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COMMUNITY-ACQUIRED PNEUMONIA

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INTRODUCTION

Community-acquired pneumonia (CAP) is an infection of the lung parenchyma acquired outside of hospitals or extended-care facilities. Even with the advent of and continuing advances in antimicrobial therapy, CAP remains a major health problem in the United States. It is the seventh leading cause of death in the United States, and the number one cause of death from infectious disease. Nearly 1 million hospitalizations with an estimated cost of $12 billion for therapy alone can be attributed to CAP.[1-3] These estimates do not factor in the associated costs of lost productivity, rehabilitation, and potential disability. Therefore, the health care and economic impact of CAP is readily evident.

Over the last 60 years, our armamentarium to battle pneumonia has expanded dramatically. This expansion in therapeutic options for CAP is driven by changes in the pathogenic organisms and the ever-evolving antimicrobial resistance acquired by these pathogens. This chapter provides an overview of CAP and recommendations for the use of the various antimicrobial agents available for its treatment.

PATHOPHYSIOLOGY

CAP development and prognosis is defined by the route of infection, host, and microbial factors. Identification of the offending organism in CAP is important to guide therapy and predict complications and outcomes. Unfortunately, even with extensive diagnostic evaluation, the etiologic agent is not identified in as many as 50% of patients.[4-16] For all patients presenting with CAP, *Streptococcus pneumoniae* is the most common pathogen isolated (Fig. 78-1) and accounts for 5% to 11% of CAP patients treated on an ambulatory basis, 5% to 43% of patients requiring hospitalization, and 11% to 38% of patients requiring intensive care unit (ICU) admission.[4,6,17,18] Other "typical" pathogens that account for CAP include the gram-negative coccobacillus *Haemophilus influenzae* and the gram-negative diplococcus *Moraxella catarrhalis*. The classically described "atypical" pathogens that cause CAP include *Chlamydia pneumoniae, Mycoplasma pneumoniae,* and *Legionella* species. The "atypical" moniker is an inaccurate description of the clinical features of the pneumonia associated with these organisms and is retained more as a classification than a specific descriptor of the disease process or clinical presentation. *Mycoplasma pneumoniae* has been shown to be the most common of the atypical pathogens and accounts for 17% to 37% of outpatient CAP and 2% to 33% of CAP requiring hospitalization.[4,6,18] *Chlamydia pneumoniae* is more common than *Legionella* species; however, *Legionella* species can lead to rapidly progressive and fatal pneumonia.

Although 90% or more of CAP can be explained by the previously mentioned organisms, other organisms can be encountered. In certain patient populations, aerobic gram-negative infections (*Pseudomonas aeruginosa*), enteric gram-negative infections, and anaerobic infections must be considered (see Box 78-1 later). Furthermore, it has recently been demonstrated that age greater than 65 alone is a specific epidemiologic risk factor for drug-resistant *S. pneumoniae* (DRSP), but not other organisms.[19,20] Of particular interest and concern in the last several years have been several reports of methicillin-resistant *Staphylococcus aureus* (MRSA) CAP. Traditionally, MRSA infection and/or pneumonia had been isolated to health care settings or high-risk groups such as intravenous drug abusers; however, since 2003, there have been several reports of severe, fulminant necrotizing MRSA pneumonia in young, healthy individuals without typical risk factors.[21,22] In addition, the clinician must also take into consideration any unusual exposure or occupational hazards that would predispose a patient to unusual pathogens such as *Chlamydia psittaci* (birds), *Coxiella burnetii* (ungulates), *Leptospira* species (rats), and *Francisella tularensis* (rabbits).

The mortality rate from CAP varies dramatically depending on the patient's severity of illness at presentation and underlying comorbid conditions. In the outpatient setting, the mortality rate is less than 1% to 5%; however, once patients require hospitalization, the mortality rate approaches 12%.[4-9] In more seriously ill patients with bacteremia who require ICU admission, the mortality rate can approach more than 40%.[10,11] The presence of underlying comorbid conditions such as chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus, renal insufficiency, congestive heart failure (CHF), coronary artery disease, malignancy, alcoholism, age greater than 70 years,

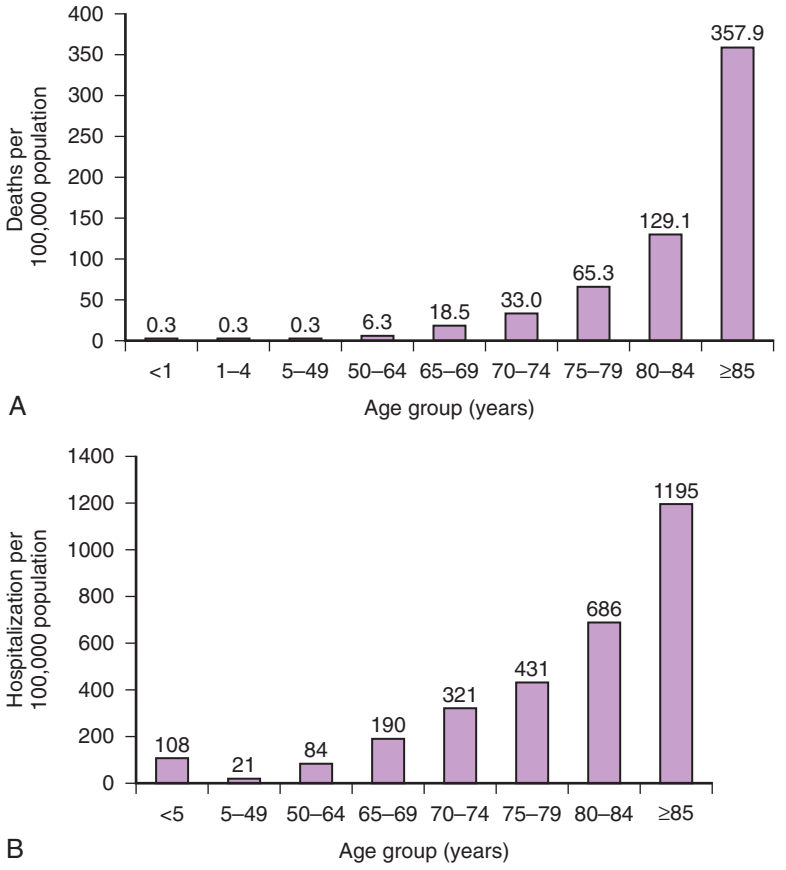

FIGURE 78-1 • Portable chest radiograph (**A**) and computed tomography scan (**B**) of patient with bacteremic multilobar pneumococcal pneumonia.

chronic neurologic disease, and/or chronic liver disease not only can contribute significantly to CAP mortality, but also may alter the etiologic organisms underlying the infection (Box 78-1).[12-14]

Risk Stratification and Treatment Setting

When CAP is strongly suspected on the basis of history, physical examination, and chest radiography, the next critical management decision is whether the patient will require hospital admission. The American Thoracic Society and Infectious Disease Society of America have defined four groups in their 2001 management of CAP consensus statement[3,23]:

1. Outpatients with no prior cardiopulmonary disease or modifying factors
2. Outpatients with cardiopulmonary disease (CHF or COPD) and/or other modifying factors (risk factors for specific organisms; see Box 78-1)
3. Inpatients, not admitted to the ICU, with or without cardiopulmonary disease or modifying factors
4. ICU-admitted patients with or without risk factors for *P. aeruginosa*

These stratification groups were defined by the expert panels in order to try to ensure adequate antimicrobial coverage of the most common organisms encountered in each group based on their risk factors and severity of illness. As discussed later in the section on Treatment Recommendations for CAP, there are specific organisms of concern for each group.

The difficulty with this stratification system is the lack of an objective quantification of severity of illness to predict if a patient needs inpatient versus outpatient care or general medical admission versus ICU admission. Therefore, more recently, many groups have attempted to apply multivariate analyses to patients' objective data to predict the need for admission and to ascertain their level of care. Two of the most

BOX 78-1 SPECIFIC PATHOGENS ASSOCIATED WITH UNDERLYING COMORBID CONDITIONS

Streptococcus pneumoniae
- Dementia
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Cerebrovascular disease
- Institutional overcrowding
- Seizures

Penicillin-resistant and drug-resistant *S. pneumoniae*
- Age > 65 years
- Alcoholism
- Immunomodulating illness or therapy (including corticosteroid therapy)
- Previous β-lactam therapy within 3 months
- Multiple medical comorbidities
- Exposure to child in day care center

Enteric gram-negatives
- Residence in a long-term care facility
- Underlying cardiopulmonary disease
- Recent antibiotic therapy
- Multiple medical comorbidities

Pseudomonas aeruginosa
- Broad-spectrum antibiotic treatment for >7 days in past month
- Structural lung disease (bronchiectasis)
- Corticosteroid therapy
- Malnutrition
- Undiagnosed human immunodeficiency virus infection
- Neutropenia

Legionnaires' disease (*Legionella* species)
- Acquired immunodeficiency syndrome
- Hematologic malignancy
- End-stage renal disease

TABLE 78-1 BRITISH THORACIC SOCIETY RESEARCH COMMITTEE PREDICTION RULE FOR COMMUNITY-ACQUIRED PNEUMONIA

Clinical Factor	Points
Confusion	1
Blood urea nitrogen > 19 mg/dl	1
Respiratory rate ≥ 30 breaths/min	1
Systolic blood pressure < 90 mm Hg *or* Diastolic blood pressure ≤ 60 mm Hg	1
Age ≥ 65 yr	1
Total points	
CURB-65 SCORE	
0	Low risk; consider outpatient treatment
1	
2	Short inpatient stay or closely supervised outpatient treatment
3	High risk; inpatient hospitalization and consider admission to intensive care unit
4 or 5	

TABLE 78-2 PNEUMONIA SEVERITY INDEX FOR COMMUNITY-ACQUIRED PNEUMONIA AS DEVELOPED BY PORT

Risk Factor	Points*
DEMOGRAPHIC	
Men	Age (yr):
Women	Age (yr) – 10:
Nursing home resident	+10
COMORBIDITIES	
Neoplasm	+30
Liver disease	+20
Congestive heart failure	+10
Stroke	+10
Renal failure	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate > 30 breaths/min	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 95° F or ≥ 104° F	+15
Pulse rate ≥ 125 beats/min	+10
LABORATORY AND RADIOGRAPHIC FINDINGS	
Arterial pH < 7.35	+30
Blood urea nitrogen > 30 mg/dl	+20
Sodium < 130 mmol/L	+20
Glucose ≥ 250 mg/dl	+10
Hematocrit < 30%	+10
Partial pressure of arterial oxygen < 60 mm Hg	+10
Pleural effusion	+10
Total points	

Total Points	Risk Class	Recommendation
<51	I	Outpatient therapy should be considered, especially Class I and II
51-70	II	
71-90	III	
91-130	IV	Inpatient hospitalization
>130	V	

*Total score is determined by beginning with the patient age and adding graded points based on objective data and findings. A risk class is then defined by the total of points to assist in determining severity of illness.

widely accepted prediction rules are the British Thoracic Society (BTS) Research Committee rule (Table 78-1) and the Pneumonia Patient Outcomes Research Team (PORT) rule (Table 78-2). Interestingly, these two prediction rules are meant to serve complementary roles as they attempt to identify different patients. The BTS rule aims to identify high-risk patients who require not only admission, but ICU admission; therefore, it is meant to prevent underestimation of severity of illness.[24,25] In contrast, the PORT rule separates patients into high and low risk of death and is meant to identify patients at low risk of death so as not to overestimate their severity of illness.[8] Many investigators have studied the role of these prediction rules in various settings and support the ability of these prediction rules to assist in the triage of patients with CAP,[26-29] while other studies reinforce that, while these prediction rules may have a role, clinicians still need to use their clinical judgment when stratifying patient care.[30]

CLINICAL PHARMACOLOGY AND THERAPEUTICS

Specific Pharmacologic Considerations for CAP

Antimicrobial agents are the cornerstone of treatment in patients with CAP. While a randomized, placebo-controlled study in patients with CAP has never been performed (nor is one likely to be performed), the overwhelming preponderance of evidence suggests that the timely administration of an antibiotic(s) to which the offending pathogens(s) are sensitive reduces the complications and improves the survival of patients with CAP. Following its discovery and introduction into clinical medicine, penicillin G was the drug of choice for CAP for almost half a century. However, with the recognition that pathogens other than *S. pneumoniae* may cause CAP and with the emergence of DRSP, penicillin G is no longer recommended in the management strategy of patients with CAP. Macrolides, quinolones, and second- and/or third-generation cephalosporins are now considered the antimicrobial agents of first choice in patients with CAP. As discussed later, the treatment recommendations depend upon the patient's comorbidities, risk stratification, and treatment setting.

Antimicrobial Resistance

Resistance to antibiotics has been an increasingly recognized problem in the therapy for CAP. Many factors contribute to resistance, including overutilization of antibiotics, patient comorbidities, and a higher percentage of the population residing in long-term care facilities. Since *S. pneumoniae* is the most common etiologic agent of CAP, resistance to this pathogen is a major concern and increasing problem. According to the Tracking Resistance in the US Today study in 2004 (TRUST-8), 19% to 25% of *S. pneumoniae* has in vitro resistance to penicillin and/or macrolides, 1.4% to ceftriaxone, and 1.1% to levofloxacin. The current definition of "intermediate-level" in vitro resistance to penicillin is a minimum inhibitory concentration (MIC) value of 0.12 mcg/ml, while "high-level" in vitro resistance is defined by MIC values of 2.0 mcg/ml.[31] Interestingly, when high-level penicillin resistance was

present, in vitro resistance to cefotaxime (42%), meropenem (52%), erythromycin (61%), and trimethoprim-sulfamethoxazole (92%) was also present.[32] A Centers for Disease Control and Prevention study has demonstrated that the breakpoint for clinically relevant resistance to penicillin is a MIC value of 4.0 mcg/ml.[33]

Significant controversy exists about the clinical relevance of these in vitro resistance patterns as few clinical failures (in the absence of meningitis) are documented, especially with macrolides and fluoroquinolones, which are commonly used to treat CAP in the outpatient setting. The unanswered question is whether continued use of these antibiotic classes for outpatient management of CAP will further push selection pressure and increase the virulence of these in vitro resistant organisms such that clinical treatment failures become more prevalent. Although the resistance patterns of *S. pneumoniae* appear to have changed the greatest, increased antimicrobial resistance is a universal phenomenon of all organisms associated with CAP. Moreover, it should be noted that resistance patterns vary considerably among geographic areas, and clinicians should be familiar with their local resistance patterns in order to adjust their therapeutic decisions accordingly.

Pulmonary Bioavailability of Antibiotics

The pulmonary vasculature and parenchyma filter the entire blood volume; however, not all antibiotics have the same degree of penetration into the lung parenchyma so as to achieve appropriate dose levels for adequate killing and prevention of resistance. With the development of the fluoroquinolones, effective high levels of lung penetration have been achieved without the development of resistance to treat even those patients with severe pneumonia using a single agent once a day (except those with risk factors for *P. aeruginosa*). In fact, levels of fluoroquinolones are greater in the epithelial lining fluid and alveolar macrophages than in serum.[34,35] These agents (levofloxacin, moxifloxacin, gatifloxacin) have excellent antipneumococcal activity as well as activity against gram-positive, gram-negative, and atypical pathogens; thus, they are ideal single agents for many patients, except those with severe CAP requiring ICU admission.

Macrolides are another highly effective class of antibiotics with excellent lung and alveolar macrophage penetration and good coverage for gram-positive and atypical organisms. As discussed previously, there has been increasing in vitro *S. pneumoniae* resistance to macrolides, which has many concerned about the clinical effectiveness of these agents in the years ahead.

Although vancomycin is not recommended for initial empirical therapy of CAP due to adequate antibiotic coverage of DRSP and methicillin-sensitive *S. aureus* with currently recommended agents, in the appropriate patient population (long-term care facility or young healthy individuals with aggressive pneumonia), failure of initial treatment should raise the suspicion of MRSA pneumonia. In these patients, vancomycin therapy has been considered the drug of choice, but recently the question of what constitutes adequate serum levels to provide appropriate lung penetration of vancomycin to treat MRSA has been raised.[36] In this setting, linezolid may have better penetration into lung tissue and be more active against MRSA.[37,38]

Time to First Dose of Antibiotics

Two retrospective analyses of large Medicare databases identified that the time between presentation to the hospital and the time to the first antibiotic dose (TFAD) is a predictor of patient outcome when patients require hospital admission. These studies demonstrated a 15% reduction in 30-day mortality when the TFAD was either 8 hours or a more stringent 4 hours.[39,40] Based on the findings in these two retrospective studies, the National Pneumonia Project of the Centers for Medicare & Medicaid Services has decided that patients (age > 65) who require hospitalization should receive antibiotics within 4 hours of hospital presentation as a quality-of-care benchmark for CAP. Many third-party payers have extrapolated these data to all patients presenting to the hospital with CAP and have begun to use it for hospital-level public reporting and "pay-for-performance" programs. Consequently, much controversy has arisen surrounding the benchmark of 4 hours to TFAD. Two recent prospective cohort studies of patients admitted to the hospital with CAP demonstrated that the delay to TFDA was strongly associated with altered mental status, absence of fever and/or hypoxia, lack of infiltrates on chest radiograph, and increasing age.[41,42] Since diagnostic uncertainty can be a barrier to TFAD, an excessive number of patients will be treated with antibiotics in order to comply with the TFAD 4-hour benchmark, thus leading to the potential for increased antibiotic resistance, costs, and adverse events. Investigators in this field believe that the benchmark should be applied to the population from which the data were derived—persons age 65 or older with radiographic evidence of CAP and no antibiotic pretreatment.[43]

With our understanding that early aggressive antibiotic therapy is one of the cornerstones in management of septic shock,[44] it seems intuitive that early recognition and antibiotic administration for CAP could improve outcomes; however, within what time frame and in what populations remain to be determined. This clearly will be an area of intense investigation and debate in the forthcoming years.

Intravenous Versus Oral Therapy and Duration of Therapy

The traditional therapeutic period for CAP had been 14 days of intravenous antibiotics until a study in 1996 demonstrated that 48 hours of intravenous antibiotic therapy followed by 12 days of oral therapy had similar outcomes to 14 days of intravenous therapy.[45] This study and several subsequent studies have confirmed that the conversion from intravenous to oral antibiotics decreases hospital length of stay, costs, and incidence of phlebitis and intravenous line infection without impacting on mortality or outcomes.[46,47] The improved pharmacokinetic profile of newer generation antibiotics due to their high degree of bioavailability, rapid gastrointestinal absorption, and equivalent blood and tissue levels regardless of oral or intravenous administration (particularly the antipneumococcal fluoroquinolones) has enhanced the ability to treat patients with moderate to moderately severe CAP with oral therapy. In fact, several studies have demonstrated that short-course high-dose therapy with antibiotics has equivalency to traditional antibiotic regimens with better patient compliance, less cost and fewer adverse events, and a possible reduction in selection pressure for resistance.[48-51]

Interestingly, in a recent randomized trial in the Netherlands, patients with mild to moderately severe CAP were randomized to 3 days versus 8 days of high-dose ampicillin therapy. There was no difference in clinical success rate or radiographic success at day 10 or day 28 between the two groups.[52] Consequently, patients with mild to moderately severe CAP requiring hospitalization can likely be treated for much shorter durations than the traditional 7- to 10-day time period without an impact on patient outcomes. These shorter durations of therapy would surely represent cost savings, reduce the number of adverse events, and decrease the selection pressure for antibiotic resistance. The conversion from the traditional 2-week treatment period to much shorter time frames will give some clinicians trepidation of treatment failure, but the data have not demonstrated differences in outcome. Therefore, as more data become available, clinicians should strongly reconsider shorter treatment courses for CAP.

Treatment Recommendations for CAP

Outpatients without Prior Cardiopulmonary Disease or Modifying Factors

In this patient population without underlying cardiopulmonary disease, and no risk factors for DRSP, aspiration, or enteric gram-negative organisms (see Box 78-1), the most likely pathogens are *S. pneumoniae*, atypical pathogens, respiratory viruses, and possibly *H. influenzae* (especially in smokers). For these patients, initial therapy with an advanced-generation macrolide (azithromycin or clarithromycin) is optimal, with doxycycline as a second choice if patients are intolerant of or allergic to macrolides (Table 78-3). Advanced-generation macrolides are preferred over erythromycin due to fewer gastrointestinal side effects and less frequent dosing, which may improve patient compliance. Although an antipneumococcal fluoroquinolone would be equally effective, use of one of these agents in this

TABLE 78-3 OUTPATIENTS WITHOUT CARDIOPULMONARY DISEASE OR MODIFYING RISK FACTORS

Organisms	Recommended Therapy
Streptococcus pneumoniae *Mycoplasma pneumoniae* *Chlamydia pneumoniae* *Haemophilus influenzae* *Legionella* spp. Respiratory viruses *Mycobacterium tuberculosis* Endemic fungi	Advanced-generation macrolide: azithromycin or clarithromycin *or* Doxycycline

TABLE 78-4 OUTPATIENT WITH CARDIOPULMONARY DISEASE AND/OR MODIFYING FACTORS

Organisms	Recommended Therapy
Streptococcus pneumoniae (including DRSP) *Mycoplasma pneumoniae* *Chlamydia pneumoniae* Mixed infection (bacteria plus atypical pathogen or virus) *Haemophilus influenzae* Enteric gram-negatives Respiratory viruses *Moraxella catarrhalis, Legionella* spp., aspiration, *Mycobacterium tuberculosis*, endemic fungi	β-Lactam (oral cefpodoxime, cefuroxime, high-dose ampicillin, amoxicillin-clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime) ***plus*** Macrolide or doxycycline *or* Antipneumococcal fluoroquinolone alone

TABLE 78-5 INPATIENTS NOT REQUIRING INTENSIVE CARE UNIT ADMISSION

Organisms	Recommended Therapy
A. No cardiopulmonary disease or modifying factors	
Streptococcus pneumoniae *Haemophilus influenzae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae* Mixed infection (bacteria plus atypical pathogen) Respiratory viruses *Legionella* spp. Miscellaneous (*Mycobacterium tuberculosis*, endemic fungi)	Intravenous (IV) azithromycin alone If macrolide allergic: doxycycline ***and*** a β-lactam *or* Antipneumococcal fluoroquinolone alone
B. Cardiopulmonary disease and/or modifying factors	
S. pneumoniae (including DRSP) *H. influenzae* *M. pneumoniae* *C. pneumoniae* Mixed infection (bacteria plus atypical pathogen) Enteric gram-negatives Aspiration (anaerobes) Respiratory viruses *Legionella* spp. Miscellaneous (*M. tuberculosis*, endemic fungi)	IV β-Lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, high-dose ampicillin) ***plus*** IV or oral macrolide or doxycycline *or* IV antipneumococcal fluoroquinolone alone

low-risk patient population is likely unnecessary and may promote selection pressure for resistance.

Outpatients with Cardiopulmonary Disease and/or Modifying Factors

Although these patients are at risk for the usual CAP pathogens, they are at increased risk for CAP due to DRSP, enteric gram-negatives, and aspiration; consequently, the empirical coverage of CAP in these patients must be adjusted accordingly to take these organisms into consideration (Table 78-4). An oral β-lactam agent may be used in combination with an advanced-generation macrolide (or doxycycline if the patient is intolerant of macrolides) in these patients. The oral β-lactam agent is chosen to be effective against DRSP (MIC = 2 mg/L), but should be administered at high doses to overcome drug resistance. Options for β-lactam agents include cefuroxime or cefpodoxime, high-dose ampicillin (1 g every 8 hours), or amoxicillin-clavulanate (2 g twice daily). Alternatively, a more appealing choice for these patients with risk factors for DRSP is the new-generation antipneumococcal fluoroquinolones. Due to the very low incidence of resistance of these agents to DRSP and their once-daily administration, patient compliance and cost may be reduced compared to the combination of a β-lactam agent and a macrolide. Moreover, if the patient has risks for aspiration or resides in a long-term care facility, coverage for anaerobes should be considered with amoxicillin-clavulanate or amoxicillin with a macrolide. If anaerobes are documented or a lung abscess is present, clindamycin or metronidazole should be incorporated into the regimen.

Inpatients without Cardiopulmonary Disease or Modifying Factors

This category of patients likely represents a small population as most patients without cardiopulmonary disease or modifying factors likely can be treated effectively on an outpatient basis. The most common organisms in this group are similar to those of the outpatient without cardiopulmonary disease: *S. pneumoniae*, atypicals, *H. influenzae*, and respiratory viruses (Table 78-5). If the severity of illness entails hospitalization (not to an ICU), these patients are effectively treated with intravenous azithromycin alone at 500 mg daily for 2 to 5 days followed by oral therapy at 500 mg daily for a total of 7 to 10 days.[53,54] If the patient is intolerant of macrolides due to adverse events, then therapy should be initiated with doxycycline and a β-lactam or an antipneumococcal fluoroquinolone.

Inpatients with Cardiopulmonary Disease and/or Modifying Factors

Therapy for these patients should include coverage for DRSP and enteric gram-negatives as this population is at risk for these pathogens. Similar to outpatients with similar risk factors, therapy with a β-lactam agent and macrolide can be initiated (see Table 78-5). The β-lactam agent should be administered at the high dose level discussed earlier to ensure adequate coverage of DRSP. A macrolide is added to cover atypical pathogens and can be administered orally or intravenously depending on the severity of illness. Doxycycline is the alternative if the patient is intolerant of macrolide therapy. Similar to outpatients with DRSP risk factors, an alternative to the β-lactam–macrolide regimen is to use an antipneumococcal fluoroquinolone alone. Once again, the fluoroquinolones simplify the regimen to once daily and may improve compliance and decrease costs. If the patient has risk factors for aspiration or lives in a long-term care facility, coverage for anaerobes should be considered with the addition of ampicillin-sulbactam, high-dose ampicillin, or other active β-lactams. The documentation of anaerobes or the presence of a lung abscess should prompt the addition of clindamycin or metronidazole to the regimen.

Inpatients Requiring ICU Admission and without Pseudomonas aeruginosa Risk Factors

Patients with severe CAP with admission to the ICU should have therapy directed against *S. pneumoniae*, *H. influenzae*, and *Legionella* and other atypicals, but stratification based on risk factors for *P. aeruginosa* infection must be considered (Table 78-6). If no *P. aeruginosa*

TABLE 78-6 INTENSIVE CARE UNIT–ADMITTED PATIENTS

Organisms	Recommended Therapy
A. No *Pseudomonas aeruginosa* risk factors	
Streptococcus pneumoniae (including DRSP) *Legionella* spp. *Haemophilus influenzae* Enteric gram-negative bacilli *Staphylococcus aureus* *Mycoplasma pneumoniae* Respiratory viruses Miscellaneous (*Chlamydia pneumoniae, Mycobacterium tuberculosis*, endemic fungi)	Intravenous (IV) β-lactam (cefotaxime, ceftriaxone) ***plus either*** IV macrolide (azithromycin) *or* IV fluoroquinolone
B. *Pseudomonas aeruginosa* risk factors	
All of the above organisms plus *P. aeruginosa*	Selected IV antipseudomonal: β-lactam (cefepime, imipenem, meropenem, piperacillin-tazobactam) ***plus*** IV antipseudomonal quinolone (ciprofloxacin) *or* Selected IV antipseudomonal: β-lactam ***plus*** IV aminoglycoside ***plus*** either IV macrolide or IV nonpseudomonal fluoroquinolone

risk factors are present, initial therapy with a β-lactam active against DRSP in combination with either azithromycin or a fluoroquinolone should be instituted. The β-lactam agent that is chosen should have activity against DRSP (cefotaxime, ceftriaxone, ampicillin-sulbactam), but those β-lactam agents that also have antipseudomonal activity (cefepime, piperacillin-tazobactam, imipenem, meropenem) are not recommended for primary treatment when *P. aeruginosa* is not suspected.

If *P. aeruginosa* risk factors are present, therapy should always include two agents with antipseudomonal activity and also cover DRSP and *Legionella* species. Therapeutic options include select β-lactams (cefepime, piperacillin-tazobactam, imipenem, meropenem) plus an antipseudomonal quinolone (ciprofloxacin), or select β-lactams with an aminoglycoside plus either azithromycin or a nonpseudomonal fluoroquinolone. If the patient has *P. aeruginosa* risk factors and is β-lactam allergic, aztreonam can replace the β-lactam agent and should be combined with an antipneumococcal fluoroquinolone and an aminoglycoside.

Special Considerations

Community-Acquired MRSA Pneumonia

As mentioned previously, an increasing incidence of community-acquired MRSA infection has been reported throughout the country. Although this clearly represents a small number of patients with CAP, it tends to affect young, healthy individuals with devastating effects. Therefore, in the appropriate patient population—a resident of a long-term care facility; a young, healthy person with rapidly progressive necrotizing pneumonia; or a person with a post–influenza syndrome pneumonia—serious consideration should be given to the addition of vancomycin or linezolid to cover MRSA, especially if there is minimal to no clinical response to initial treatment. With recent reports clearly documenting the increasing incidence of MRSA cutaneous infections,[55] it is likely that MRSA CAP will become more prevalent, and clinicians must be aware of the possibility of this organism as a community-acquired pathogen.

Health Care–Associated Pneumonia

Patients who develop pneumonia in the setting of an acute or chronic health care facility must be distinguished from those who develop pneumonia in the community; the former patients are referred to as having health care–associated pneumonia, which includes hospital-acquired pneumonia and ventilator-associated pneumonia. This distinction is important as these patients are at high risk of having infection with MRSA and multidrug-resistant (MDR) bacterial pathogens. The MDR pathogens include *P. aeruginosa*, extended-spectrum β-lactamase–producing *Klebsiella pneumoniae, Acinetobacter baumanii, Enterobacter* species, and *Enterococcus* species.[56] Health care–associated pneumonia contributes significantly to morbidity, length of hospitalization, increased health care costs, and increased mortality. Early broad-spectrum antimicrobial coverage with multiple antibiotics is recommended in these patients, with de-escalation once the implicated pathogen has been identified. In general, this requires the combination of an antipseudomonal cephalosporin (cefepime, ceftazidime), carbapenem (imipenem, meropenem), or penicillin (piperacillin-tazobactam) plus either an antipseudomonal fluoroquinolone or an aminoglycoside.

Supportive and Emerging Therapies for CAP

Supplemental oxygen is usually required for those patients with CAP admitted to a hospital. The oxygen saturation of these patients should be closely followed. Patients with CAP who progress to develop severe sepsis and septic shock will require resuscitation with intravenous fluids and vasopressor agents. Drotrecogin alfa activated (activated protein C) should be considered in patients with CAP who develop organ failure or septic shock. The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study demonstrated a reduction in 28-day all-cause mortality in patients with CAP and severe sepsis who were treated with this agent.[57]

The role of corticosteroids in patients with severe CAP is controversial. Confalonieri and colleagues, in a small randomized, placebo-controlled study, demonstrated that hydrocortisone given as a bolus of 200 mg followed by an infusion of 10 mg/hr for 7 days reduced the complication rate and mortality in patients with severe CAP.[58] Additional studies are required to determine the role of corticosteroids and other immunomodulating agents in the management of patients with severe CAP.

CONCLUSIONS

Community-acquired pneumonia is the leading cause of infectious mortality in the United States. Recognition of the clinical syndrome consistent with pneumonia, assessing patients' risk factors for specific organisms, determining their medical comorbidities, and evaluating their severity of illness will allow the clinician to ascertain pertinent pathogens and choose appropriate empirical coverage for CAP. Clinicians should have an understanding of their local resistance patterns as this may alter the empirical coverage chosen. When and if specific pathogens are isolated, empirical coverage should be de-escalated as guided by microbiologic data to maximize kill and minimize the development of resistance. Due to the evolution of existing infectious pathogens and newly discovered pathogens (e.g., that causing severe acute respiratory syndrome), the recommendations included herein will invariably change with time to address these factors.

As our armamentarium for the treatment of CAP has rapidly evolved over the last 60 years since the discovery of penicillin, so has the ability of the bacterial pathogens evolved to develop resistance mechanisms to thwart the effectiveness of these new antibiotics. Therefore, judicious use of antibiotics to cover appropriate organisms for each individual patient will minimize the risk of developing resistance. In this manner, it is hoped the medical profession can offer curative therapy to all patients with CAP and continue to decrease morbidity and mortality from "the old man's friend."

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