ABSTRACT

Community-acquired pneumonia (CAP) is becoming a more prominent health problem in the United States, in part because of the increasing prevalence of antibiotic resistance. It is known that increased use of antibiotics heightens the level of resistance, yet in roughly 40% of CAP cases, the etiologic agent is not identified. Broad antibiotic use may cover for most pathogens, but this approach is not always the most judicious or safest. Complicating matters is the presence of illnesses that present like pneumonia; the most notorious in recent times is anthrax infection. Careful diagnosis based on established risk factors can help to narrow the choices for appropriate antibiotics. This article will review the changing epidemiology of CAP and bacterial resistance to several types of antibiotics, the identified risk factors for CAP in various patient populations, and the most likely target organisms based on the patient profile.


Infectious disease specialists are grappling with 2 recent trends: the increasing prevalence of both community-acquired mixed infections and antibiotic resistance. This article will focus on community-acquired pneumonia (CAP) to highlight the key concepts for management of which infectious disease specialists should be aware.

In developing an approach to abrogate antibiotic resistance, it is important to understand how and in what context resistance develops. O'Brien et al were among the first to observe the dissemination of a resistance gene for gentamicin on bacterial plasmids, making resistance prevalent very quickly. In their study, bacteria of different genera were isolated from Boston, Philadelphia, Chicago, Seattle, Los Angeles, Miami, and Venezuela within months during the first decade of gentamicin use. The gentamicin resistance gene had been transferred to or at least emerged on the plasmid, resulting in widespread dissemination and an intercontinental epidemic. Thus, it became apparent that as a result of antibiotics, bacteria are designed—really are selected for—avoiding the targeted effects of antibiotics.1 In fact, most antibiotic resistance appears within a few years of the introduction of the antibiotic (Figure 1). Clearly, for the most commonly used antibiotics (eg, penicillin, streptomycin, tetracycline, erythromycin, gentamicin), resistance emerged within 1 to 3 years of use. Vancomycin was unusual in that resistance emerged 15 years later, but, nonetheless, resistance did emerge.2

In the United States, antibiotic overuse is an important problem, as illustrated from the following data points from the National Center for Health Statistics in 1996:

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• 160 million antibiotic prescriptions were written in the United States during that year;
• 25,000 tons of antibiotics are consumed per year, corresponding to a 4% to 5% increase per year;
• An estimated 60 prescriptions per 100 persons per year are written, or 19 pounds of antibiotics per 100 persons per year, assuming half are used in humans and half are used in animals.  

CAP is an important problem in the United States. According to the National Center for Health Statistics for 1996, 5.1 million cases of CAP occurred that year in the United States, with 1.2 million of those patients hospitalized for CAP. CAP resulted in 83,727 deaths, of which 40,000 were due to pneumococcal pneumonia. It was the sixth leading cause of death.  

The American Thoracic Society and the Infectious Diseases Society of America have recently published updates to their guidelines for CAP taking into account epidemiological trends in resistant organisms and the emergence of new classes of antibiotics that appear to have a key role to play in treating resistant strains.  

IDENTIFYING THE TARGET ORGANISMS

So, what is the etiologic profile of CAP? Bochud et al recently showed in a 4-year, prospective study of 170 patients (median age 43 years) in an outpatient setting that approximately 22% of pneumonia cases were caused by pyogenic organisms, of which 34 of 37 cases were pneumococcal pneumonia, 21% were caused by atypical organisms (ie, Mycoplasma, Chlamydia, Legionella, and Coxiella), and 1% were caused by viral agents (Influenza A, B, and parainfluenza, and adenovirus). However, in 56% of cases, no etiologic agent could be identified. When analyzed by age distribution, the results show that atypical organisms were involved in cases primarily with patients under age 45 years. For those over 61 years of age, pyogenic organisms were the major cause. The vast majority of these patients (93%) had received a macrolide in this study; 8% were hospitalized and had a median age of 67 years. Two deaths occurred and both patients were over 80 years of age. In 18% of the pneumococcal pneumonia cases, positive blood cultures were present. Also, 35% were smokers and 13% were alcoholics, which are common themes in identifying those at risk.  

The elderly are a particularly difficult patient population to treat, in part because their sputum samples do not always produce florid cultures. A recent prospective study by El-Solh et al identified the major causative pathogens for severe pneumonia in community elderly patients living at home (n = 57) compared with nursing home patients (n = 47). Every patient had blood cultures, serology, and microbiological samples of pleural fluid cultures and lower respiratory tract secretions with invasive bronchoalveolar lavage. The cohort had severe pneumonia, each person requiring mechanical ventilation. As shown in Figure 2, no etiologic agent was identified in about 40% of both cohorts, similar to the results from Bochud et al. Gram-negative rods accounted for 14% to 15% of the causative organisms in both groups, while Legionella was seen only in patients with CAP who were living in their own homes (9%). Of particular note, Staphylococcus aureus account-
ed for 27% of the causative pathogens in the nursing home patients, but only 7% in the patients from the community. El-Solh et al also observed that mortality was approximately 55% among this cohort and was predicted by inadequate antimicrobial treatment (odds ratio [OR] 2.6), multilobe disease (OR 3.7), septic shock (OR 4.3), and poor 24-hour urine output (OR 5.6). While the last 3 factors may not be surprising, the effect of inadequate treatment is significant and should be considered when managing the elderly.

Time to treatment is an important aspect of quality of care. A study of more than 25 000 Medicare patients from 3555 acute care hospitals in the United States in 1997 showed that 25% of the patients received antibiotics for CAP more than 8 hours after hospital arrival. Thirty-four percent had blood cultures performed more than 24 hours after arriving at the hospital. Not surprisingly, there was considerable variability among different states regarding these time intervals. The study also showed, based on more than 17 000 of these patients, that the adjusted OR of 30-day mortality was 15% better if antibiotics were given within 8 hours or less, compared with those who received antibiotics after more than 8 hours. A study of Legionella pneumonia also showed 26% mortality, with 51% of the cohort (n = 39) receiving a β-lactam only on the first day. The median delay for erythromycin therapy in survivors was 1 day, in nonsurvivors 5 days. The important message is that knowing the likely organisms and treating them early are key steps in successful treatment of CAP.

**CAP Resulting in Death in Younger Populations**

Recognizing CAP and knowing the etiology are also important in younger patients (ie, < 45 years). A recent study of 27 patients in England and Wales who died from CAP showed that, as seen before, 37% were due to an unidentified pathogen and 30% were due to pneumococcal pneumonia, which should be covered during first-line treatment, even in younger patients. Similarly, S aureus accounted for 11% of the cases, so it should be covered in severe disease of young people as well during initial treatment. Perhaps most disappointing was that the diagnosis of lower respiratory tract infection by the general practitioner was missed in 45% of patients. Of the patients admitted to the hospital, 45% were started on antibiotics by a general practitioner and 69% received antibiotics within 2 hours of admission. Also, many of the patients admitted to the hospital had 1 or more markers of CAP (ie, white blood cell count < 4 or > 20 x 10^9/L, arterial pH < 7.35, blood urea > 7 mmol/L). In fact, British Thoracic Society antibiotic guidelines for severe CAP were followed in only 10 of the 27 cases.

The good news is that antibiotics appear to have had a profound effect in avoiding the number of preterm deliveries in pregnant women with pneumonia and reducing the rate of maternal mortality. In an analysis of pneumonia in pregnancy from studies conducted from 1939 to 2000, Lim et al found that the introduction of antibiotics coincided with the occurrence of preterm delivery from 43% to 13% and the rate of maternal mortality from 24% in 1939 to 0% in 2000.

![Figure 2. Distribution of Respiratory Pathogens in Elderly Living at Home vs Nursing Home Elderly](image-url)
**Chlamydia Pneumonia**

Chlamydia is a common cause of pneumonia and respiratory tract infection. A study of Finnish military trainees provided important insights into the clinical presentation and diagnosis of Chlamydia pneumonia. One-half of the trainees (43 of 86) had laboratory evidence of C. pneumoniae infection. Serological testing suggested that 23 had a primary infection and 20 had a reinfection. Most of the morbidity occurs with primary infection; 12 of the trainees with primary infection were hospitalized, versus 1 with reinfection.13

In nursing home residents, the attack rates (during outbreaks in 3 nursing homes, N = 549) ranged from 44% to 68% with all of them having cough and 64% having fever. A total of 16 cases of pneumonia was diagnosed by chest radiograph, with 6 deaths resulting. The interval after the index case was identified as 16 days in smokers but 22 days in nonsmokers.14 Interestingly, population prevalence antibody studies suggest that the C. pneumoniae strain TWAR is present worldwide and that nearly everyone is infected and reinfected during their lifetimes.15

**Pneumonia Imposters**

Occasionally, a patient will present with symptoms characteristic of classical pneumonia, but pneumonia cannot always be assumed—especially in this age of anthrax infections. Vaccination for both influenza and pneumococci in appropriate populations may help minimize the problem by reducing the rate of infection. Other diseases may present as pneumonia. Davies et al conducted a prospective, population-based surveillance of invasive group A streptococcal disease: 323 patients were identified for an annual incidence of 1.5 cases per 100 000. In total, 48% of the patients presented with skin and soft tissue infections and 11% presented with “pneumonia.” Necrotizing fasciitis and toxic shock accounted for 6% and 13%, respectively. Of those with pneumonia, the median age was 55 years, which was older than the median age of the cohort (41 years). The mortality for those with pneumonia was 33%, compared with 15% in the cohort. Therefore, it is important to consider other possibilities besides pneumonia, even in the presence of classical symptoms. This is especially important in the elderly because it can clearly be fatal.16

Methicillin-resistant *S* aureus (MRSA) is becoming a bigger problem in community-acquired pneumonia. Oliveira et al recently published a case review of patients (N = 17, mean age 63 years) hospitalized with influenza between 1999 and 2000 in the Washington, D.C., area. Of the 17 cases, 41% had chronic obstructive pulmonary disorder with influenza pneumonia; Twenty percent had been vaccinated. Eighty-two percent received antiviral medication on admission for 5 days, but the mortality rate was 29%. *S* aureus was isolated in 5 patients, and 4 of the 5 had MRSA. Of note, there was no evidence that any of the 4 patients had been hospitalized in the prior 6 months. Therefore, MRSA should be covered as well as pneumococcal pneumonia during first-line treatment of severe CAP.17

**Risk Factors**

Risk factors are an important consideration in identifying and treating CAP. The most reliable risk factors have been shown to be age, smoking, exercise, and weight gain. A recent prospective study of participants in the Health Professionals Follow-up Study and the Nurses Health Study II identified 290 and 305 cases

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**Table. Independent Predictors of Mortality with Pneumococcal Bacteremia (Odds Ratios)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients N = 421 (P)</th>
<th>HIV Patients with Available CD4 Cell Counts n = 212 (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂ &lt; 50</td>
<td>33.8 (&lt; 0.001)</td>
<td>47.5 (&lt; 0.001)</td>
</tr>
<tr>
<td>High-level penicillin resistance</td>
<td>6.0 (&lt; 0.02)</td>
<td>7.8 (&lt; 0.01)</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>2.4 (&lt; 0.02)</td>
<td>3.1 (&lt; 0.03)</td>
</tr>
<tr>
<td>Multilobar infiltrates/effusions</td>
<td>2.4 (&lt;0.02)</td>
<td>(.07)*</td>
</tr>
<tr>
<td>Age &lt; 0.02</td>
<td>8.2 (&lt; 0.02)</td>
<td>(.09)*</td>
</tr>
<tr>
<td>CD4 &lt; 122</td>
<td>—</td>
<td>(.051)*</td>
</tr>
</tbody>
</table>

*These variables did not reach statistical significance and thus were not included in the model, so no odds ratio was generated.

of pneumonia in men and women, respectively, during a 6-year follow-up out of a total cohort of 104,491. Not surprisingly, smoking was a significant risk factor: 58% of the men and 59% of the women were former or current smokers (multivariate relative risk 1.46 [confidence interval]: 1.00-2.14) and 1.55 [CI: 1.15-2.10], respectively. Age was a risk factor for men only, with a 4-fold risk of CAP over the age of 70 years. Exercise and maintaining a healthy weight were protective in women, but men who gained more than 40 pounds since age 21 years had almost a 2-fold higher risk of CAP than those who did not gain weight. Clearly, the risk factors present opportunities to work with patients to prevent pneumonia simply by changing lifestyle. Interestingly, alcohol consumption was not a risk factor.18

Gender and acquired immune deficiency syndrome (AIDS) status also affect risk. Nuorti et al showed that the relative risk of invasive pneumococcal pneumonia (as a bloodstream infection or as meningitis) was 4 times higher in women compared with men, 46 times higher in those with AIDS versus those not having AIDS, and 4.5 times higher in those with AIDS who are black versus those with AIDS who are not black. This study was conducted in San Francisco, and 55% of the invasive pneumococcal disease was attributed to human immunodeficiency virus (HIV) infection. Of note, 83% of the isolates were those in the current polysaccharide vaccine.19 The Table lists the identified independent predictors of mortality for all patients compared with those who are HIV infected. Of particular note, penicillin resistance was a strong predictor of mortality for all patients, independent of HIV status. Other predictors include a low pO2, Hispanic ethnicity, multilobe disease/effusions, age, and a CD4 count below 122 in HIV-infected patients.20

**Antibiotic Resistance of Concern with CAP**

**Penicillin Resistance**

A particularly disturbing trend is the increase in the number of penicillin-resistant pneumococcal strains, which increased...
approximately 30% between 1995 to 1998. Figures 3A and 3B show the increase in resistance based on the study by Whitney et al. Of the penicillin-resistant strains, 60% are resistant to other antibiotics commonly used to treat invasive pneumococcal disease. This was confirmed by the SENTRY antimicrobial surveillance program, which showed that the penicillin-susceptible S pneumoniae isolates were 90% to 100% susceptible to other antibiotics (ie, amoxicillin, erythromycin, azithromycin, tetracycline, and cefotaxime). The penicillin-intermediate isolates were 60% to 70% susceptible to the other antibiotics, but the penicillin-resistant isolates were only 30% to 60% susceptible to the other antibiotics.

**Macrolide Resistance**

Macrolide resistance occurs through 1 of 2 mechanisms: an altered drug target or macrolide efflux. An altered drug target occurs when the gene for the 23S rRNA is altered such that it blocks binding to the macrolide; this is the primary cause of macrolide resistance in Europe. Macrolide efflux occurs via a novel genetic insertion element, which confers resistance to 14- and 15-membered macrolides. This is responsible for 26% of the macrolide resistance in pneumococci in North America. A Finnish study showed that decreased use of macrolide antibiotics (ie, erythromycin, roxithromycin, azithromycin, and clarithromycin) reversed the trend of increasing erythromycin resistance among group A streptococci. Consumption decreased from 2.40 to 1.38 doses per 1000 inhabitants during a 2-year period. During the 4-year follow-up, erythromycin resistance among group A streptococci isolates from throat swabs and pus samples decreased from 16.5% to 8.6%.

**Quinolone Resistance**

Quinolones affect antibiotic properties through inhibition of DNA synthesis and the resistance mechanisms are almost all due to chromosomal, not plasmid, changes. The resistance mechanisms are usually either through an altered drug target or modifications affecting the cell drug concentration via an altered outer membrane porin or overexpression of active efflux pumps. Sanders proposes the “8-fold rule” for quinolone resistance based on the observation that with each mutation conferring resistance, irrespective of mechanism, susceptibility decreases 4- to 8-fold, resulting in stepwise increasing resistance and increase in minimum inhibitory concentration. The type of mutation may affect resistance to other quinolones not used in the selection process, but this varies greatly. However, Sanders suggests that this 8-fold rule may be used to predict susceptibility to a particular antibiotic in a given infection.

**Conclusion**

In summary, CAP has many causes, of which 20% to 30% have a bacterial (pneumococci, in particular) etiology. We are now seeing up to 40% pneumococci resistant to penicillin, and in some areas of the country, HIV accounts for 50% of the burden of invasive pneumococcal disease. The atypical organisms cause ~20% of CAP cases, and they should be covered dur-

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**Case Study**

A 70-year-old man presents to the hospital with fever and a productive cough of 3 days duration on December 10th.

**History**

Influenza has been seen in the community.

**Physical Examination**

His temperature is 102°F, pulse 100 beats per minute, respiratory rate 24 breaths per minute. There is right lower lobe dullness associated with decreased breath sounds.

**Laboratory Results**

His sputum examination shows gram-positive cocci in clusters.

**Intervention**

What is the diagnosis? What treatment would you prescribe?

**Discussion**

Following influenza, bacterial infections of the lung occur and the gram-positive cocci in clusters suggest S aureus. The patient has 3 criteria for systemic inflammatory response syndrome and clinical findings of right lower lobe pneumonia. Because of the emergence of MRSA, the patient should receive vancomycin until the antibiogram returns.
ing first-line therapy because some of them are life threatening. Similarly, MRSA should also be covered in severe CAP treatment because of the increasing prevalence. Late or inappropriate therapy is the major risk factor for dying.

Lifestyle is important, and age, smoking, physical activity, and obesity are risk factors. The extent of the risk they impose may differ between men and women. Most of them are modifiable and are opportunities to offer multiple strategies of care and to work with patients.

REFERENCES