Drug-Resistant *Streptococcus pneumoniae*

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*Streptococcus pneumoniae* remains a major cause of infection in both children and adults, annually resulting in significant morbidity and mortality. The past two decades have seen an alarming worldwide increase in the incidence of drug-resistant *S. pneumoniae* (DRSP). DRSP is now common throughout the United States, and physicians are questioning how best to approach this epidemic. With the introduction of a number of newer antimicrobial agents, the potential for improved preventive measures, and a better understanding of DRSP, the approach to the management of DRSP infections may change greatly in the next few years. In this article we will review the development of DRSP, identify populations at increased risk of exposure to DRSP, address what approaches might be used to limit its spread, and suggest initial empirical therapy when treating patients with pneumonia due to DRSP.

*Streptococcus pneumoniae* remains a common pathogen and a major cause of morbidity and mortality. *S. pneumoniae* infections are estimated to cause 500,000 cases of pneumonia, 55,000 cases of bacteremia, and 6,000 cases of meningitis annually in the United States [1]. The clinical course of *S. pneumoniae* infections is affected by a number of factors including the site and severity of infection, the underlying health of the patient, and the adequacy of antimicrobial therapy. Therefore, it is not surprising that estimates of mortality are reported to range from <1% to >50%.

Initially, all *S. pneumoniae* isolates were exquisitely susceptible to penicillin (MIC, $\leq 0.06 \mu g/mL$), and this antibiotic served as the drug of choice. Beginning in the 1960s, however, clinical resistance to penicillin and other agents began to be reported. Today, drug-resistant *S. pneumoniae* (DRSP) is recognized worldwide.

In this article we will review the development of DRSP, identify populations at risk of exposure to DRSP, address what approaches might be used to limit its spread, and, finally, describe strategies for treating pneumonia when DRSP is of concern.

Development of Penicillin-Resistant *S. pneumoniae*

Penicillin resistance was first induced in *S. pneumoniae* by Schmidt and Sesler in 1943 [2] after they repeatedly administered therapy with low-dose penicillin to mice. However, the clinical significance of penicillin resistance in *S. pneumoniae* was not appreciated until 1967, when Hansman and Bullen [3] recovered a penicillin-resistant *S. pneumoniae* isolate (MIC, 0.6 $\mu g/mL$) from a patient with hypogammaglobulinemia and bronchiectasis. In 1974, the incidence of penicillin resistance in Australia and New Guinea was reported to be 12%; by 1980, it had reached 33% [4, 5]. The authors of these studies had no explanation for the high incidence of "penicillin-insensitivity" in New Guinea but were the first to suggest that both the high carriage rate for *S. pneumoniae* and the widespread use of penicillins, especially penicillins that often result in relatively low blood levels (injected procaine penicillin and oral penicillin V), might be the cause [4]. In 1977, *S. pneumoniae* isolates highly resistant to penicillin (MICs, 4–8 $\mu g/mL$) were reported in South Africa, and in 1978, multidrug-resistant strains (those resistant to three or more different classes of antimicrobial agents) were identified [6].

Penicillin resistance results from multiple alterations of several of the penicillin binding proteins (PBPs) and affects the binding affinity of penicillin to these PBPs. These alterations are due to apparently stable genetic mutations and are chromosomally mediated but do not result in any loss or gain in *S. pneumoniae* virulence [7, 8]. A majority of penicillin-resistant *S. pneumoniae* isolates are of selected serotypes (i.e., 6, 9, 14, 19, and 23), and this observation along with others suggests a clonality for some penicillin resistance [9].

*S. pneumoniae* is defined as penicillin susceptible when the MIC is $\leq 0.06 \mu g/mL$. The nomenclature for penicillin resistance is confusing because different authors have used different terms [10]. In this article, penicillin resistance will be defined as intermediate (Pen-I) when the MIC for *S. pneumoniae* is 0.1–1.0 $\mu g/mL$ and high (Pen-R) when the MIC is $>1.0 \mu g/mL$ (table 1). Finally, it is important to remember that these MIC breakpoints were selected on the basis of the efficacy of penicillin in treating *S. pneumoniae* meningitis [12]; therefore, some investigators have questioned the relevance of Pen-I in the setting of nonmeningeal infections [13].

Since mutations in PBPs also affect the activity of other β-lactam agents, the term *penicillin-resistant* *S. pneumoniae* is
not entirely accurate. For example, resistance to cephalosporins increases in a stepwise fashion with the development of penicillin resistance and is due to alterations in PBPs 2a and 1a. However, not all β-lactam agents bind to the same PBPs or bind with the same affinity; therefore, certain β-lactam agents retain activity even when penicillin resistance is present. This is especially true for the penicillins amoxicillin and piperacillin, the cephalosporins cefotaxime and ceftriaxone, and imipenem/cilastatin, and these agents are frequently active against both Pen-I and Pen-R isolates.

### Development of Resistance to Other Antimicrobials

The increasing incidence of penicillin-resistant *S. pneumoniae* has been paralleled by an increase in resistance to other classes of antimicrobial agents. A recent Centers for Disease Control and Prevention (CDC) study of the drug susceptibility of clinical *S. pneumoniae* isolates obtained from sterile sites and collected from 13 hospitals in 12 states quantified the extent of DRSP in a large geographical area. Of the 544 isolates, 16.4% were resistant to at least one of the nine antibiotics tested. Penicillin resistance was noted in 6.6% of isolates, including 1.3% of isolates that were Pen-R. Most penicillin-resistant *S. pneumoniae* isolates were resistant to at least one additional class of antimicrobial agents, and 5.9% of all isolates were identified as multidrug-resistant *S. pneumoniae* (MRSP) [14]. This finding suggests that penicillin resistance serves as a marker of resistance to other drugs.

The incidence of erythromycin resistance is reported to be as high as 19% in the United States [15]. Resistance may develop because of modifications of the ribosome or the presence of a macrolide efflux system. *S. pneumoniae* strains that are resistant to erythromycin are also considered resistant to all other macrolides; however, because the tissue concentrations of new macrolides often exceed that of erythromycin, these newer macrolides might still be effective in certain settings of nonbacterial localized infection. The incidence of macrolide resistance is higher among penicillin-resistant isolates. The incidence of resistance to trimethoprim-sulfamethoxazole has also increased considerably in the past two decades. In the United States, the reported incidence of resistance varies from 18%–60% [16, 17].

The incidence of fluoroquinolone-resistant *S. pneumoniae* remains low (<5%). Whether this reflects the limited use of these agents in patients with suspected *S. pneumoniae* infections, their limited use in children, their expense, or other reasons is not known. Resistance to other antibiotics that are rarely used in the United States to treat *S. pneumoniae* infections, such as tetracycline, clindamycin, chloramphenicol, and rifampin, is unusual, but the incidence of resistance is higher in other parts of the world where the use of these agents is widespread. However, erythromycin-resistant *S. pneumoniae* strains are often resistant to clindamycin.

Most reports of the incidence of DRSP involve large geographical areas, but the incidence of DRSP varies considerably not only between communities but also within a single community and even between different types of patients. A recent 10-month study was performed in a single large metropolitan area of the United States to investigate the prevalence of DRSP among 431 patients with invasive *S. pneumoniae* infection [18]. The community-wide rate of resistance was reported to be 25%, but the prevalence of DRSP varied considerably from <5% to one-third of isolates, depending on the hospital. The incidence of DRSP was greatest among white children <6 years old, a population that frequently receives empirical antimicrobial therapy. The experience with DRSP to date suggests that if the present approach to managing these infections continues, DRSP will almost certainly become common throughout the United States and that even in communities where DRSP remains uncommon, resistance may develop rapidly [8]. This circumstance underscores the importance of continuous surveillance of the incidence of DRSP, especially among specific populations at increased risk [19].

Several important lessons have been learned about the DRSP epidemic. First, excessive selective pressure, especially when associated with the empirical use of antibiotics (i.e., treatment of upper respiratory and otitis infections in children), and close exposure to carriers appear to be the major causes for the development of DRSP [10]. Second, the incidence of DRSP can increase rapidly, eventually resulting in a high prevalence of the organism. In some countries 70% of isolates are reported to be DRSP [20]. Finally, resistance to other antibiotics and the incidence of MRSP frequently parallel the incidence of penicillin resistance [18].

### Identification of Drug-Resistant *S. pneumoniae* in Patients with Pneumonia

One of the most important factors affecting outcome for patients with infections is the rapid introduction of appropriate

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**Table 1. MIC breakpoints for common agents used to treat *Streptococcus pneumoniae* infection.**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (µg/mL)</th>
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<tr>
<td></td>
<td>Susceptible</td>
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<tr>
<td>Penicillin</td>
<td>≤0.06</td>
</tr>
<tr>
<td>Cefotaxime, ceftriaxone,</td>
<td>≤0.5</td>
</tr>
<tr>
<td>ceferroxime, or cefepine*</td>
<td>≤0.12</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤0.25</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>=4.0</td>
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<tr>
<td>Chloramphenicol</td>
<td>=0.5/9.5</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>≤2.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤2.0</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>≤2.0</td>
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**NOTE:** Data are from [11].

* Currently, these are the only cephalothin derivatives that have established susceptible, intermediate, and resistant National Committee on Clinical Laboratory Standards–recommended MICs for *S. pneumoniae*.
Frequent empirical treatment with antimicrobial agents are recently received antibiotic therapy, and among family members on 21 January 2018 by guest.

The spread of DRSP in the community is important, but even when been well described. Since 1980 antimicrobial use by office-ording group [30].

Populations at Increased Risk of Exposure to DRSP

Because of the limitations of diagnostic testing, it is important to recognize which patients are at increased risk for exposure to DRSP (table 2). Obviously, knowing the prevalence of DRSP in the community is important, but even when DRSP is rarely isolated, there still may be populations at increased risk for exposure. Community carriage rates are best studied among children, for whom day care attendance and frequent empirical treatment with antimicrobial agents are known risk factors for DRSP infection [10]. For adults, rates of DRSP carriage are highest among those who are institutionalized in nursing homes, hospitals, or prisons, possibly among military personnel, among the elderly, among those who recently received antibiotic therapy, and among family members when at least one child is attending a day care center [24–27].

What Measures Might Limit the Spread of DRSP?

The development of DRSP has heightened interest in preventive measures. Presently available polyvalent S. pneumoniae vaccines, which contain capsular polysaccharide from 23 different serotypes/groups, include >85% of serotypes in which penicillin resistance is found. Unfortunately, vaccination rates have remained low (25%–30%), and the protection afforded by vaccination is often incomplete and frequently not lifelong [28]. Antibody titers are raised in only 60%–70% of persons who are vaccinated, and the antibody response is even less in persons >85 years of age, those who are immunosuppressed, and those who are asplenic [28, 29]. Because vaccination is subject to these limitations but has minimal side effects, some investigators have suggested revaccination every 6 years and possibly more frequently for persons with potentially limited antibody responses. Spread of DRSP is common in certain settings such as nursing homes, hospitals, and day care centers, which raises the question of whether the workers in these settings should also be vaccinated.

An effective S. pneumoniae vaccine is not presently available for children <2 years old, a group in which S. pneumoniae colonization is common and in which empirical antibiotic therapy is frequent. Not surprisingly, this population serves as a major reservoir for DRSP. Protein-conjugate vaccines are currently being tested in clinical trials, and although these vaccines are restricted to a small number of serotypes, the availability of an adjuvant vaccine directed against the most common DRSP serotypes could substantially reduce the incidence of S. pneumoniae colonization and infection as well as the need for antibiotics. This could have a potentially significant impact on the incidence of DRSP.

The spread of S. pneumoniae among nursing home residents and hospitalized patients might be reduced by vigorous adherence to infection control measures including handwashing, limited empirical use of antimicrobial agents, and aggressive monitoring for DRSP. A more detailed discussion on minimizing the impact of DRSP was recently published by the DRSP working group [30].

Finally, a reduction in the overprescription and inappropriate use of antimicrobial drugs would be beneficial. Increased rates of antimicrobial use and the development of resistance have been well described. Since 1980 antimicrobial use by office-based physicians has increased by 28% for all age groups, and

<table>
<thead>
<tr>
<th>Table 2. Risk factors for drug-resistant S. pneumoniae infection.</th>
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<tr>
<td>Extreme of age (especially &lt;6 years)</td>
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<tr>
<td>Recent antimicrobial therapy</td>
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<tr>
<td>Coexisting illness or underlying disease</td>
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<tr>
<td>HIV infection</td>
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<tr>
<td>Immunodeficiency</td>
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<tr>
<td>Attending day care center</td>
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<tr>
<td>Family member of child attending day care center</td>
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<tr>
<td>Recently or currently hospitalized</td>
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<tr>
<td>Institutionalized (e.g., nursing home or prison)</td>
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<tr>
<td>Member of the military (?)</td>
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NOTE. Data are from [10, 24–27].

antimicrobial therapy. Unfortunately, despite extensive diagnostic testing, a causative agent is identified in only ~50% of all cases of pneumonia, and the efficacy of using clinical, laboratory, and radiographic findings to determine an etiology (syndromic approach) is also questionable [21, 22]. The performance of blood cultures probably should be considered for all hospitalized patients with pneumonia. Performing cultures of extrapulmonary sites of infection such as pleural fluid, joint fluid, or the CNS is appropriate when these sites are suspected of being infected. To date, no large studies have been performed to evaluate the role of sputum gram stain or culture in the management of lower respiratory tract infections due to DRSP, much less to compare their diagnostic accuracy with that of “gold-standard techniques” (i.e., a culture of blood, a transthoracic needle aspirate, or pleural fluid). Clearly, even if S. pneumoniae could reliably be identified by gram staining, determining antimicrobial susceptibilities would require that a sputum culture be performed, and the sensitivity and specificity of sputum cultures have been questioned by many investigators [22, 23].

Even when an organism is isolated, antibiotic susceptibility testing still needs to be performed. The most widely used tests for detecting penicillin resistance are the oxacillin disk diffusion assay and the Etest (AB BIODISK, Solna, Sweden). With the oxacillin disk diffusion assay, penicillin resistance is suspected when the zone of inhibition is ≤19 mm for a 1-μg oxacillin disk. Unfortunately, while this test is sensitive, it is not very specific; therefore, it is best used as a screening test. The Etest is more specific but costlier. Both tests require 18–24 hours before results are known. Therefore, early treatment of most cases of clinical pneumonia is often necessarily empirical.
rates of antibiotic treatment for children <15 years old are three times as high as the rates for any other age group. Reducing these rates and using antimicrobial therapy more judiciously, especially for infections that are not life-threatening, would be helpful [30]. The CDC is currently in the preliminary phase of developing guidelines.

What Is Known Presently Regarding the Treatment of DRSP Pneumonia?

Unlike the situation with DRSP meningitis, which has been the subject of considerable clinical research [31], the information available regarding the proper treatment of DRSP pneumonia is limited. To date, three prospective studies that included large numbers of subjects, most or all of whom had *S. pneumoniae* pneumonia, have been reported. These studies compared the outcomes of treatment of infections caused by penicillin-susceptible, Pen-I, and Pen-R *S. pneumoniae*. A total of ~1,100 subjects were enrolled, but Pen-R *S. pneumoniae* isolates were uncommon, and Pen-R isolates for which the MIC was \( \geq 4 \mu g/mL \) were rare.

In the first of these three studies, which followed a prospective noninterventional design, Friedland [13] enrolled 108 children without evidence of meningitis and 78 children with pneumonia. There were 34 cases of Pen-I *S. pneumoniae* infection and one case of Pen-R *S. pneumoniae* infection. Pen-I isolates were more common among subjects who were HIV positive or had received antibiotics within the month before enrollment. The MIC of penicillin for the one Pen-R strain was \( \geq 4 \mu g/mL \). The clinical success of antimicrobial therapy was similar for subjects with Pen-I strains and those with penicillin-susceptible strains. Friedland concluded that Pen-I is not a significant factor in the treatment of *S. pneumoniae* pneumonia or occult bacteremia but could not comment on the efficacy of penicillin in treating Pen-R *S. pneumoniae* infection.

In the second study, which was performed over a 10-year period, Pallares et al. [32] recruited 504 adults who had severe culture-proven *S. pneumoniae* pneumonia. A total of 412 isolates were recovered from blood samples. Although 145 (29%) of the isolates were either Pen-I or Pen-R, only 65 (13%) were Pen-R, but the penicillin MIC was not \( >4 \mu g/mL \) for any of them, and only 6% were cephalosporin resistant. The mortality was higher among subjects infected with Pen-I or Pen-R isolates than among those infected with penicillin-susceptible *S. pneumoniae* (38% vs. 24%, respectively; \( P = .001 \)). However, after polymicrobial infections were excluded and predictors of mortality were adjusted, no significant difference in mortality was found.

Pallares et al. [32] concluded that current levels of *S. pneumoniae* resistance to penicillin and cephalosporins are not associated with increased mortality. These investigators stated that high-dose intravenous penicillin G (150,000 to 200,000 U/[kg·d]) might be effective for treating patients with *S. pneumoniae* pneumonia when the MIC of penicillin ranges from 0.12 \( \mu g/mL \) to 2 \( \mu g/mL \). Furthermore, ceftriaxone or cefotaxime would be good alternatives if the MIC of penicillin is higher, but only if the MIC of ceftriaxone or cefotaxime is \( \leq 2 \mu g/mL \).

In the third comparative study by Plouffe et al. [33], 39 of 499 clinical *S. pneumoniae* isolates were classified as DRSP, but only five Pen-R isolates, for which the MICs were \( \geq 4 \mu g/mL \), were recovered. The outcomes were similar for subjects infected by DRSP and those infected by susceptible *S. pneumoniae*, but those infected with DRSP had hospital stays that were a mean of 3.7 days longer. However, no effort to stratify patients on the basis of severity of illness or comorbid factors was reported.

The results of these three studies are limited because the studies were neither randomized nor designed to compare antibiotic efficacy. In addition, the incidence of Pen-R *S. pneumoniae* (MIC, \( \geq 4 \mu g/mL \)) was low, and the authors were unable to determine whether high-dose iv penicillin or ceftriaxone or cefotaxime would be effective when the MIC of these drugs reached a level of \( \geq 4 \mu g/mL \). Finally, the role of resistance to other antimicrobial agents was not evaluated.

In addition to these clinical studies, there have been several recent review articles that have included recommendations on treating DRSP pneumonia [8, 34–36]. Friedland and McCracken [8] believed that intravenous therapy with a \( \beta \)-lactam agent (penicillin G, 150,000–250,000 U/[kg·d], or another \( \beta \)-lactam agent at an equivalent dose) was adequate for infections due to Pen-I strains of *S. pneumoniae*, but for Pen-R strains, they noted several reports of failure. Patients infected by Pen-R *S. pneumoniae* frequently had underlying diseases such as cancer, chronic liver disease, or diabetes mellitus, and their conditions might have influenced outcome. Friedland and McCracken recommended using vancomycin or imipenem for patients suspected of being infected with Pen-R *S. pneumoniae*, e.g., for debilitated patients with nosocomial pneumonia. These investigators noted that another treatment possibility was an extended-spectrum cephalosporin, but only if its MIC was \( \leq 8 \mu g/mL \) for the infecting strain.

While ceftriaxone or cefotaxime have been recommended for treatment of *S. pneumoniae* infections in certain settings, the activity of these agents is not shared by all extended-spectrum cephalosporins. For example, the efficacy of ceftizoxime has been questioned by several investigators [37, 38]. In one study that was conducted to evaluate the activity of penicillin, ceftriaxone, cefotaxime, and ceftizoxime against clinical *S. pneumoniae* isolates, as measured by MICs and time-kill curves, the authors noted that “ceftizoxime is far less active than cefotaxime or ceftriaxone against many pneumococcal isolates” [37]. On the basis of these findings, the authors concluded that “ceftizoxime should not be used to treat proven or suspected pneumococcal infection in areas where resistance to penicillin is prevalent.”

Mandell [34] suggested that vancomycin might be used in cases of community-acquired pneumonia when infection with Pen-R *S. pneumoniae* was a concern. Bryant and Salmon [35]
suggested that when treating S. pneumoniae empyema, ceftriaxone or cefotaxime be used if the S. pneumoniae isolate was only Pen-I and was cephalosporin susceptible. These investigators recommended that vancomycin be used if the isolate is Pen-R and the MIC is >4.0 μg/mL. Finally, Strachan and Friedland [36] stated that although the MIC breakpoint above which penicillin therapy is likely to be ineffective for nonmeningeal infections is unknown, it is probably >4.0 μg/mL.

What Factors Might Change the Present Approach to the Treatment of Patients with S. pneumoniae Pneumonia?

A central problem in the management of pneumonia is that in a significant proportion of cases an etiology is not determined, and even when a pathogen is isolated, susceptibility results are not available for at least 18–24 hours. Since a patient’s clinical course can be affected by the prompt initiation of appropriate antimicrobial therapy, selecting such therapy is of the utmost importance. Therefore, until a rapid and accurate test that is capable of identifying DRSP within a relatively short time (<6 hours) is developed, initial treatment of pneumonia will continue to be empirical. Unfortunately, such a test appears to be years away.

Studies performed to date have shown that the use of high-dose penicillin or certain cephalosporins is adequate for treating S. pneumoniae pneumonia, regardless of whether the organism is penicillin susceptible or Pen-I [32, 33]. Studies investigating the role of therapy in patients with severe pneumonia, significant underlying disease, extrapulmonary involvement, or infections caused by Pen-R organisms for which the MIC is >4 μg/mL or that show increases in resistance to other commonly used antimicrobial agents have yet to be reported. Therefore, this remains a controversial area. Outcome-based studies in these areas need to be performed before many physicians will feel comfortable using high-dose penicillin or certain cephalosporins in these settings.

Presently, because of fear of inducing resistance both in S. pneumoniae and enterococci, empirical use of vancomycin is discouraged, and it is often strictly reserved for special situations. Newer antibiotics that are effective against DRSP infections are either just now becoming available or are in phase 3 trials. The availability of several new drugs or classes of drugs may dramatically alter the empirical treatment of pneumonia in cases where DRSP is a concern. These classes include new fluoroquinolones, the streptogramins, and totally new classes of antibiotics such as the oxazolidinones [11, 39–41].

Despite low levels of fluoroquinolone resistance, use of older fluoroquinolones (ciprofloxacin or ofloxacin) in treating S. pneumoniae pneumonia has been discouraged by a lack of clinical studies and reports of clinical failures [42, 43]. This area remains controversial because there are publications supporting the use of older fluoroquinolones [21, 44]. The newer-generation fluoroquinolones such assparfloxacin and levofloxacin have been best studied. These newer fluoroquinolones accumulate at high concentrations in pulmonary tissue, demonstrate increased activity on a weight basis when compared with older quinolones such as ofloxacin and ciprofloxacin, and have excellent in vitro activity (MIC, 0.25 μg/mL). The incidence of S. pneumoniae resistance to fluoroquinolones has remained low; therefore, these agents presumably should be effective in treating DRSP pneumonia [45]. The safety profile of the fluoroquinolones is good, but some fluoroquinolones do affect cytochrome P-450, while phototoxicity has been reported as a side effect of others (sparfloxacin).

There has been a limited number of clinical trials to determine the efficacy of these newer agents, but several reviews of the early clinical experience with them have recently been published. Results of early studies are promising. An analysis of two double-blind randomized trials that included 1,137 adults hospitalized with community-acquired pneumonia was recently reported; 345 of the cases were caused by S. pneumoniae [46]. Efficacy was significantly better in the sparfloxacin group than in the comparator group (subjects receiving either amoxicillin, with or without clavulanic acid, or erythromycin). In this study, the rates of resistance to amoxicillin and to erythromycin were 8% and 5%, respectively. On the basis of these results, the authors concluded that sparfloxacin is an appropriate and reliable choice for the empirical treatment of community-acquired pneumonia, regardless of the suspected bacterial pathogen. Nevertheless, while pneumococci are not necessarily penicillin resistant, future trends in susceptibility to fluoroquinolones will require monitoring, along with post-marketing surveillance for evidence of questionable clinical efficacy, should more-resistant strains emerge. The results of future clinical trials will be important in determining the role of the new fluoroquinolones in treating S. pneumoniae pneumonia.

Approach to the Treatment of Adults with Pneumonia

In determining appropriate antimicrobial therapy, it is important to remember that the clinical presentation and the virulence of DRSP do not differ from those of susceptible strains of S. pneumoniae and that susceptibility results from any culture will not be available for at least 24 hours. Guidelines for treating both community-acquired pneumonia (CAP) [22] and hospital-acquired pneumonia (HAP) [23] in immunocompetent adults have recently been published. In both sets of guidelines, initial antibiotic choices were empirical. For patients with CAP, antimicrobial choices were based on the most likely pathogen, according to specific groups of patients. These groups were defined by the presence of certain clinical factors including age and the presence of comorbid disease (congestive heart failure, chronic obstructive pulmonary disease, structural lung disease, chronic renal insufficiency, or liver failure) and the severity of illness. For patients with HAP, antimicrobial choices were guided by the most likely pathogen in specific patient groups on the basis of the severity of illness, presence of specific risk factors for certain pathogens, and length of hospital stay before
Community-acquired pneumonia

Outpatients

≤60 years and no comorbidities

Macrolide, tetracycline (smokers, newer macrolide)

Amoxicillin/clavulanate ± macrolide, fluoroquinolone

>60 years and/or comorbidities

Second-generation cephalosporin, TMP/SMZ, β-lactam/β-lactamase inhibitor

Amoxicillin/clavulanate ± macrolide, fluoroquinolone (comorbidities, fluoroquinolone)

Inpatients

Mild-to-moderate

Second-generation or antipseudomonal third-generation cephalosporin, β-lactam/β-lactamase inhibitor ± macrolide

Ceftiraxone or cefotaxime, β-lactam/β-lactamase inhibitor + erythromycin, fluoroquinolone alone

Severe

Macrolide + antipseudomonal third-generation cephalosporin, imipenem/cilastatin, ciprofloxacin

Imipenem/cilastatin, fluoroquinolone, vancomycin

Hospital-acquired Pneumonia

Mild-to-moderate HAP

Core antibiotics: second-generation or antipseudomonal third-generation cephalosporin, β-lactam/β-lactamase inhibitor (if penicillin allergic, fluoroquinolone or clindamycin + aztreonam)

Ceftiraxone, cefotaxime, β-lactam/β-lactamase inhibitor

Severe HAP of early onset, no risk factors

Core antibiotics + additional antibiotics, depending upon risk factors

Fluoroquinolone

Severe HAP of late onset or risk factors

Aminoglycoside or ciprofloxacin + antipseudomonal penicillin, β-lactam/β-lactamase inhibitor, cefazidime or cefoperazone, imipenem/clavulanate, aztreonam ± vancomycin

Aminoglycoside or fluoroquinolone + antipseudomonal penicillin, β-lactam/β-lactamase inhibitor + vancomycin, imipenem/clavulanate

NOTE. ATS = American Thoracic Society; HAP = hospital-acquired pneumonia; TMP-SMZ = trimethoprim-sulfamethoxazole.

* Data are from [22, 23].

† Assumes that the prevalence of Pen-R isolates in the community is low.

‡ Assumes a low prevalence of macrolide resistance in the community; if the incidence of macrolide resistance is high, consider a fluoroquinolone (see text).

§ With additional risk factors, other agents should be added [23].

The development of pneumonia. The authors of both sets of guidelines recognized that antibiotic choices might need to be modified on the basis of local resistance patterns. Concerns over DRSP were not specifically addressed in either study.

Because of the increasing incidence of DRSP, some modifications of these guidelines is in order (table 3). The recommendations regarding diagnostic testing in both guidelines probably remain the same. Whether additional testing should be performed when DRSP might be a concern is presently unknown. Diagnostic testing is justified in the treatment of certain patient populations, not only to identify a specific pathogen but also to stratify for severity of illness. The results of large studies in which intensive diagnostic testing was performed suggest that not all tests are necessary. For example, results from serological testing are often unavailable for weeks, long after a patient has either recovered or died of the infection. In addition, diagnostic testing for patients with pneumonia who are treated in an outpatient setting is frequently very limited because it is expensive and because the tests rarely alter management except in cases where the diagnosis or severity of pneumonia is in doubt or where pneumonia might be complicated by other factors (i.e., the patient is a smoker who is at increased risk of cancer).

Certain diagnostic studies should be considered for all hospitalized patients with pneumonia. These studies include blood cultures, chest radiographs (preferably posteroanterior and lateral), and certain laboratory tests. It is helpful to perform blood cultures, since they can identify the infecting pathogen, or if negative, suggest a less severe process. Findings on a chest radiograph can indicate other noninfectious or infectious causes of disease (e.g., cancer or tuberculosis), more severe illness (multiorgan infiltrates), or the presence of pleural effusions and lung abscesses, which would influence therapy. Laboratory test results can indicate organ dysfunction and severe hypoxemia.

To treat CAP in the outpatient setting, the age of the patient (≤60 years or >60 years) and the presence of underlying disease should be considered in determining appropriate empirical antibiotic therapy. If a patient is young and does not have comorbid disease, then the current recommendations of a macrolide or a tetracycline are appropriate. For smokers, one of the newer macrolides is recommended. These agents offer a broad spectrum of activity that covers the most common organisms, they are effective for empirical treatment when the risk for DRSP is low, and adverse outcomes are extremely rare. When resistance to macrolides is common in a community or a patient is at risk for infection with DRSP, then an oral
fluoroquinolone alone or amoxicillin/clavulanate plus a newer macrolide can be used. Older patients (>60 years) and/or patients with comorbid processes are at increased risk for morbidity and mortality. Among older otherwise healthy and stable patients, the risk of infection due to DRSP is low, and amoxicillin/clavulanate, with or without a macrolide, is usually acceptable therapy. When a comorbid process or more serious CAP that does not require hospitalization is present, different antibiotics are required, and amoxicillin/clavulanate, with or without one of the newer macrolides, or an oral fluoroquinolone alone should be considered. Historically, in this population ≤20% of patients initially treated as outpatients ultimately have required hospitalization, but the mortality has been reported to be <5%.

For hospitalized patients with mild-to-moderate CAP—i.e., those usually treated on the ward—intravenous antimicrobial choices include cefotaxime or ceftriaxone or a β-lactam/β-lactamase inhibitor like piperacillin/tazobactam, with or without a macrolide, or possibly a fluoroquinolone alone. If higher levels of Pen-R (MIC, ≥4 μg/mL) is a concern, then imipenem/cilastatin, with or without a macrolide, or a fluoroquinolone should be considered. Mortality among hospitalized patients with mild-to-moderate CAP has historically been reported to be 8%–14%.

For severe CAP, which usually requires intensive care, the use of endotracheal aspiration, a protected specimen brush, or bronchoalveolar lavage should be considered for obtaining specimens for culture. Endotracheal aspiration, especially for patients who have not received prior antibiotics, may be helpful in excluding possible pathogens. In addition, a chest radiograph should be obtained, and blood cultures and cultures of any other clinically apparent sites of infection (i.e., the CNS or pleural fluid) should be performed. If there is concern that the patient might be infected with highly Pen-R S. pneumoniae (MIC, ≥4 μg/mL), strong consideration should be given to administering intravenous therapy that includes vancomycin, imipenem/cilastatin, or one of the newer fluoroquinolones until the results from diagnostic studies are obtained.

While the diagnostic approach to the patient with HAP is similar, the treatment of HAP differs from that of CAP. When HAP is present, it is recognized that all patients are at risk of infection by several “core” pathogens. These core pathogens include S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus, and aerobic gram-negative bacilli but not Pseudomonas aeruginosa or Acinetobacter species. On the basis of these core pathogens, a set of core antimicrobial agents have been suggested. Additional antimicrobial agents have been added on the basis of other factors, including the severity of illness, presence of specific risk factors, and length of hospitalization before the development of HAP. When the risk of DRSP infection is significant, then the regimen of these core antimicrobial agents should be modified. For patients with mild-to-moderate HAP, imipenem/cilastatin, a β-lactam/β-lactamase inhibitor (i.e., piperacillin/tazobactam), a fluoroquinolone, or possibly clindamycin plus aztreonam should be considered. For patients with severe HAP, coverage must be directed both at P. aeruginosa and Acinetobacter species, as well as the possibility of DRSP; therefore, the addition vancomycin may be considered.

These recommendations should be further expanded on the basis of additional findings. Because of the limited tissue concentration in the meninges, when meningitis is suspected (regardless of the severity of pneumonia), there is good evidence to suggest that cefotaxime would be effective unless there is concern about resistance, in which case vancomycin should be used. Furthermore, the use of vancomycin might be considered if bacterial pericarditis is suspected; however, the role of vancomycin in treating this type of infection has not been reported. The use of vancomycin should be restricted to other sites of infection unless highly resistant DRSP is identified or suspected or a physician is concerned about the outcome for a patient.

Summary

Although there is limited experience in treating infection due to DRSP, a clearer picture of this epidemic is coming into focus. It is appreciated that the incidence of resistant S. pneumoniae varies considerably throughout the United States, although it is increasingly becoming a country-wide problem; and once DRSP is identified locally, its incidence might increase rapidly. Resistance to penicillin often parallels the development of resistance to other antimicrobial agents, especially in specific groups (table 2). The outcome for patients infected with DRSP can be improved with the rapid institution of effective antimicrobial therapy. Intravenous treatment with high-dose penicillin or a third-generation cephalosporin appears to be effective in eradicating S. pneumoniae when the MIC of penicillin is <4 μg/mL, except where tissue penetration is low, such as in meninges [30]. When possible, the empirical use of vancomycin should be discouraged to prevent the development of resistance.

While much is understood about the DRSP epidemic, questions remain for which answers are presently unknown and which may affect therapy in the future. These questions are as follows: will the incidence of high-level DRSP accelerate or plateau? How high can the MIC for DRSP rise? Does the initial use of ineffective therapy while awaiting results of susceptibility studies affect outcome and if so in what settings? What will be the role of newer antimicrobial agents in treating pneumonia? And most importantly, can the judicious use of empirical therapeutic regimens consisting of newer antimicrobial agents with excellent activity against DRSP, combined with an adjuvant vaccine for S. pneumoniae, reduce the rate of DRSP?

References