Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality worldwide, and since 1993, guidelines for management have been available. The process, which first began in the United States and Canada, has now been implemented in numerous countries throughout the world, and often each geographic region or country develops locally specific recommendations. It is interesting to realize that guidelines from different regions often interpret the same evidence base differently, and guidelines differ from one country to another, even though the bacteriology of CAP is often more similar than different from one region to another. One of the unique contributions of the 2007 US guidelines is the inclusion of quality and performance measures. In addition, US guidelines emphasize management principles that differ from some of the principles in European guidelines because of unique epidemiological considerations. In addition, certain therapy principles apply in the United States that differ from those in other regions, including the need for all patients to receive routine therapy for atypical pathogens, the emergence of community-acquired methicillin-resistant *Staphylococcus aureus* in some patients following influenza, and the need for all patients admitted to the intensive care unit to receive at least two antimicrobial agents. In the future, as guidelines evolve, there will be an important place for regional guidelines, particularly if these guidelines can recommend locally specific strategies to implement guidelines, which if successful, can lead to improved patient outcomes.
Why Do We Need CAP Guidelines?

The need for guidelines and a policy to achieve a more uniform approach toward empirical treatment tends to vary from country to country, from hospital to hospital, and from department to department. In the United States the most recent guidelines were published in 2007 as a joint effort of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA). These guidelines were widely adopted worldwide and used to guide the management of CAP. In the United States, part of the interest and relatively uniform adoption and application of guidelines has come from the fact that Medicare, the largest insurer in the country, has developed performance measures for CAP that all hospitals must follow and that are publically reported.

In addition, in the near future, US hospitals will be “paid for performance” that will include how often they adhere to CAP guideline recommendations in the care of patients.

In recent years, the number of published articles about medicine has increased at an impressive pace. In PubMed, the number of articles about pneumonia published during the period 1978–1993 and 1993–2008 was 1.5 times and 2.5 times higher than before 1978, whereas the number of articles mentioning “recommendations” and “guidelines” together with “pneumonia” was 11 times and 96 times higher than before 1978, respectively (unpublished data) (Fig. 1). This reflects not only the development and adoption of guidelines in the United States but also the fact that many countries have adapted the process to their own health care environment, preferring national recommendations rather than one guideline that is applied worldwide for each disease.

A study comparing bacteremic pneumococcal pneumonia in Sweden and the United States from the time before pneumococcal resistance was a cause of concern in the latter country is a good example of varying antibiotic practices and why each country needs to develop recommendations to fit its needs. In this study, the empirical therapy of CAP in American and Swedish patients, respectively, was penicillin or ampicillin in 34% versus 83%, a cephalosporin in 29% versus 6%, an aminoglycoside in 20% versus 3%, and two or more drugs in 37% versus 5%. Because combination treatment is still infrequently used in Sweden for the empirical treatment of hospitalized patients with CAP, implementation of North American guidelines, which recommend both a β-lactam and a macrolide, or a respiratory quinolone, would be considered an overuse of antibiotics in Sweden. The same would apply in several other European countries.

Part of the impetus to guideline development has come from the numerous studies worldwide showing that, with the implementation of CAP guidelines, several outcomes have improved, including reduced costs and length of stay, in-hospital mortality, and the number of days on mechanical ventilation (in those intubated). Because of these benefits, in the United States, measurement of adherence to guidelines has been conducted on a national level.

How, When, and Where Have Guidelines Been Developed?

The first set of guidelines for CAP were the Canadian and the ATS guidelines, developed by different scientific societies but sharing four of the authors, which were both published in 1993. These guidelines established an approach that has been generally used by other organizations, namely using a literature review, more recently with evidence grading, stratification of patients according to severity of illness and risk factors for specific pathogens, and provision of management recommendations for each subset of patients. Other North American guidelines were published after those first guidelines, including IDSA in 1998, 2000, and 2003; the Centers for Disease Control and Prevention (CDC) in 2000; the Canadians (with collaboration of Pulmonary/Infectious Diseases) in 2000; ATS again in 2001; and the ATS/IDSA Joint Guidelines in 2007.
Since 1998, these North American guidelines have addressed the management of CAP when there are concerns about drug-resistant Streptococcus pneumoniae (DRSP).

The development of guidelines also occurred in other parts of the world as follows:

Europe: European Respiratory Society (ERS) with the European Society of Clinical Microbiology and Infectious Diseases.8,9
  - Germany: pulmonary and infectious diseases societies10
  - Spain: pulmonary society11
  - United Kingdom: British Thoracic Society (BTS)12
  - Portugal: pulmonary society13
  - France: infectious diseases society14,15
  - Sweden: infectious diseases society16

Middle East including Saudi Arabia and the Gulf coast countries17

South America
  - Latin America: Latin American Thoracic Association18
  - Argentina19
  - Chile20
  - Brazil: pulmonary and infectious diseases societies21

Africa
  - South Africa: pulmonary and infectious diseases societies22

Asia
  - Japan: pulmonary and infectious diseases societies23

**Does the Use of Guidelines Improve the Outcome of Adults with CAP?**

As has been the case with clinical practice guidelines generally, guidelines for CAP have been controversial and are not always followed by treating physicians.24 Physicians usually try to tailor antimicrobial therapy to address the specific risk factors of individual patients, which includes their epidemiological profile, their history of antimicrobial tolerance, and their underlying degree of acute and chronic illness. Although this approach may lead to choices that are not consistent with guideline recommendations, numerous studies have evaluated the possible clinical benefits associated with adherence to clinical practice guidelines for CAP. The most consistent data come from studies of severe CAP, where guideline adherence is associated with reduced mortality.25,26 Some studies have also suggested an improved outcome in patients with non-severe CAP, but most have been retrospective, in circumstances single geographic regions. A recent study by McCabe et al evaluated the association between guideline-concordant therapy and the end points of in-hospital survival, time until discharge from hospital, and discontinuation of parenteral therapy.27 They studied 54,619 non-ICU hospitalized CAP patients from a database of 113 community hospitals and tertiary care centers. They found that 35,477 (65%) received initial guideline-concordant therapy and that after adjustment for confounders, guideline-concordant therapy was associated with decreased in-hospital mortality (odds ratio (OR), 0.70), sepsis (OR, 0.83), and renal failure (OR, 0.79), and reduced both length of stay and duration of parenteral therapy by ~0.6 days (p < 0.001 for both end points). These findings were linked to treatment with fluoroquinolone or macrolide agents.

**How Different Is the Epidemiology of CAP in the Different Areas of the World?**

One of the reasons some argue that guidelines should be local is that the etiology could differ between different countries and regions. However, when CAP etiology has been studied, it seems to vary more by patient type and with the diagnostic methodologies used than by region. Bartlett and Mundy, in a classical review published 15 years ago, described that the percentage of different microorganisms in CAP varied for Streptococcus pneumoniae between 20 and 60%, Haemophilus influenzae between 3 and 10%, gram-negative bacilli between 3 and 10%, atypical pathogens between 20 and 30%, viruses between 2 and 15%, and aspiration between 6 and 10%.28 On the other hand, Vergis and Yu compared the etiology of CAP in different studies performed in Spain, Japan, Italy, the United States, and the Netherlands.29 They found a consistent incidence of S. pneumoniae as the commonest pathogen in most places, whereas M. pneumoniae rated second; Chlamyphila pneumoniae third, Legionella pneumophila fourth, and H. influenzae in fifth place, independent of the world area under consideration (Fig. 2). Luna et al found a similar rating of microorganisms in a study in Argentina.30 Analyzing the role of the different pathogens in the etiology of CAP in studies that used a comprehensive and systematic approach for identifying etiology in the United States, Europe, the Asia-Pacific area, and Latin America, it is clear that the relative importance of the different pathogens does not differ worldwide (Fig. 3). Arnold et al reported the global incidence of atypical pathogens in CAP, dividing the world into four areas.31 In this study there were no differences in the incidence of these microorganisms in the different world areas.

In some parts of the world, economic factors such as malnutrition and the incidence of HIV/AIDS could impact on the etiology of CAP. The World Health Organization divides countries according to their per capita income into low (less than US$200/year), lower medium, high medium, and high income. There is a clear correlation between lower income and malnutrition, which could also relate to the presence of HIV infection. Pneumonia is the second or third cause of death among the 10 countries with a high HIV/AIDS prevalence, and most of these are low income countries. On the other hand, pneumonia is the second or third cause of death in the two countries with lower income among the 10 countries with a high prevalence of HIV/AIDS, but the fifth cause among those with the highest income.32 In countries with a high incidence of HIV/AIDS, this factor, not the geographic location, leads to Pneumocystis jirovecii or other HIV-associated pathogens as a cause of CAP.22 Differences in the health care systems, in local practices regarding hospitalization criteria, and in antimicrobial availability, but not differences in the possible pathogenic
microorganisms, are the main reasons justifying the need to have local instead of global guidelines for CAP. However, there are specific regional considerations of pathogens, with some parts of the world having a high enough incidence of tuberculosis, that this diagnosis needs to be considered in patients presenting with CAP, and there are unusual pathogens specific to certain locales, such as melioidosis in Southeast Asia and Thailand.

**How Different Is the Evidence on Which Most Guidelines Are Based?**

The method of developing guidelines has evolved during the last 15 to 20 years, and committees generally review a large number of studies, with the latest European guideline citing 565 references. The synthesis of the data is dependent on the composition of the committee, and depending on the background and experience and specialty of the experts, the interpretation and importance of any study may vary. Even though the bibliography of different guidelines is similar, data interpretation varies according to the characteristics of different national health care systems, and sometimes different experts, using the same evidence, arrive at opposite conclusions and recommendations. For example, the study by Gleason et al is mentioned in both the 2005 European Respiratory Society and the 2007 IDSA/ATS CAP guidelines. The Europeans used this study findings about the efficacy of combining a β-lactam and a macrolide or the use of fluoroquinolone monotherapy to conclude that data supporting “the use of such antimicrobial agents in these patients remains very limited.” The American guidelines concluded that the recommendations using these antimicrobial regimens “were based on retrospective studies demonstrating a significant reduction in mortality.” From a global perspective, the development of high-quality and updated guidelines adapted to the regional, national, or local realities is necessary, and one international guideline does not fit all needs.

**Issues and Recommendations in US Guidelines, and How These Compare to Other Global CAP Guidelines**

The recently published ATS/IDSA guideline reflects issues in management that may be unique to North America. Specifically, North American guidelines reflect bacteriologic considerations that may not be relevant elsewhere; antibiotic regimens differ from those used in other parts of the world, particularly Europe and the United Kingdom, based on a combination of bacteriologic data and philosophy about interpreting the importance of some data. In addition, US guidelines have recently incorporated quality and performance measures into recommendations, an approach that is specific to the US health care environment.

**Epidemiology of CAP in the United States and Its Relationship to Guideline Considerations**

In 2004, pneumonia, along with influenza, was the eighth leading cause of death in the United States, the sixth leading cause of death in those over age 65, and the number one cause of death from infectious diseases. In the United States, patients with CAP are primarily managed out of the hospital, but those admitted to the hospital consume the greatest

---

**Figure 2** Frequency of pathogens of community-acquired pneumonia in different studies performed in different cities and countries (Spain, Japan, Italy, Ohio (US), Israel, Murcia (Spain), Leiden (the Netherlands), (four different cities in the US and overall proportions), according to a comparison published in a study by Vergis et al. SP: Streptococcus pneumonia; MP: Mycoplasma pneumonia; CP: Chlamydia pneumoniae; HI: Haemophilus influenzae; LP: Legionella pneumophila.

**Figure 3** Etiology of community-acquired pneumonia in Europe, Latin America, and the United States, and overall, according to published epidemiologic studies aimed at reporting such etiology performed in more than 10,000 patients from Europe, Latin America, the United States, and on average in all those sites. S. pneum, Streptococcus pneumoniae; M. pneum, Mycoplasma pneumoniae; C. pneum, Chlamydia pneumoniae; H. infl, Haemophilus influenzae; EGNB, enteric gram-negative bacilli; L. pneum, Legionella pneumophila. Unpublished data.
The elderly have both an increased incidence of pneumonia and an increased mortality, compared with younger populations. In one study, the mortality of CAP was 8.8% overall but was only 4.5% in those aged 18 to 44, compared with 12.5% in those over age 65. CAP may have not only short-term, but longer-term mortality implications, with one large Medicare study of over 150,000 patients admitted to the hospital for CAP being compared with Medicare patients admitted to the hospital for other diagnoses (having five controls for each pneumonia patient). CAP patients had both a higher inpatient mortality than the controls as well as a higher 1 year mortality rate. Although the in-hospital mortality rate for CAP patients was 11%, at 1 year, these same Medicare patients had over a 40% mortality rate.

Bacteriologic Considerations in the United States

Atypical Pathogens

One of the major differences between CAP therapy recommendations in the United States versus other parts of the world is the recommendation that all patients receive empirical therapy not only for pneumococcus but also for atypical pathogens, which include *Legionella pneumophila*, *Chlamydia phila pneumoniae*, and *Mycoplasma pneumoniae*. This approach is based on studies that show a high frequency of atypical pathogens among both outpatients and inpatients, as well as a wealth of outcomes data (mostly retrospective, and from ill inpatients, many of whom are severely ill) that the addition of a macrolide to a β-lactam is associated with reduced mortality. It is uncertain whether the benefit of macrolide therapy being added to β-lactams is due to atypical pathogen coinfection or the antiinflammatory effect of macrolides, but the benefit appears to be greater for the addition of macrolides than for the addition of a quinolone. Although atypical pathogens have been thought to be most common in young and healthy individuals, in one study from Ohio they were present in patients of all ages, including the elderly, and even those in nursing homes.

Atypical organism pneumonia may not be a constant phenomenon, and the frequency of infection may vary over the course of time and with geography. In one study of Medicare patients evaluated over three different calendar years, the benefit of providing empirical therapy directed at atypical pathogens was variable, being more important in some years than in others. Although there are data to suggest that atypical pathogens occur with similar frequency outside the United States, as already described, their role is thought to be less important in European guidelines and in recommendations from the British Thoracic Society.

Pneumococcus

In the United States, there are several considerations for pneumococcus that differ from thinking in other countries. First, although as many as 40% of pneumococci may be penicillin resistant, current levels of resistance are relatively low in the United States, and resistance rarely leads to an adverse clinical outcome. In addition, unlike the situation in many countries in Europe, macrolide resistance is more often efflux mediated than ribosomal mediated, and thus macrolide resistance is at a lower level in the United States than in Europe. Based on these findings, US guidelines allow some select outpatient and inpatient populations (young, no cardiopulmonary comorbidity, no recent antibiotic therapy, no recent hospitalization) to receive macrolide monotherapy. In spite of this recommendation, relatively few patients actually receive macrolide monotherapy. Finally, several studies, some from North America, have shown that if pneumococcal bacteremia is present, dual initial therapy, usually with the addition of a macrolide to a β-lactam, is associated with a reduced mortality compared with single-agent therapy, and thus it may not be possible to use focused monotherapy, even with sensitive pathogens.

Drug-Resistant Streptococcus Pneumoniae (DRSP)

In the United States, most penicillin-resistant pneumococci are of the “intermediate” type and are not highly resistant. Recently, the US definitions of resistance have changed for nonmeningal infection, with *sensitive* being defined by a penicillin minimum inhibitory concentration (MIC) ≤2 mg/L, intermediate as an MIC of 4 mg/L, and resistant as an MIC ≥8 mg/L. With these new definitions, the number of patients with resistance has declined. Although the clinical impact of resistance on outcomes such as mortality has been hard to show using older definitions, with the new definitions of resistance, very few pathogens will be defined as resistant, but those that are may affect outcome. In one large study of...
failures are not always associated with an increased risk of failures in CAP have appeared in North America, but such failures are more likely to be clinically relevant. Reports of macrolide resistance, especially in Europe, and is due to an inability of the antibiotic to be clinically relevant because local concentrations of macrolides at respiratory sites of infection may be adequate for effective therapy. However, resistance is at a higher level, and not resistance or accuracy of therapy, was found to be the most important predictor of mortality.

As mentioned, macrolide-resistant pneumococcus is also occurring with increasing frequency, and up to 40% or more of organisms may be resistant to these agents in vitro. However, most macrolide resistance in the United States is low level and due to an efflux mechanism, a type of resistance that may not be clinically relevant because local concentrations of macrolides at respiratory sites of infection may be adequate for effective therapy. However, resistance is at a higher level, especially in Europe, and is due to an inability of the antibiotic to bind to its ribosomal site of action; this form of resistance is more likely to be clinically relevant. Reports of macrolide failures in CAP have appeared in North America, but such failures are not always associated with an increased risk of mortality. Even patients without macrolide-resistant pneumococcal infection can fail macrolide therapy, but they tend to be older individuals with serious underlying disease. In one US-based study, patients with organisms harboring in vitro macrolide resistance, even if bacteremic, have been reported to recover with only macrolide monotherapy.

Resistance of pneumococcus is uncommon with quinolones, which are ordinarily a reliable class of antibiotics for these organisms, and a widely used class of drugs in the United States. In general, one important risk factor for resistance is repeated use of a given agent in the same patient. In one North American study, pneumococcal resistance to β-lactams (penicillins and cephalosporins), macrolides, and quinolones was more likely if a patient had received the same agent in the past 3 months. With these data in mind, new US guidelines have suggested that CAP patients not receive the same antibiotic as in the recent past, with the cutoff of defining this time interval as being within the past 3 months. One other consideration with the empirical use of quinolones relates to the local frequency of tuberculosis. Quinolone therapy can mask the diagnosis of tuberculosis and should not be used if this diagnosis is possible. In the United States, this is generally not a concern unless the patient is in a high-risk group or is HIV positive, whereas in other parts of the world, the use of quinolones is more limited because of concerns with using it in patients who might have tuberculosis.

Need for Dual Therapy of Pneumococcal Bacteremia

As mentioned, in several retrospective studies, most from North America, the use of dual therapy for pneumococcal bacteremia has been associated with a lower mortality than that for therapies involving a single agent. In one retrospective review of 225 patients with pneumococcal bacteremia, 99 received single effective therapy, 102 dual effective therapy, and 24 received more than dual effective therapy. Even though multiple drugs were given to sicker patients as reflected by Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Pneumonia Severity Index, the odds ratio for death was threefold higher for those who received single effective therapy. At least three other studies have also shown a benefit of combination therapy for pneumococcal bacteremia, with the greatest impact being in those with severe illness. It is difficult to translate these data into guideline recommendations because all of these were retrospective, and the implications for continued therapy once blood culture results are known is unclear given that the studies only looked at outcomes in relation to initial empirical therapy.

Community-Acquired Methicillin-Resistant Staphylococcus aureus

In the United States, some patients with CAP have been affected by a severe necrotizing bilateral pneumonia caused by community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA), a pathogen that seems more common in the United States than in Europe. Initially the descriptions about CA-MRSA were of patients with severe pneumonia and a high mortality, but more recently the spectrum of illness caused by this pathogen has expanded to include patients with milder illness, not all of whom need ICU care. CA-MRSA differs from nosocomial MRSA and is a clonal disease, emanating from the USA 300 clone of S. aureus. It can infect previously healthy individuals, and the classic clinical presentation of this pathogen causing CAP is as a complication of a preceding viral or influenza infection. The organism can lead to a severe, bilateral, necrotizing pneumonia, which may be related to staphylococcal virulence factors such as the Panton-Valentine leukocidin (PVL); thus therapy may need to involve both an antibacterial agent and an antitoxin-producing agent. In the latest IDSA/ATS CAP guidelines, there was a recommendation to consider this pathogen in patients with severe CAP and a compatible clinical picture, but there was no recommendation to routinely cover this organism for all ICU-admitted patients. The role of this organism outside the United States is yet to be determined, and, as mentioned, the spectrum of illness is expanding to include patients with nonsevere CAP.

Prognostic Scoring for Patients with CAP

The two best-studied and most widely used prediction rules for pneumonia severity are the Pneumonia Severity Index (PSI), which was developed by investigators in the United States, and the CURB-65 rule, a modification of a prognostic model developed by the British Thoracic Society. Although some consider the former approach an American
one, and the latter not, current guidelines in the United States recognize the important role and validity of both approaches for assessing patient prognosis and for guiding the site of care decision (care at home, admission, or ICU care).61

The PSI uses multiple demographic and historical findings, physical findings, and laboratory data, each assigned a point score, and the total score is used to categorize patients into one of five classes, each with a different risk of death. This tool was developed to define mortality risk, but it has been applied to guide the site of care decision, with controversial results because it may underestimate severe illness in previously healthy individuals and overestimate severity in patients with advanced age and chronic illness.59 The CURB-65 rule is simpler, using only five assessments: confusion (due to the pneumonia), blood urea nitrogen >7 mmol/L, respiratory rate ≥30 /min, blood pressure <90 mm Hg systolic or ≤60 mm diastolic, and age ≥65 years, each receiving 1 point, with scores falling between 0 and 5, and with mortality risk rising with the score.60 In recent studies, both tools have worked well to identify patients at low risk of dying, but the CURB-65 score does not account for decompensated chronic illness as a result of CAP.61,62 In Japan, another tool, the A-DROP score has been used, which assesses patient age, dehydration, respiratory failure, orientation, and low blood pressure, and this tool performs similarly to the CURB-65.63 No prognostic scoring tools consider “social factors,” such as whether the patient has a stable home environment for outpatient care, the ability to take oral medications, the absence of acute alcohol or drug intoxication, and stability of other acute and chronic medical problems. These social factors are likely to differ widely among countries, and based on such considerations, the decision about hospitalization for CAP is not uniform worldwide.

It is not clear how to decide who should be admitted to the ICU, but the current US guidelines have recommended ICU admission for patients with either of one of two major criteria or three of several minor criteria.77 The major criteria are need for mechanical ventilation and septic shock. The minor criteria are PaO₂/FiO₂ ratio <250, respiratory rate >30/min, confusion, multilobar infiltrates, systolic blood pressure (BP) <90 mm Hg despite aggressive fluid resuscitation, blood urea nitrogen (BUN) <20 mg/dL, leucopenia (<4000 cells/mm³), thrombocytopenia (<100,000 cells/mm³), and hypothermia (<36°C).35 Other findings in severe pneumonia are hyponatremia (<130 mEq/L) and an arterial pH <7.3, the latter being one of the most important indicators of need for ICU admission. One study in the United States that applied these criteria found that the presence of four minor criteria had a higher positive predictive value than three criteria, with a similar negative predictive value.54 In that study, this rule outperformed other criteria for deciding the need for ICU admission.63

**Recommended Diagnostic Tests**

In US CAP guidelines,35 there is limited diagnostic testing recommended for outpatients, but for all patients, a chest radiograph should be used to establish the presence of pneumonia, if it can be obtained. In general, the US guidelines rely on empirical therapy, chosen on the basis of epidemiological risk factors for specific pathogens, and pathogen-directed therapy guided by diagnostic testing is not the main approach. Thus the history for all patients should focus on epidemiological clues that suggest specific pathogens. Sputum Gram’s stain and culture should be done prior to therapy but only if the sputum is of good quality and can be rapidly transported to a microbiology laboratory. Blood cultures should be limited to those with severe CAP and collected prior to the initiation of antibiotic therapy. Blood cultures should also be considered for those with cavitory infiltrates, leukopenia, active alcohol abuse, chronic liver disease, severe COPD, asplenia, and pleural effusion. Finally those with severe illness and those who have failed outpatient therapy should have *Legionella* and pneumococcal urinary antigen testing, and if intubated an endotracheal aspirate should be sent for culture. Routine serum serological testing is not recommended.35 The recommendations in the latest European guidelines are similar, with limited testing recommended for outpatients. For inpatients, the European guidelines recommend blood cultures for all admitted patients33 and also recommend urinary antigen testing for *Legionella* and pneumococcus in those with severe illness, but they do not recommend routine serological testing for atypical pathogens. The European guidelines also recommend consideration of molecular diagnostic methods for pneumococcus and viruses. In the past, European guidelines endorsed the use of biomarkers such as C-reactive protein (CRP) to guide the use of antibiotics, but the new guidelines are less definitive, recommending that CRP and procalcitonin (PCT) be considered to guide severity assessment but not making their measurement mandatory.33

The recommendation to limit the use of blood cultures in US guidelines is different from the approach in European guidelines but is based on a large Medicare study of 13,043 patients, which showed that it was possible to define risk factors for a true positive blood culture, and that blood cultures should only be drawn in patients with multiple risks to prevent the drawing of samples from patients whose incidence of false positive results exceeded the incidence of true positives.65 These risks for a positive blood culture were absence of prior antibiotics and findings associated with severe illness such as systolic BP<90 mm Hg, fever <35 or >40°C, pulse >125/min, BUN >30 mg/dL, serum sodium <130, WBC <5000 or >20,000.

**Specific Therapy Recommendations in US Guidelines, Compared with Other Guidelines**

The current IDSA/ATS guidelines for CAP divide patients into three groups: outpatients, those admitted to the hospital but not the ICU, and those admitted to the ICU. For each group of patients, there is a list of likely pathogens, and the initial empirical therapy is chosen with these organisms in mind (►Table 1). If a specific pathogen is subsequently identified by diagnostic testing, then therapy can be focused. In this scheme, it is also important to identify patients with HCAP.
Community-Acquired Pneumonia Guidelines: A Global Perspective

Niederman, Luna

305

Table 1 Common Pathogens Causing CAP in Specific Patient Populations in the United States in Order of Decreasing Frequency

<table>
<thead>
<tr>
<th>Inpatient, Cardiopulmonary Disease and/or Modifying Factors</th>
<th>S. pneumoniae (including DRSP), H. influenzae, enteric gram-negative bacilli, S. aureus, M. pneumoniae, respiratory viruses, others (C. pneumoniae, M. tuberculosis endemic fungi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe CAP, with Risks for P. aeruginosa</td>
<td>S. pneumoniae (including DRSP), Legionella sp., H. influenzae, enteric gram-negative bacilli, S. aureus, M. pneumoniae, respiratory viruses, others (C. pneumoniae, M. tuberculosis endemic fungi)</td>
</tr>
<tr>
<td>All of the pathogens above, plus P. aeruginosa.</td>
<td></td>
</tr>
</tbody>
</table>

DRSP, drug-resistant Streptococcus pneumoniae.

and to exclude them from CAP management because these patients require their own management approach, with some needing therapy similar to CAP and others requiring therapy that is similar to that for nosocomial pneumonia.66 As mentioned, European guidelines have rejected the concept of HCAP. However, in the United States, the concept may be valuable for several reasons, including the large number of patients residing in nursing homes, as well as the application of performance measures and the fact that HCAP patients are exempted from requiring the use of therapy compliant with CAP guidelines. The ability to treat these patients in whatever manner is deemed best is a benefit of being able to designate them as having HCAP and not CAP.

In choosing empirical therapy for CAP, certain principles should guide therapy, but in North America, these principles are not the same as those used in parts of Europe and the United Kingdom.1,3,12,18,38,67 The principles that apply to empirical therapy in US guidelines are: to give the first dose of therapy rapidly and before the patient leaves the emergency department; all patients should be treated for atypical pathogens and pneumococcus, plus other pathogens based on risk factors; monotherapy with macrolides can be used but should be limited to selected inpatients and outpatients with no cardiopulmonary disease or recent antibiotic therapy; anti-pseudomonal therapy should only be used for patients with pseudomonal risk factors; MRSA therapy (vancomycin/linezolid) should be used cautiously; and no ICU-admitted CAP patient should receive monotherapy. The greatest differences from European guidelines are the recommendation for routine atypical pathogen coverage in North America and a trend to use penicillins and to avoid quinolones in the United Kingdom. In addition, macrolide monotherapy is recommended more widely in the United States than in Europe (Table 2).

In North American guidelines, for outpatients with no comorbid cardiopulmonary disease and no history of recent antibiotic use, therapy can be with an advanced macrolide (azithromycin or clarithromycin) or doxycycline. If the patient has comorbid illness or a history of recent antibiotic therapy (in the past 3 months), then DRSP is a concern, and therapy should be with a selected oral β-lactam (amoxicillin, amoxicillin/clavulanate, cefuroxime, or cefpodoxime) combined with a macrolide or doxycycline.35 Alternative therapy for these patients at risk for DRSP would be an oral fluoroquinolone as monotherapy (gemifloxacin, levofloxacin, or moxifloxacin). If the patient has received an antibiotic in the past 3 months, then ideally an agent from a different class should be chosen to avoid the risk of repeated use of the same agent, which can promote the emergence of pneumococcal resistance. In contrast to these recommendations, European and British guidelines rely more on oral penicillins and tetracyclines for these patients, and place less emphasis on the need for macrolides, while discouraging the routine use of quinolones.12,67

For the non-ICU inpatient, therapy could be with an intravenous macrolide (azithromycin) alone, provided that the patient has no underlying cardiopulmonary disease and no risk factors for infection with DRSP, enteric gram-negatives, or anaerobes. Although not widely used, the efficacy of this approach has been documented in this population.56 For inpatients with cardiopulmonary disease or other risks for DRSP, and sometimes gram-negatives, therapy should be with either a selected intravenous β-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, or ertapenem) combined with a macrolide or doxycycline, or, alternatively they can receive monotherapy with an intravenous anti-pneumococcal quinolone (levofloxacin or moxifloxacin).35 In US guidelines, cefuroxime is not a recommended intravenous β-lactam
choice because of concerns of failure in the setting of in vitro resistance. This is not a concern in guidelines outside the United States. The latest European guidelines consider the addition of a macrolide to a β-lactam to be optional outside the ICU. They allow for the use of penicillin G as the β-lactam and have recently considered quinolone monotherapy to be an acceptable option. Thirty-three. When quinolones are used, the US guidelines recommend that levofloxacin be dosed at 750 mg per day to optimize antipneumococcal activity, similar to moxifloxacin. The European guidelines note that moxifloxacin has better antipneumococcal activity than levofloxacin and may make a good choice for sequential oral therapy following intravenous therapy because of its high bioavailability. Thirty-three

In the ICU population, all individuals should be treated for DRSP and atypical pathogens, but only those with appropriate risk factors (corticosteroids, broad spectrum antibiotics for more than 1 week in the past month, malnutrition, or structural lung disease such as bronchiectasis) should have coverage for *Pseudomonas aeruginosa*. In addition, no ICU-admitted patient should ever receive empirical monotherapy with any agent, including a quinolone. Limited data from Europe comparing quinolone monotherapy to combination therapy in severely ill patients have shown that monotherapy (with levofloxacin) may not be as effective as combination therapy for patients in shock and for those treated with mechanical ventilation. Sixty-eight In addition, in one US study of patients with more severe illness (PSI class V), quinolone monotherapy had twice as high a mortality as the use of a β-lactam/macrolide combination. Sixty-nine For patients without pseudomonal risk factors, therapy should be with a selected intravenous β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam), combined with either an intravenous macrolide or an intravenous quinolone (levofloxacin or moxifloxacin). For patients with pseudomonal risk factors, therapy can be with a two-drug regimen, using an antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin or high-dose levofloxacin (750 mg daily if normal renal function), or alternatively, with a three-drug regimen, using an antipseudomonal β-lactam plus an aminoglycoside plus either an intravenous nonpseudomonal quinolone or macrolide. There are no good studies of severe CAP regimens in patients who are penicillin allergic, but the general recommendation for severe CAP, without pseudomonal risks, is to use aztreonam plus an antipneumococcal quinolone. If pseudomonal risks are present, then the same severe CAP regimens as already described should be used, replacing the antipseudomonal β-lactam with aztreonam. Although European guidelines support the idea of combination therapy for severe CAP, they do permit the use of quinolone monotherapy for patients without septic shock. Thirty-three

In addition to the therapy regimens discussed, some patients with severe CAP, particularly after an episode of influenza, need added coverage for *S. aureus*, including MRSA. Optimal therapy has not been defined, and vancomycin alone may not be sufficient and has led to clinical failure, presumably because it is not active against the PVL toxin that accompanies community-acquired MRSA. For that reason, it may be necessary to add clindamycin to vancomycin or to use linezolid (with rifampin in severe illness) because both of these latter agents can inhibit toxin production. Seventy The current guidelines do not offer a specific recommendation on the need for antitoxin agents if community-acquired MRSA is being treated. This organism is not common in Europe and it is not included in severe CAP recommendations from those countries.

### Performance Measures

In the United States, a recent development has been the promotion of publicly reported performance measures for hospitalized patients, intended to assure a minimum standard of care. The latest IDSA/ATS guidelines have addressed these performance measures, endorsing some, but rejecting others, particularly the standard related to the timing of antibiotic administration. Thirty-five For patients with CAP, Medicare

<table>
<thead>
<tr>
<th>Table 2 Principles of Antibiotic Therapy for CAP in American Guideline Recommendations versus European Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy should be timely and empirical, with limited diagnostic testing, separating health care associated pneumonia from community-acquired pneumonia</td>
</tr>
<tr>
<td>All patients should receive therapy for atypical pathogens</td>
</tr>
<tr>
<td>Intravenous therapy should be used, rather than oral therapy at the time of admission</td>
</tr>
<tr>
<td>Macrolides may have a role</td>
</tr>
<tr>
<td>Usually with a beta-lactam (part of dual therapy)</td>
</tr>
<tr>
<td>As monotherapy, but only in selected patients (more outpatient than inpatient)</td>
</tr>
<tr>
<td>Certain beta-lactams are not commonly used or recommended (e.g., cefuroxime, penicillin G)</td>
</tr>
<tr>
<td>Quinolones can be used as first-line therapy and as single agents in non-ICU patients</td>
</tr>
<tr>
<td>No patient with severe CAP treated in the ICU should receive empirical monotherapy, even with a quinolone</td>
</tr>
<tr>
<td>Selected patients with severe CAP require empirical therapy for methicillin-resistant <em>Staphylococcus aureus</em>, particularly after influenza</td>
</tr>
<tr>
<td>Performance measures need to be followed</td>
</tr>
<tr>
<td>Importance of time to initial therapy</td>
</tr>
</tbody>
</table>
Table 3 Community-Acquired Pneumonia Performance Measures Defined by Medicare: Recent and Future Standards

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exempt if diagnostic uncertainty when first evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose of antibiotics within 6 hours of arrival at hospital</td>
<td></td>
</tr>
<tr>
<td>Oxygenation assessment within 24 hours of admission</td>
<td></td>
</tr>
<tr>
<td>Correct antibiotic choice for admitted patients (health care associated pneumonia patients exempt)*</td>
<td></td>
</tr>
<tr>
<td>Non-ICU</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td></td>
</tr>
<tr>
<td>Includes no monotherapy with any agent, including fluoroquinolones</td>
<td></td>
</tr>
<tr>
<td>Blood cultures within 24 hours for all patients admitted to ICU</td>
<td></td>
</tr>
<tr>
<td>Blood cultures before antibiotics for those drawn in the emergency department</td>
<td></td>
</tr>
<tr>
<td>Smoking cessation advice</td>
<td></td>
</tr>
<tr>
<td>Evaluation of need and offering of pneumococcal and influenza vaccines to all appropriate candidates*</td>
<td></td>
</tr>
<tr>
<td>30 day risk-adjusted mortality rate*</td>
<td></td>
</tr>
<tr>
<td>30 day risk-adjusted readmission rate</td>
<td></td>
</tr>
</tbody>
</table>


(Center for Medicare Services) has developed a set of “core measures” that are collected for every hospital and reported on the Hospital Compare Web site, with the implication that hospitals with the best performance are providing the highest level of care (Table 3). The core measures include timely administration of antibiotics, measurement of oxygenation, selection of the correct antibiotics in the hospital and in the ICU, collection of blood cultures in seriously ill patients prior to antibiotic administration, provision of smoking cessation advice, and provision of pneumococcal and influenza vaccines to at-risk individuals.70a Because of either a high level of success with some measures (assessment of oxygenation) or problems (antibiotic timing), the performance measures have been periodically revised.

This approach has led to a variety of adverse, unintended consequences, best illustrated by the previous standard of requiring all patients to receive their first dose of antibiotics within 4 hours of arrival to the hospital, a standard that was modified to extend to 6 hours. Although retrospectively collected data have shown a lower mortality for patients given therapy within 4 hours, compared with those given therapy later, the explanation may not be timely administration alone.71 It is possible that delay in therapy may be a surrogate marker for patients with diagnostic uncertainty and of patients with impaired host responses who have indistinct clinical presentations and thus are not easily recognized as having pneumonia.72 In addition, when hospitals have increased the number of patients getting early antibiotics, in an effort to comply with core measures, there are data to suggest that there are more patients who are given timely therapy who do not actually have pneumonia, than in the period before such an effort at timely therapy was made.73 In addition, some of the patients given this timely therapy did not have pneumonia, yet developed antibiotic complications such as antibiotic-associated colitis.74

Although the standard for pneumococcal vaccination seems appropriate, when the vaccine has been used in children it has led to unintended consequences, some useful, and some not. Initially, widespread use of the seven-valent conjugate vaccine in children led to “herd immunity” in the older caregivers of vaccinated children, with a decline in the frequency of infection by vaccinated strains.75 However, more recently, in the children who have been vaccinated, there has been an emergence of “replacement strains,” with infection being caused by pneumococcal strains that are not included in the vaccine, some of which have led to necrotizing pneumonia.76

Guidelines outside the United States, including the recently published European guidelines, have not formally included performance measures, and the value of these standards needs careful consideration. The 2007 US guidelines endorse four performance measures, which do not include all of the Medicare core measures.77 These are use of empirical therapy that is consistent with guideline recommendations because these therapies have been shown to reduce cost, length of stay, and mortality; giving the first dose of therapy in the emergency department, after establishing the diagnosis of CAP (but there is no endorsement of a specific time period for administration); collecting data about CAP mortality and the need for ICU transfer after admission to a medical ward; determining how many at-risk patients receive pneumococcal and influenza vaccine.

In the end, it may be necessary for all guidelines to consider performance measures because it has been well demonstrated that the mere presence of guidelines leads to little change in behavior. If guidelines do improve outcomes, then there should be some monitoring of whether guidelines are used and of the outcomes and benefits that follow from their use. However, in order for this to occur, we will need to better understand how to implement guideline recommendations. One US study showed that the best implementation and outcomes occurred when the presence of a guideline was supplemented by a clinical champion who prospectively intervened to make sure that recommendations were being followed.77 Although this approach worked in one hospital it is clear that each health care system will need to approach...
implementation in a unique way, and this may be the greatest justification for developing guidelines unique to each country so that there will be maximum “buy in” when efforts are made to implement these guidelines to improve patient outcomes.

References


Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001;161(15):1837–1842


