A number of different studies have dealt with the problem of evaluating the effects of antibiotic use on antibiotic resistance (especially penicillin resistance) in *Streptococcus pneumoniae*. The final aim of these studies has been to find which antibiotic therapy represents an increased risk for antibiotic-resistant infections either for the individual patient or for the community at large. In a variation of this theme, Vanderkooi et al. [1], in this issue of *Clinical Infectious Diseases*, have tried to identify risk factors, including previous antibiotic treatment, predictive of antibiotic resistance in invasive *S. pneumoniae* infections. The authors suggest that information about patient history and previous antibiotic use can help in choosing more-appropriate empirical therapy for pneumococcal infections. The investigators, who examined >3000 invasive pneumococcal infections in the Toronto area over a span of 7 years, found that previous use of trimethoprim-sulfamethoxazole (TMP-SMX), clarithromycin, azithromycin, and fluoroquinolones was a strong predictor for infection with an isolate that was resistant to the same class of antibiotics, whereas the association between previous use of penicillin and penicillin-resistant isolates was less strong. They also observed that previous use of agents from any antibiotic class except fluoroquinolones was associated with pneumococcal infections due to isolates that were resistant also to agents from other antibiotic classes, including penicillin. This coselection was especially observed following use of azithromycin.

The experience of Vanderkooi et al. [1], although interesting, cannot be directly applied to different areas or contexts. The capability to predict resistance on the basis of previous use of antibiotics and the strength of the associations found between resistance and the use of specific antibiotics would differ in relation to the frequency of resistance in each community. In the Toronto area, the rate of antibiotic resistance among invasive *S. pneumoniae* appears to be at a moderate level, with resistance rates in 2002 (the last year of the study) of 6.2% for penicillin, 13.1% for erythromycin, 10% for TMP-SMX, and 1.2% for levofloxacin. In other areas of the world, the situation looks far bleaker. In the United States, the rates of resistance to penicillin, erythromycin, TMP-SMX, and levofloxacin among invasive pneumococcal isolates were 24%, 15%, 29%, and <1%, respectively, of all isolates monitored in 1998 by the Active Bacterial Core surveillance (ABCS) program [2]. In some areas, such as Tennessee, the proportion of penicillin-resistant isolates was higher, and isolates with very high levels of resistance to penicillin (MIC, ≥8 μg/mL) have emerged [3]. The success of the 7-valent conjugate pneumococcal vaccine in significantly reducing the rate of antibiotic-resistant invasive pneumococcal infections following its introduction in 2000 [4, 5] might be only transitory, because the prevalence of penicillin resistance among nonvaccine strains that are replacing the vaccine strains is increasing [6]. In Europe, the proportion of invasive *S. pneumoniae* strains that are resistant to penicillin appears to vary widely according to geographical area, although it has remained substantially stable during the past few years, according to the European Antibiotic Resistance Surveillance System (EARSS) [7]. In 2003, the EARSS [7] observed a mean penicillin nonsusceptibility rate of 10%, but this finding included countries with rates >30% (in Spain, France, and some Eastern European countries) and <5% (in United Kingdom, Germany, and the Scandinavian countries). In contrast, the prevalence of erythromycin resistance among pneumococci is continuously in-
creasing throughout Europe, and in several countries, including France, Italy, Belgium, and Spain, 30%-50% of all isolates are resistant to this agent [7]. To complicate the picture, multiple-drug resistance is emerging: penicillin-resistant S. pneumoniae are increasingly becoming resistant to other antibiotics, including cephalosporins, macrolides, TMP-SMX, and tetracycline [2].

In the study by Vanderkooi et al. [1], there are 2 aspects that deserve to be emphasized because of their importance. The first is the stronger potential that long-acting macrolides have versus erythromycin in the selection of macrolide-resistant S. pneumoniae. This potential has been known for some years and has been clearly shown in population-based studies. In Italy, where the rate of erythromycin resistance among invasive S. pneumoniae isolates has steadily increased since the mid 1990s, erythromycin resistance is lower in the northern regions than in the southern regions. Differences in prescribing practices in the different Italian areas exist, and a strong association between use of macrolides and rates of erythromycin resistance has been found [8]. The strongest correlation between resistance and macrolide use was found with clarithromycin and azithromycin, long-acting macrolides that are used more often than erythromycin in Italy. In 2000, the numbers of defined daily doses per 1000 inhabitants were 0.3, 3.5, and 1.0 for erythromycin, clarithromycin, and azithromycin, respectively, according to data from the Italian Ministry of Health (available at: http://www.ministerosalute.it/medicinali/osmed/osmed.jsp). The peculiar pharmacokinetics of long-acting macrolides that ensures a low serum concentration of the antibiotic for a prolonged time seems to be responsible for the selection of resistant strains. It is important to note that long-acting macrolides are also associated with selection of penicillin-resistant isolates both at the patient level [1] and the population level [8].

The second aspect concerns resistance to fluoroquinolones. In the study by Vanderkooi et al. [1], both fluoroquinolone use and acquisition of pneumococcal infection in a nursing home or hospital were independent risk factors for a fluoroquinolone-resistant infection. If the patient had received a fluoroquinolone and was a resident of a nursing home, the proportion of infections due to levofloxacin-resistant isolates jumped from 0.14% to 23%. Patients in nursing homes are likely to receive antibiotics to treat the 2 most frequent bacterial infections seen in geriatric patients, respiratory infections (pneumonia and acute exacerbations of chronic bronchitis) and urinary tract infections [9]. Therefore, they are likely to receive multiple courses of antibiotics, including “older” fluoroquinolones that have the potential to select for S. pneumoniae isolates with first-step mutations in the quinolone-resistance determining regions of topoisomerase IV genes [10]. In turn, these isolates are more likely to acquire second-step mutations in the DNA gyrase genes that confer resistance to the newer “respiratory” quinolones [10]. Nursing home residents aged ≥65 years have a risk of acquiring an invasive pneumococcal infection that is 4.3 times that for community residents of the same age, according to the ABCS network in the United States [11]. In 2000–2001, resistance to fluoroquinolones was significantly more common among isolates obtained from patients in long-term care facilities than among community patients of the same age, with rates of resistance to ciprofloxacin and levofloxacin of 8.7% and 4.2%, respectively, among isolates from the former group and 2.2% and 0.4%, respectively, among isolates from the latter group [11]. In Hong Kong, where high rates of fluoroquinolone resistance among S. pneumoniae have been observed since 1999, risk factors associated with infection due to levofloxacin resistance were fluoroquinolone exposure and nursing home residence [12]. The hypothesis that nursing homes represent an environment in which fluoroquinolone-resistant S. pneumoniae strains emerge and spread deserves careful evaluation. Characteristics of the inhabitants, crowded living conditions, and frequency of antibiotic use contribute to nursing homes becoming “factories” that produce resistant bacteria, to use Stuart Levy’s expression [13]. Because of the lack of effective preventive strategies against the large majority of pneumococcal infections in elderly persons [14], it is likely that the prevalence of antibiotic resistance in S. pneumoniae will further increase in this population, jeopardizing the efficacy of valuable classes of antibiotics, such as fluoroquinolones.

Guidelines for empirical therapy of pneumococcal infections, especially community-acquired pneumonia, should incorporate some of the messages of the study of Vanderkooi et al. [1]. Such guidelines should give a preference to antibiotics that are effective for the individual patient but that also minimize the risk of selecting antibiotic-resistant strains in the patient’s community.

Acknowledgments


References

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