Community-Acquired Pneumonia*
A North American Perspective

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The North American guidelines for pneumonia generally show agreement in both the Canadian and American approaches. However, much new data have appeared since the original recommendations, and revisions are needed. The general approach to empiric therapy that has been proposed in both the Canadian and American Thoracic Society documents does appear to be valid, and future recommendations will probably use the original approach as a framework for a more refined approach.

Guidelines for community-acquired pneumonia were first published in North America in 1993 as a report from a Canadian Consensus Conference.1 The recommendations focused on the initial antimicrobial therapy of community-acquired pneumonia, including both traditional community and nursing home-acquired pneumonia. After the initial success of this process, the American Thoracic Society (ATS) used the Canadian Consensus Conference Guidelines as a template for their own guidelines, which were subsequently published in November 1993.2 There are many similarities between these two North American guidelines and distinct differences between the North American approach and the approaches developed elsewhere, particularly in Europe.

Comparison of the Two North American Guidelines

In both of the North American guidelines, the role of atypical pathogens was emphasized more strongly than in the European guidelines (Table 1). Thus, for both outpatients and inpatients, the option of using a macrolide, either as monotherapy or in otherwise healthy individuals or as part of a combination regimen in patients with comorbid illness, is one of the recommendations included in the North American approach. This recommendation, following from a concern about the importance of atypical pathogens, is somewhat different from many of the earlier European recommendations, although more recently, the importance of atypical pathogens has also been recognized in the European guidelines.

The two North American guidelines are also similar in that patients are stratified into different categories, each with its list of likely etiologic pathogens, and from that list follows suggested empiric therapy. To categorize patients, there is an assessment of the age of the patient, the presence of underlying comorbid illness, an evaluation of the severity of illness, and determination of the place of therapy. While both of the North American guidelines have an algorithm that is based on these factors, the Canadian document differs from the American document by the inclusion of patients with nursing home-acquired pneumonia. The ATS excluded these patients because of a concern that each nursing home had its own unique epidemiology and bacteriology, making it difficult to recommend specific empiric therapy regimens.

The two North American guidelines also differ with regard to the scope of the issues that they discussed. The Canadian guidelines described the process of developing recommendations and then presented an empiric approach to initial antimicrobial therapy. Issues related to the hospitalization decision and diagnostic studies were discussed, but not in great detail. The ATS document had specific sections that included the following: a discussion of the likely etiologic pathogens; the approach to diagnosis, including recommended diagnostic tests for both outpatients and inpatients; a discussion of the value of extensive serologic testing and sputum Gram’s staining; a discussion of the syndromic approach to pneumonia concluding that classification of patients into “typical” or “atypical” pneumonia syndromes was not useful; an algorithm for empiric therapy; a discussion of the principles of antibiotic therapy; and an approach to the nonresponding patient. As such, the ATS document focused not only on initial antimicrobial therapy, but also on assessment of the patient’s response to initial antimicrobial therapy. The concept of early switch to oral therapy

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in a responding patient was also mentioned, but it was not examined in great detail.

In developing guidelines in North America, both the Canadian and American groups relied on prospectively done studies of pneumonia. Expert opinion and published data served as major driving forces behind the Canadian document. The ATS document was more explicit in describing the method, using only prospective trials, conducted within the last 10 years, so that studies involving newly recognized pathogens would be included. In addition, the ATS group looked at trials that included at least 1 year of patient data so that there was no seasonal bias to the data, and they relied on studies of adults in North America and western Europe. In addition, studies that routinely incorporated extensive diagnostic testing were sought, although in the end, the group rejected the value of such routine diagnostic testing. Studies that involved both inpatients and outpatients were examined, although more data were available on inpatients than on outpatients.

Recommendations in the North American Guidelines

The Canadian document recommended that patients with community-acquired pneumonia be divided into two groups, those with nonsevere pneumonia and those with severe pneumonia. For the patients without severe illness, individuals treated either out of the hospital or in the hospital were lumped together and then further subdivided into one group without comorbid illness and <65 years of age and another group with comorbid illness and/or ≥65 years of age. For the otherwise healthy individuals, a macrolide was the first choice, followed by tetracycline as a second option. For the patients with advanced age (≥65 years) and/or comorbidity, recommended therapy was either a second-generation cephalosporin, a β-lactam/β-lactamase inhibitor combination, or trimethoprim-sulfamethoxazole, with the option of adding a macrolide to any of these agents. For patients with severe illness treated in the hospital, those admitted to a hospital ward were separated from those admitted to the ICU. Although the therapeutic recommendations were similar whether comorbidity was present or absent, different pathogens were identified for patients with and without comorbid illness. For patients with severe illness admitted to the hospital but not to the ICU, the recommendation was to use a second- or third-generation cephalosporin, with the option of adding a macrolide. For patients admitted to the ICU, the recommendation was to use a macrolide, with the possibility of adding rifampin, and the use of at least one or maybe two antipseudomonal drugs.

The Canadian document also discussed nursing home-acquired pneumonia, separating those with nonsevere illness from those with severe pneumonia, providing recommendations for patients who, regardless of illness severity, were to remain in the nursing home. Those with nonsevere illness were treated with either a second-generation cephalosporin, trimethoprim-sulfamethoxazole, or amoxicillin-clavulanate, with the option of adding a macrolide to any of these therapies. Those with more severe illness who remained in the nursing home were to receive oral therapy with ciprofloxacin plus penicillin or either an oral second-generation cephalosporin or IM ceftriaxone. Patients treated with a cephalosporin could receive optional oral macrolide therapy while penicillin-allergic patients could receive clindamycin (IM) plus ciprofloxacin (oral).

The ATS recommendations were similar; however, patients fell into four groups, two treated out of the hospital and two treated in the hospital. The two outpatient groups included individuals who were <60 years of age and had no comorbid illness and individuals who were either >60 years of age or who had comorbid illness or both factors. For young and otherwise healthy outpatients, the recommendation was to use monotherapy with a macrolide, or alternatively tetracycline. For older outpatients, or for those with comorbid illness, the recommendation was to use either an oral second-generation cephalosporin, a β-lactam/β-lactamase inhibitor combina-

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**Table 1—Comparison of the Two North American Guidelines for Community-Acquired Pneumonia**

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<th>Canada</th>
<th>United States</th>
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<td>Population included</td>
<td>Outpatients, inpatients, nursing home residents</td>
<td>Outpatients, inpatients</td>
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<td>Topics discussed</td>
<td>Likely pathogens, empiric therapy</td>
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<td>Algorithm</td>
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<td>Severe pneumonia usually in ICU</td>
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<td>severe pneumonia; severe pneumonia on ward</td>
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tion, or trimethoprim-sulfamethoxazole with the option of adding a macrolide to any of these choices. These outpatient recommendations were very similar to the Canadian recommendations. The major difference was in picking an age of 60 years rather than 65 years as a distinguishing feature. The age of 60 years was chosen because some of the members of the panel believed that any individual over the age of 65 years might not be an appropriate candidate for outpatient therapy. Therefore, to avoid concerns about age alone as a indication for admission to the hospital, an age of 60 years was chosen, allowing for outpatient therapy of those ≥60 years. For patients admitted to the hospital, but not to the ICU, the recommendation was to use a second or nonpseudomonal third-generation cephalosporin or a β-lactam/β-lactamase inhibitor combination, with or without a macrolide. For the patients with severe illness, admitted to the ICU, the ATS and Canadian recommendations were similar, suggesting the use of an IV macrolide plus at least one or possibly two antipseudomonal drugs. One other difference between the two approaches was that the Canadian document defined severe pneumonia to include admitted patients in or out of the ICU, while the ATS approach implied that most patients with severe pneumonia were usually in the ICU.

**How Should These Recommendations Be Modified for the Future?**

Both the American and Canadian groups are considering an update and revision of their community-acquired pneumonia guidelines, because much has changed since the documents were published in 1993. A number of studies have confirmed some of the recommendations while other data have suggested a need for changes.

The issue of bacteriology is a complicated one and some studies have confirmed the general view of bacteriology that formed the basis of the North American recommendations, whereas others have not.3-5 The general view of bacteriology in the North American recommendations was that pneumococcus is the most common pathogen for any group of individuals with community-acquired pneumonia. *Haemophilus influenzae* is important and is the second most common pathogen in the elderly, in hospitalized individuals, and even in outpatients it may be important, especially in cigarette smokers. *Legionella* is an important pathogen, but primarily in the setting of severe pneumonia, and Gram-negatives may also be important, accounting for 20 to 40% of the pathogens in the elderly. The view that Gram-negatives are important is somewhat at variance with the European recommendations. Recent data from John Hopkins University, in non-HIV-infected patients, generally confirms this view of pneumonia bacteriology, emphasizing the preeminence of pneumococcus and the relatively infrequent finding of atypical pathogens.9 However, in this study, as in many others, no etiologic pathogen could be found in up to 40% of patients, and the failure to identify an etiologic pathogen in a large number of community-acquired pneumonia patients necessitates the continued use of empiric antibiotic therapy.

Neither North American statement was explicit in dealing with the issue of penicillin-resistant pneumococcus. However, recent studies have shown that although the incidence of penicillin resistance among pneumococcus is rising, the clinical implications are still uncertain.6,7 Most penicillin-resistant pneumococci are of intermediate sensitivity and not high-level resistance. Most penicillin-resistant organisms can still be effectively treated with high doses of penicillin or ampicillin as well as certain third-generation cephalosporins, such as cefotaxime or ceftriaxone.6 In one study performed in the United States, bacteremic pneumococcal pneumonia was evaluated, and the incidence of penicillin resistance was observed to increase from 4% in 1991 to 14% in 1994. However, most penicillin-resistant pneumococci were intermittently sensitive and >95% of all bacteremic pneumococcal isolates were still sensitive to commonly used drugs such as cefotaxime, doxycycline, erythromycin, imipenem, azithromycin, ofloxacin, and ciprofloxacin.7 Thus, it is uncertain how the recommendations for therapy should change with an awareness of penicillin resistance. One thing that is quite clear is that if patients have been receiving a recent course of β-lactam antibiotics or have underlying severe immunosuppressive illness, penicillin resistance is more likely and sputum cultures should be obtained specifically to define whether penicillin-resistant pneumococcus is present.9 If penicillin resistance is suspected, therapy with selected third-generation cephalosporins (cefotaxime, ceftriaxone) may be appropriate. If a high level of resistance is documented, therapy with vancomycin may be necessary. The role of older quinolones in high doses (*ie*, ciprofloxacin, 750 mg bid) or the newer quinolones (sparfloxacin, levofloxacin, trovafloxacin, or grepafloxacin) in the therapy of penicillin-resistant pneumococcal pneumonia still needs to be defined. Data from a US study of penicillin-resistant pneumococcus has also shown that resistance to trimethoprim-sulfamethoxazole is rising, and this drug would probably not be adequate empiric therapy for patients with community-acquired pneumonia.7

The other area where new information has been obtained since the original guidelines is in the safety of switching patients from IV to oral therapy at an early time point. It appears that criteria can now be
developed for an early switch of patients in stable condition from IV to oral therapy as soon as day 3 of hospitalization with discharge on day 4.\textsuperscript{9} Future recommendations will have to be more explicit on criteria for switch therapy.

**Validation of Guidelines**

In order for guidelines to be accepted on both a national and local level, it is important to confirm that the recommendations actually have clinical utility. To this end, we have been involved in studies of the ATS guidelines. These validation studies have focused on risk factors for a complicated course and antibiotic choices, and have examined whether the ATS recommendations are accurate. In the first step of the validation process, we identified all of the risk factors for a complicated course included in the ATS document and retrospectively evaluated a group of almost 5,000 patients to identify how many risk factors each patient had.\textsuperscript{10} In general, we found a relationship between the number of risk factors for a complicated course and clinical outcomes, such as mortality, percent needing the ICU, average length of stay, and charges for hospital care. These data, to some extent, validate the stratification scheme included in the ATS document and add impetus to the general approach that was proposed.

In a follow-up of this validation study, we also examined other recommendations.\textsuperscript{11} We found that as many as 65% of patients admitted to a hospital floor, but not to the ICU, with an overall mortality rate of only 5%, met criteria for severe pneumonia. Our criteria initially included the presence of any one of the following: A respiratory rate $>30$ breaths/min; a PaO\textsubscript{2}/FIO\textsubscript{2} $<250$; need for mechanical ventilation; bilateral, multilobar, or rapidly expanding infiltrates; shock; and oliguria or acute renal failure.

Although these definitions appeared to be appropriate, at the time we were surprised to find in our validation study that 65% of patients admitted to the hospital, but not to the ICU, had one of the above-listed criteria. Our study showed that many patients had transient diastolic hypotension or bilateral infiltrates. Thus, a new definition for severe pneumonia is needed, and this probably would include the need for mechanical ventilation or the presence of two other risk factors for severe pneumonia, if the patient is not mechanically ventilated.

In evaluating the therapeutic options, we found that patients who received monotherapy with a recommended β-lactam, or combination therapy with a recommended β-lactam plus a macrolide, had a significantly lower mortality than patients who received nonrecommended therapy.\textsuperscript{11} This is an interesting finding and one that goes a long way toward validating the empiric therapy recommendations in the North American guidelines. The reason for the benefits of recommended therapy cannot be directly determined from the validation study, but it is interesting that the addition of a macrolide conferred benefit to hospitalized patients. This fits very well with recent studies suggesting that atypical pathogens are common in patients with community-acquired pneumonia and that serologic evidence for atypical pathogen infection can be found in up to half of all outpatients and inpatients with community-acquired pneumonia.\textsuperscript{4,5} Whether atypical pathogens serve as primary infecting agents or as co-pathogens that potentiate the severity of bacterial pneumonia is yet to be determined. However, the need for relatively routine treatment of atypical pathogens was suggested by the validation study.

**References**