¶	Cephalosporin (3rd generation) ± aminoglycoside; carbapenem	Aztreonam; β-lactam/β-lactamase inhibitor; fluoroquinolone‡
Pseudomonas aeruginosa/	Aminoglycoside + antipseudomonal β-lactam; ticarcillin, piperacillin, mezlocillin, ceftazidime, cefepime, aztreonam, or carbapenem	Aminoglycoside + ciprofloxacin; ciprofloxacin + antipseudomonal β-lactam
Legionella	Macrolide† ± rifampin; fluoroquinolone‡ (including ciprofloxacin)	Doxycycline ± rifampin
Mycoplasma pneumoniae	Doxycycline; macrolide†	Fluoroquinolone‡
Chlamydia pneumoniae	Doxycycline; macrolide†	Fluoroquinolone‡
Chlamydia psittaci	Doxycycline	Erythromycin; chloramphenicol
Nocardia	TMP-SMX; sulfonamide ± minocycline or amikacin	Imipenem ± amikacin; doxycycline or minocycline
Coxiella burnetti (Q fever)	Tetracycline	Chloramphenicol
Influenza virus	Amantadine or rimantadine (influenza A); zanamavir or oseltamivir (influenza A or B)	—
Hantavirus	Supportive care	—

TMP-SMX = trimethoprim-sulfamethoxazole; ± = with or without. * Minimum inhibitory concentration (MIC) <2 μg/mL. † Erythromycin, clarithromycin, azithromycin, or dirithromycin; ***S. pneumoniae***, especially strains with reduced susceptibility to penicillin, should have verified in vitro susceptibility. ‡ Levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin, or other fluoroquinolone with enhanced activity against ***S. pneumoniae***; ciprofloxacin is appropriate for ***Legionella, C pneumoniae,*** fluoroquinolone-susceptible ***S. aureus***, and most gram-negative bacilli; ciprofloxacin may not be as effective as other quinolones against ***S. pneumoniae***. § MIC ≥ 2 μg/mL./In vitro susceptibility tests are required for optimal treatment; against Enterobacter species, the preferred antibiotics are fluoroquinolones and carbapenems. ¶Coliforms = ***Escherichia coli***, ***Klebsiella***, ***Proteus***, and ***Enterobacter***

Other diagnostic tests such as DNA probes and nucleic acid amplification tests are under development and must be improved and clinically validated. Invasive studies such as transthoracic needle aspiration and bronchoscopy should be reserved for a select patient population.

TREATMENT

The CAP treatment guidelines focus on initial choice of therapy and are generally divided into pathogen-directed therapy and empiric treatment and by severity of the patient's illness and underlying condition.

Outpatients

The 2000 IDSA CAP guidelines divide antibiotic therapy recommendations into pathogen-directed and empiric categories (2). The pathogen-directed antimicrobial therapy recommendations are straightforward and consistent with clinical data and recommendations used in the past (Table 5). In contrast, there is less consensus about empiric antibiotic choices. For outpatients with CAP, doxycycline, a macrolide (azithromycin, clarithromycin, or erythromycin), or a newer fluoroquinolone with enhanced activity against *S. pneumoniae* are the IDSA-preferred agents for empiric treatment. It is also noted that regional susceptibility data should influence prescribing decisions and that penicillin-resistant *S. pneumoniae* may be resistant to doxycycline and macrolides.

The ATS stratifies patients with CAP into those with modifying factors (e.g., cardiopulmonary disease) and those without modifying factors. In patients without modifying factors, the ATS recommends monotherapy with a macrolide or doxycycline (12). In patients with modifying factors, they recommend combination therapy with a β-lactam plus a macrolide or monotherapy with an antipneumococcal fluoroquinolone. However, the ATS noted that the newer fluoroquinolones have improved pneumococcal coverage and offer coverage of gram-positive, gram-negative, and atypical pathogens with once-a-day dosing. The ATS ranked the currently available antipneumococcal fluoroquinolones by their antipneumococcal activity (moxifloxacin >gatifloxacin >levofloxacin) and noted that gemifloxacin, an investigational fluoroquinolone, is more active against *S. pneumoniae* than moxifloxacin or gatifloxacin. Although these in vitro differences may not be clinically significant at present, the ATS noted that these differences may lead to differences in clinical success and resistance rates in the future.

The Centers for Disease Control Drug Resistant *Streptococcus pneumoniae* Therapeutic Working Group took another approach. It recommends macrolides as first-line agents, although the group recognizes that macrolide activity against *S. pneumoniae* is suboptimal (10). This group discourages use of respiratory fluoroquinolones except in situations in which there is doxycycline or macrolide failure or allergy, and in cases of documented infection with penicillin-resistant S pneumoniae (penicillin minimum inhibitory concentration [MIC] ≥ 4 μg/mL).

Currently, preferentially using macrolides over respiratory fluoroquinolones as empiric therapy for CAP has some limitations. Although macrolides provide excellent coverage of atypical pathogens, during the past several years *S. pneumoniae* have become increasingly resistant to this class of antimicrobials (14). Patients who fail macrolide therapy may develop bacteremic pneumonia and, in addition to requiring an additional antimicrobial agent, may also require hospitalization (15). Cultures and sensitivities to document the infecting pathogen generally are not done for outpatients with CAP. Therefore, respiratory fluoroquinolones may be preferred over macrolides, doxycycline, and β-lactams for empiric therapy for patients with CAP because of their excellent activity against *S. pneumoniae* and other usual CAP pathogens, including the atypicals.

Inpatients

For empiric therapy of CAP in patients hospitalized in the general medical ward, the IDSA recommendations are: an extended-spectrum cephalosporin (ceftriaxone or cefotaxime) plus a macrolide, a β-lactam/β-lactamase inhibitor (ampicillin/sulbactam or piperacillin/tazobactam) plus a macrolide, or a fluoroquinolone with extended activity against *S. pneumoniae* (2). The ATS recommendations for patients without modifying factors are monotherapy with azithromycin or an antipneumococcal fluoroquinolone (12). For patients with modifying factors, the ATS recommends combination therapy with a β-lactam plus a macrolide, doxycycline, or monotherapy with a respiratory fluoroquinolone.

For patients with CAP admitted to the intensive care unit, the IDSA guidelines recommend an extended-spectrum cephalosporin (ceftriaxone or cefotaxime) or a β-lactam/β-lactamase inhibitor (ampicillin/sulbactam or piperacillin/tazobactam) plus a fluoroquinolone with enhanced activity against *S. pneumoniae* or a macrolide (2). The ATS guidelines recommend an intravenous β-lactam plus either an intravenous macrolide or an intravenous fluoroquinolone (12).

Special Populations

For those patients in whom Pseudomonas aeruginosa infection is suspected, the ATS recommends an antipseudomonal β-lactam in addition to ciprofloxacin or an antipseudomonal β-lactam plus an aminoglycoside plus either a macrolide or a nonpseudomonal fluoroquinolone (12). In patients who have structural lung disease such as cystic fibrosis or severe chronic obstructive pulmonary disease (COPD), the IDSA recommends use of an antipseudomonal agent (piperacillin, piperacillin/tazobactam, a carbapenem, or cefepime)

and a fluoroquinolone (including high-dose ciprofloxacin) (2). For those patients with allergies to β-lactams, a fluoroquinolone with or without clindamycin is suggested. In patients with suspected aspiration pneumonia, the IDSA recommends a fluoroquinolone with or without clindamycin, metronidazole, or a β-lactam/β-lactamase inhibitor.

CONCLUSION

Diagnosis and treatment of CAP remain clinically challenging because it is difficult to determine the offending pathogen and because antimicrobial resistance continues to increase. A number of organizations have reviewed available scientific data, identified the strengths and weaknesses of existing data, and made diagnostic and therapeutic recommendations in the form of clinical practice guidelines. Given the increasing resistance of ***S. pneumoniae*** to macrolides and doxycycline, a respiratory fluoroquinolone may represent the best choice of therapy for outpatients. The various guidelines include a fluoroquinolone with enhanced activity against ***S. pneumoniae*** in their therapeutic choices for inpatients because of the increased incidence of drug-resistant ***S. pneumoniae***. To continue to provide the most effective treatment to patients, these guidelines will need to be revised as new data on diagnostic methods, antimicrobial susceptibility, and new antimicrobials become available.

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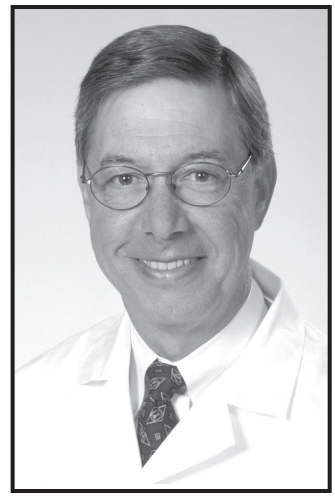

Dr. Joseph Dalovisio, MD, is Head of the Section on Infectious Diseases at Ochsner Clinic Foundation. He also is Clinical Professor of Medicine at Tulane University School of Medicine and at Louisiana State University School of Medicine, and Medical Director of Ochsner Home Health. Dr. Dalovisio is the Vice President of the Infectious Diseases Society of America.