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Antimicrobial Treatment of Community-Acquired Pneumonia

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Community-acquired pneumonia (CAP) is the sixth leading cause of death overall and the most common cause of death from infectious disease in the United States [1,2]. Approximately one-half million patients are hospitalized each year in the United States for the treatment of CAP [3]. Based on their clinical condition, patients are admitted to medical wards or, if severely ill, to the intensive care unit. Intensive care unit patients carry the highest mortality rates of all patients with CAP [4]. The guidelines of the American Thoracic Society (ATS) [4], the European Respiratory Society [5,6], the Canadian Infectious Diseases Society and the Canadian Thoracic Society [7], the Infectious Diseases Society of America (IDSA) [8,9], and the Centers for Disease Control and Prevention [10] agree that patients with CAP who are admitted to the hospital represent a major concern and suggest that specific empiric therapy be instituted as early as possible to improve clinical outcomes. This article reviews the current literature related to patients hospitalized for CAP, the criteria for hospital and intensive care unit admission, and the empiric and specific antibiotic therapeutic regimens.

Epidemiology

Severe CAP is defined as a clinical syndrome that develops in patients who have pneumonia that requires hospitalization in a ward or intensive care unit [4]. There are 1 million hospitalizations annually owing to CAP in the United States, with a cost of approximately 9 billion dollars per year [11]. Approximately 10% of all hospitalized patients require intensive care unit admission [12–14]. Hospitalized patients with CAP are at risk for significant mortality depending on the severity of illness. Several studies have reported a mortality rate of approximately 10% for hospitalized ward patients and a rate of 30% to 60% for patients who require intensive care unit admission [4]. A meta-analysis of published clinical studies that evaluated short-term mortality in hospitalized CAP patients reported a 5.1% mortality rate for ambulatory or ward hospital patients and a 36.5% mortality rate for patients treated in an intensive care unit [15].

The most important determinants for hospitalization and the assessment of severity in CAP are the patient's chronic comorbid conditions or prior antibiotic use [4,8,9,16–20]. Prior antibiotic use has been defined in CAP clinical practice guidelines as the use of any antibiotic regimen in the past 3 months. Such use is associated with increased risk of morbidity and mortality [8]. The most common comorbid illnesses are chronic obstructive pulmonary disease, which is present in as many as half of these patients, followed by alcoholism, chronic heart disease, and diabetes

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mellitus [4,8,9,16–20]. Other comorbid associated conditions include renal failure, neurologic disease, malnutrition, hepatic disease, bacteremia, a smoking history, and gross aspiration [16–22]. Approximately one third of patients with CAP were previously healthy [20]. Elderly and nursing home patients are at significant risk for CAP and have high mortality rates, although some experts consider pneumonia occurring in nursing home patients to be hospital-acquired pneumonia owing to the similarities in the etiologic pathogens [23]. The main causes of death in patients with severe CAP include refractory hypoxemia, refractory shock, and other pneumonia-related complications, predominantly multiorgan failure [24–26]. Mortensen et al [27] evaluated the causes of death and the timing and risk factors associated with pneumonia-related and pneumonia-unrelated mortality for patients with CAP within 90 days of presentation. Pneumonia-related death was 7.7 times more likely to occur within 30 days of presentation when compared with pneumonia-unrelated mortality. The prognosis beyond 45 days was influenced by the patient's age, sex, and other significant comorbid conditions [27].

Severity assessment and criteria for hospital and intensive care unit admission

One of the most critical decisions for physicians treating a patient with CAP is whether to hospitalize the patient in ward or intensive care unit service [28]. This decision is usually made in the outpatient office or emergency department and has implications for the antibiotic class selection, route, and duration of therapy.

Several studies have developed prediction rules to determine the site of care for patients with CAP based on the severity of illness [29–32]. Fine and colleagues [29] developed a pneumonia-specific severity of illness (PSI) score as part of the pneumonia Patient Outcome Research Team Study (PORT). The primary goal of the PSI was to identify low-risk patients who might be managed safely at home. The 20 parameters include three demographic variables, five comorbid conditions, five physical examination findings, and seven laboratory/imaging results. For each variable present, points are added to the score, and the final score is then divided into five risk classes. Patients in risk classes I to III are at low mortality risk, with a rate less than 1%, and can be managed as outpatients. Patients with a risk classification of IV have a 9% mortality rate, and class V patients have a 27% mortality rate [29]. The study suggested that patients

in classes IV and V might require hospitalization. In a follow-up study, the same investigators suggested a three-step process to decide the initial site of CAP treatment based on (1) an assessment of pre-existing conditions that compromise the safety of home care, (2) calculation of the PSI score, and (3) clinical judgment [33].

To evaluate the safety of the PSI, Marrie et al conducted a randomized controlled study using a critical pathway for the management of pneumonia. Nine hospitals in the critical pathway group were compared with 10 hospitals in the conventional management group at 19 Canadian teaching and community hospitals [30]. The PSI score was used to assist with the site of care decision. Implementation of a critical pathway that included the PSI score resulted in a reduced use of institutional resources (fewer bed days per patient managed and a decrease in the admission of low-risk patients), with no differences in the rates of acute complications, re-admission, or mortality.

There is no consensus regarding accepted criteria for the definition of severe CAP or for patients requiring intensive care unit admission. A set of seven clinical criteria was recommended in 1993 by the ATS guidelines [30,34]. A follow-up study by Ewig et al suggested a modified ATS criteria set to define severe CAP. These investigators included the presence of two of three minor criteria ($\text{PaO}_2/\text{FiO}_2$ ratio < 250 , bilateral pneumonia or multilobar infiltrates, and systolic blood pressure < 90 mm Hg) or one of two major criteria (need for mechanical ventilation, or septic shock or the need for vasopressors for more than 4 hours) [32]. These criteria have been adopted in the more recent ATS guidelines for patients with severe CAP [4]. Cordero and colleagues [35] validated the ATS severity criteria in HIV-infected patients.

The British Thoracic Society (BTS) published a rule that identified severely ill patients based on three criteria—an increased respiratory rate, increased blood urea nitrogen, and decreased blood pressure—and later converted this rule to include four criteria by adding mental status changes [36]. Subsequently, a new prediction rule was studied based on the modified BTS rule. This rule was called CURB (Confusion, blood Urea nitrogen > 7 mmol/L, Respiratory rate ≥ 30 /minute, and low systolic [< 90 mm Hg] or diastolic [< 60 mm Hg] Blood pressure) [37,38]. Age greater than 65 years was independently associated with a poor outcome and was added to create a six-level CURB-65 score. A similar score with blood urea nitrogen omitted was created to apply this rule to the outpatient setting [39]. This score, CRB-65, is a five-level score correlating with

mortality, allowing the identification of patients at low, intermediate, and high risk of death [39].

Angus et al [40] compared different sets of criteria and predictors using the pneumonia PORT database and found that the currently recommended criteria carried only a modest value level of reliability. The individual scoring systems evaluated included the initial ATS (published in 1993) [34] and revisited [32], the BTS [36], and the PSI score [29,40]. The most recent ATS criteria rule published in 2001 was the best discriminator of intensive care unit admission and the need for mechanical ventilation (area under the receiver-operating characteristic curve of 0.68 and 0.74, respectively), but none of the prediction rules was particularly good. The PSI score was the best predictor of medical complications and death (area under the receiver-operating characteristic curve of 0.65 and 0.75, respectively) [40]. Severity assessment criteria are useful to help physicians identify patients who may need hospitalization or intensive care unit admission, but they are not meant to remove physicians' clinical judgment in the decision-making process.

Antimicrobial treatment

Treatment guidelines have been developed by several professional organizations to standardize therapy for CAP, including for patients who have severe CAP [4,7–10]. The published practice guidelines reflect the evolution of expert opinion, changes in resistance patterns, and the availability of new clinical data regarding the treatment and diagnosis of CAP in immunocompetent adults. All of these guidelines support the concept that the treatment of hospitalized patients with CAP should be focused on the possible associated etiologic agents [4,8,9]. Early and aggressive therapeutic approaches are the

main interventions to decrease mortality in patients with CAP.

Empiric treatment with combination antimicrobial therapy should be initiated preferably within the first 4 hours of presentation and at least in the first 8 hours of admission [26,41]. Earlier administration of antibiotics is associated with improved survival and is currently considered an important parameter to assess the process of care of this disease [26,41]. Houck et al reported that antibiotic administration within 4 hours of arrival was associated with decreased mortality and length of stay among a random sample of older inpatients with CAP who had not received antibiotics as outpatients [41]. Empiric therapy should be directed against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and gram-negative bacilli with beta-lactam medications or new respiratory fluoroquinolones. *Legionella* spp (and other atypical pathogens) should be covered with a macrolide or a fluoroquinolone [4,7–9]. Mixed infections with typical and atypical pathogens occur in approximately 10% to 20% of cases and should always be considered to ensure that patients are treated with appropriate empiric antimicrobial therapy [4,7–9]. In cases in which the infecting pathogen can be identified, directed therapy should be employed [4,7–9]. In all clinical series, approximately 40% to 70% of patients with CAP have no pathogen identified [18,21,42]. The failure to identify a pathogen has not been associated with a worse outcome, but the empiric regimen should cover *S pneumoniae* and atypical pathogens [12,13].

The most common empiric antibiotic regimen suggested for patients with CAP and receiving ward service includes a third-generation cephalosporin in combination with a macrolide or fluoroquinolone (Table 1) [4,7–9]. In a retrospective record review of 12,945 Medicare inpatients (aged 65 years or older),

Table 1
Empiric antimicrobial therapy to treat community-acquired pneumonia in the ward service

Empiric treatment	Comments
Intravenous fluoroquinolone monotherapy (levofloxacin, gatifloxacin, or moxifloxacin) or Intravenous beta-lactam third-generation cephalosporins (ceftriaxone or cefotaxime) or Beta-lactam/beta-lactamase inhibitor (ampicillin-clavulanate) plus Intravenous macrolide (azithromycin)	Covers well <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , enteric gram-negative bacilli (<i>Klebsiella</i> spp) Fluoroquinolones also cover these pathogens, including DRSP. <i>Legionella</i> spp, <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , and <i>Chlamydia psittaci</i>

Abbreviation: DRSP, drug-resistant *S pneumoniae*.
Adapted from Refs. [4,7–10]; with permission.

Gleason et al [43] showed that initial treatment of CAP with a second-generation cephalosporin plus a macrolide, a non-antipseudomonal third-generation cephalosporin plus a macrolide, or a fluoroquinolone alone was independently associated with lower 30-day mortality in patients with PSI classes IV and V. Burgess and Lewis [44] performed a retrospective evaluation of 213 hospitalized (not in the intensive care unit) patients with CAP and concluded that the addition of a macrolide to a non-antipseudomonal third-generation cephalosporin as initial therapy for the treatment of CAP may not be necessary. Nevertheless, other reports suggest that the use of a combination regimen with a macrolide or a fluoroquinolone alone is associated with a better outcome than the use of a beta-lactam alone [45–48].

Oosterheert et al published a systematic review of the use of empiric therapy for hospitalized patients with CAP [46]. They reviewed eight nonexperimental cohort studies, one prospective study, and no randomized controlled trials. Six studies demonstrated a significant reduction in mortality with the use of a fluoroquinolone as monotherapy or a combination of beta-lactams and macrolides. Only one study showed a reduction in hospital length of stay [46]. The suggested benefit of having a macrolide might occur owing to the coverage of unrecognized atypical pathogens, possible anti-inflammatory effects, or coverage of resistant pathogens.

Clinical practice guidelines suggest that patients with severe CAP who are admitted to the intensive care unit should be stratified as to whether they are at risk for *Pseudomonas* spp infection [4,8]. If a patient has no risk factors for pseudomonas infection, the treatment should always include two antibiotics—one that will cover pneumococcus (including drug-resistant isolates) and another that will cover atypical pathogens, especially *Legionella* spp (Table 2). Patients with risk factors for *P aeruginosa* who are admitted to the intensive care unit require specific attention and should receive appropriate antipseudomonal agents (see Table 2).

The authors and their colleagues performed a systematic review to determine the benefit of using combination therapy versus monotherapy in patients with severe CAP who were admitted to an intensive care unit [49]. Only four studies met predefined inclusion criteria: one randomized control trial and three cohort studies. The methods used to determine the severity of illness varied. Two studies (one randomized control trial and one cohort study) used the ATS severity criteria, and two cohort studies used the PSI score. The only randomized control trial had a much lower mortality rate than the other studies and used an unusual antimicrobial combination therapy (beta-lactam versus teicoplanin plus ciprofloxacin) that is not one of the recommended regimens put forth by the different clinical guidelines. It

Table 2

Empiric antimicrobial regimen to treat severe community-acquired pneumonia in the intensive care unit

Empiric treatment	Comments
Intravenous beta-lactam Third-generation cephalosporins (ceftriaxone or cefotaxime) or Beta-lactam/beta-lactamase inhibitor (ampicillin-clavulanate or piperacillin-tazobactam) plus either Intravenous macrolide (azithromycin) or Intravenous fluoroquinolone (levofloxacin, gatifloxacin, or moxifloxacin)	Covers well <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , enteric gram-negative bacilli (<i>Klebsiella</i> spp) Fluoroquinolones also cover these pathogens, including DRSP. <i>Legionella</i> spp, <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> , and <i>Chlamydia psittaci</i>
Intravenous beta-lactam Antipseudomonal beta-lactam/beta-lactamase inhibitor (cefepime, piperacillin-tazobactam, imipenem, meropenem) plus either Intravenous aminoglycoside or intravenous ciprofloxacin plus Intravenous macrolide (azithromycin) if aminoglycoside used, but not with the use of ciprofloxacin	<i>Pseudomonas aeruginosa</i> (and the other pathogens above)

Abbreviation: DRSP, drug-resistant *S pneumoniae*.

Adapted from Refs. [4,7–10]; with permission.

was concluded that the limited number of studies of antimicrobial therapy in patients with severe CAP are heterogeneous and contain limited information to compare the differences in mortality for patients with severe CAP treated with combination therapy versus monotherapy [49].

Specific antimicrobial therapy

S pneumoniae is isolated in as many as one-third of all ward and intensive care unit patients [16–19, 21,24,35,42]. Several studies published by Moroney et al [50], Kalin et al [51], and Metlay et al [52] evaluated clinical outcomes in patients with bacteremic pneumococcal pneumonia. Antimicrobial resistance in bacteremic *S pneumoniae* showed no contribution to mortality or the requirement for intensive care unit admission but may have been associated with an increased risk of adverse outcome such as suppurative complications of infection (eg, empyema) [50–52]. Waterer et al [53] found that single-effective drug therapy for severe bacteremic pneumococcal pneumonia was associated with a greater risk of death than was dual-effective therapy. Two other studies suggested a benefit of having a macrolide added to the beta-lactam therapy in patients with bacteremic pneumococcal pneumonia [54,55]. Not adding a macrolide to a beta-lactam-based initial antibiotic regimen was an independent predictor of in-hospital mortality [54]. Concerns regarding drug-resistant *S pneumoniae* therapy are discussed elsewhere in this issue.

H influenzae therapy depends on the production of beta-lactamases; if these enzymes are not present, amoxicillin should be appropriate. The microbial production of beta-lactamases requires the use of a third-generation cephalosporin, beta-lactam/beta-lactamase inhibitors, or a fluoroquinolone. Alternative agents include the newer macrolides such as clarithromycin or azithromycin, or doxycycline. Enterobacterias are managed with a third-generation cephalosporin, beta-lactam/beta-lactamase inhibitors, or a fluoroquinolone.

In the past several years, a change in the clinical presentation of *Staphylococcus aureus* has emerged, especially the emergence of community-acquired strains that are methicillin resistant. This microorganism should be treated with vancomycin or linezolid as an alternative.

The preferred antimicrobial agents for atypical microorganisms such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* spp

are fluoroquinolones, macrolides, or doxycycline. Macrolides or tetracyclines are preferred for infections caused by *Coxiella burnetii* or *Chlamydia psittaci* [4,7–9].

Viral pneumonias resulting in community outbreaks of influenza, respiratory syncytial virus, and parainfluenza can be life threatening in elderly and immunocompromised patients [18,20,21,24,56]. Influenza pneumonia may be complicated by direct involvement of the lung parenchyma or by secondary bacterial infection caused by *S pneumoniae*, *S aureus*, *H influenzae*, or other gram-negative pathogens [8, 57]. Amantadine or rimantadine are useful for patients with influenza A. The newer agents oseltamivir or zanamivir cover influenza A or B [8]. Patients infected with “Sin Nombre” Hantavirus may present with acute respiratory failure requiring intensive care unit admission and mechanical ventilation [58]. This condition is associated with a high mortality rate, and only supportive therapy is available [58]. Recently, two other pathogens have been described as being associated with severe CAP: SARS coronavirus and metapneumovirus [59,60].

P aeruginosa has been reported in patients with severe CAP who have specific risk factors, such as chronic or prolonged use of broad-spectrum antibiotic therapy, bronchiectasis, malnutrition, HIV, and immunosuppression [4,18,35,61,62]. Specific treatment includes an intravenous antipseudomonal beta-lactam/beta-lactamase inhibitor plus intravenous aminoglycoside or intravenous ciprofloxacin, plus an intravenous macrolide if aminoglycoside used, but not with the use of ciprofloxacin (see Table 2).

Other organisms described as possible pathogens, including the endemic fungi, *Mycobacterium tuberculosis*, and *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia, deserve mention herein, although they are usually excluded from CAP guidelines [4, 7–9]. These pathogens should be suspected in immunocompromised patients and in certain endemic areas and require specific antifungal and antituberculous therapy.

Aspiration pneumonia owing to anaerobic infections should be treated with carbapenems, clindamycin, or beta-lactam/beta-lactamase inhibitors [63].

Duration of therapy

Generally, the duration of therapy in patients with severe CAP is 7 to 10 days, but patients with atypical pathogens such as *Legionella* spp should receive longer treatment for 10 to 14 days [4]. Several studies

report the use of a critical pathway to improve the treatment of patients with CAP, including those with severe disease [64–69].

Antimicrobial treatment failure or nonresolving pneumonia is usually underestimated and is discussed elsewhere in this issue. The most common causes include microbial resistance to the initial antimicrobial regimen, suppurative complications, or the presence of nosocomial pneumonia [70].

After the initial clinical improvement, hospitalized patients should be switched from intravenous to oral antibiotic therapy while maintaining similar antimicrobial coverage and tissue concentrations as with the parenteral form. Criteria for determining when the patient can make the transition to oral antibiotics include the ability to tolerate antibiotics by mouth, a functioning gastrointestinal tract, a stable blood pressure, a change toward normalization of the white blood cell count, and improving symptoms such as cough, dyspnea, and fever [71–73]. A meta-analysis by Rhew et al evaluated early intravenous to oral conversion and discharge strategies in patients with CAP. The findings suggested that these interventions are associated with a significant and safe reduction in the mean length of hospital stay [71].

Several of the quality indicators already mentioned, including the early administration of antibiotics, appropriate antibiotic use following clinical practice guidelines, use of a critical pathway, and a switch to oral therapy and early discharge, all show improved clinical outcomes in CAP [4,8,9]. In addition, measures directed at prevention, such as vaccination for pneumococcal and influenza infections, and counseling to quit smoking for patients at risk may help to decrease the incidence of CAP [4,8,9]. Other important processes of care include the collection of blood cultures before antibiotic administration or in the first 24 hours, a test for legionella infections in intensive care unit patients, and an evaluation of oxygenation (measurement of blood gases or pulse oximetry).

Summary

CAP is a life-threatening condition that requires hospitalization and, in 10% to 20% of patients, intensive care unit admission. Underlying comorbid conditions (most commonly, chronic obstructive pulmonary disease, alcoholism, chronic heart disease, and diabetes mellitus) are frequently seen in this group of patients. The most common etiologic agents found in CAP are *S pneumoniae*, *Legionella* spp, and gram-negative rods (especially *Klebsiella pneumo-*

niae and *P aeruginosa* in intensive care unit patients with risk factors [eg, bronchiectasis]), although half of cases lack a specific etiologic diagnosis.

The early and rapid initiation of empiric antimicrobial therapy concordant with recommended clinical practice guidelines should be based on an epidemiologic approach, possible etiologic agents, and the severity of illness. Initial antimicrobial therapy should consist of an antipneumococcal fluoroquinolone alone or an intravenous beta-lactam antibiotic plus a macrolide for hospitalized patients. An intravenous beta-lactam antibiotic plus a macrolide or antipneumococcal fluoroquinolone should be provided for intensive care unit patients without risk of having pseudomonas. Antipseudomonal therapy is indicated in patients with risk factors for pseudomonas who are admitted to the intensive care unit. Modification of the initial regimen should be considered once specific pathogens have been identified. The optimal management of patients hospitalized with CAP requires further research and re-evaluation as new data are available.

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