Predicting Antimicrobial Resistance in Invasive Pneumococcal Infections

Otto G. Vanderkooi,1,2 Donald E. Low,1,2 Karen Green,2 Jeff E. Powis,1,2 and Allison McGeer,1,2 for the Toronto Invasive Bacterial Disease Network

1Department of Laboratory Medicine and Pathobiology, University of Toronto, 2Shared Department of Microbiology, Toronto Medical Laboratories and Mount Sinai Hospital, Toronto, Canada

(See the editorial commentary by Pantosi and Moro on pages 1298–1300)

Background. The prevalence of multiantimicrobial resistance among Streptococcus pneumoniae continues to increase worldwide. In patients presenting with infection possibly due to pneumococci, recognition of risk factors that would identify those likely to have an antibiotic-resistant isolate might assist clinicians in choosing the most appropriate empirical therapy.

Methods. A prospective cohort study of invasive pneumococcal infection was conducted in Toronto, Canada. Risk factors for antimicrobial resistance were evaluated by means of univariate and multivariate modeling.

Results. A total of 3339 patients with invasive pneumococcal infection were identified between 1995 and 2002. Multivariate modeling revealed that risk factors for infection with penicillin-resistant as opposed to penicillin-susceptible pneumococci were year of infection (odds ratio [OR], 1.28; \( P < .001 \)), absence of chronic organ system disease (OR, 1.72; \( P < .001 \)), and previous use of penicillin (OR, 2.47; \( P < .001 \)), trimethoprim-sulfamethoxazole (TMP-SMX; OR, 5.97; \( P < .001 \)), and azithromycin (OR, 2.78; \( P < .001 \)). Infection with TMP-SMX–resistant pneumococci was associated with absence of chronic organ system disease (OR, 1.64; \( P < .001 \)) and with previous use of penicillin (OR, 1.71; \( P < .001 \)), TMP-SMX (OR, 4.73; \( P < .001 \)), and azithromycin (OR, 3.49; \( P < .001 \)). Infection with macrolide-resistant isolates was associated with previous use of penicillin (OR, 1.77; \( P < .001 \)), TMP-SMX (OR, 2.07; \( P < .001 \)), clarithromycin (OR, 3.93; \( P < .001 \)), and azithromycin (OR, 9.93; \( P < .001 \)). Infection with fluoroquinolone-resistant pneumococci was associated with previous use of fluoroquinolones (OR, 12.1; \( P < .001 \)), current residence in a nursing home (OR, 12.9; \( P < .001 \)), and nosocomial acquisition of pneumococcal infection (OR, 9.94; \( P < .001 \)).

Conclusions. Knowledge of antimicrobial use during the 3 months before infection is crucial for determining appropriate therapy for a patient presenting to the hospital with an illness for which S. pneumoniae is a possible cause. Nosocomial acquisition and nursing home acquisition are significant risk factors for infection with fluoroquinolone-resistant pneumococci.

Streptococcus pneumoniae is a leading cause of pneumonia, bacteremia, sepsis, and meningitis, with an estimated annual incidence of invasive disease of 12–17 cases per 100,000 population [1]. Antimicrobial therapy has resulted in reduced morbidity and mortality rates associated with invasive pneumococcal disease [2], especially when administered early in the course of illness [3]. However, the success of antimicrobial therapy is threatened by the increasing prevalence of antimicrobial resistance among S. pneumoniae [4–11]. There is increasing evidence that discordant empirical therapy administered at presentation to the hospital results in increased rates of morbidity and mortality among patients with serious bacterial infections [12–18]. Because most initial antimicrobial therapy is empirical, it would be of value for clinicians to be able to predict which patients are at increased risk for infection with a resistant strain of S. pneumoniae.

Several studies have documented that both carriage of and infection with antimicrobial-resistant pneumococcal isolates are associated with extremes of age [19, 20], underlying illness [20], institutionalization [20], previous antimicrobial use [19, 20], and community
or household exposure to resistant isolates [21]. However, these studies have not considered whether these factors could be used to improve the choice of antimicrobials for treating patients with serious disease. The objectives of this study were to determine whether patient and disease characteristics could be used to predict patterns of antimicrobial resistance in isolates of S. pneumoniae that caused invasive disease.

**METHODS**

**Population-based surveillance.** From 1 January 1995 through 31 December 2002, the Toronto Invasive Bacterial Diseases Network studied all invasive pneumococcal infections in persons living in metropolitan Toronto and the regional municipality of Peel in Ontario, Canada (1995 population, 3.5 million). Invasive pneumococcal infection was defined as illness in which S. pneumoniae was isolated from a normally sterile body site. Personnel from all hospital laboratories and the 2 largest private laboratories serving residents of the study area (which was defined by postal code of residence) telephoned the study office when S. pneumoniae was isolated from specimens obtained from residents. Primary data, including age, sex, and site of infection, were provided by participating laboratories. Informed consent was obtained to collect isolates and detailed clinical data. Annual audits were performed to evaluate the accuracy of reporting. The study was approved by the research ethics boards at all participating institutions.

Cases were considered to be nosocomial if the disease was not present or incubating at admission to the hospital [22]. Clinical diagnoses (e.g., pneumonia) were recorded on the basis of notes made by attending physicians. Antimicrobial therapy during the 3 months before presentation to the hospital included both oral and parenteral medications and was identified by chart review, by patient interview, and by contacting the patient’s primary care physician and all other physicians identified as having provided care. For this study, if there was disagreement between physician records and patient recollection about antibiotic use, the physician records were deemed to be correct [23]. For purposes of this analysis, penicillin refers to any antimicrobial in the penicillin class.

**Laboratory analysis.** Isolates were sent to the central laboratory at Mount Sinai Hospital (Toronto), where they were confirmed as S. pneumoniae by standard methodology, including colonial morphology on blood agar, bile solubility, and susceptibility to optochin. Antimicrobial susceptibility testing was performed using microbroth dilution techniques, and results were interpreted according to NCCLS guidelines [24–26]. Antimicrobial agents were supplied by their respective manufacturers or were purchased from Sigma.

**Statistical analysis.** Data were analyzed using SAS for Windows, release 8.02 (SAS Institute), and Epi Info, version 2002 (Centers for Disease Control and Prevention). Differences in group proportions were assessed by means of χ² analysis or Fisher’s exact test. Differences in means were assessed by Student’s t test (for normally distributed variables) or the Wilcoxon rank-sum test. Logistic regression models were used for multivariable analysis of risk factors for antimicrobial resistance in infecting isolates of pneumococci. Variables considered for inclusion in the models were those revealed by univariate analysis to be potentially associated with these outcomes (P < .15). We first evaluated the colinearity of variables and attempted to select variables that represented independent risks of disease severity. We then used stepwise backward elimination of non-significant variables to arrive at a final model.

The primary analysis of the impact of previous antimicrobial use classified patients for whom we could not determine whether antibiotics had been received in the 3 months before presentation as not having received antibiotics. There were few significant differences in the results of analyses for factors associated with nonsusceptibility (defined as resistance or intermediate susceptibility to antimicrobial agents) versus resistance: when differences exist, they are identified. For analysis of the impact of previous antimicrobial use, the primary analysis included patients for whom we could not determine whether antibiotics were used in the 3 months preceding infection. Such patients were classified as not having used antibiotics. There were no statistically significant differences between results of the primary analysis and results of a secondary analysis that excluded patients for whom previous antibiotic use could not be determined. ORs presented define the odds that a patient with invasive pneumococcal infection and a particular risk factor will be infected with an isolate that is resistant (versus susceptible or of intermediate susceptibility) to the antibiotic being considered.

**RESULTS**

The demographic and clinical characteristics of the 3339 patients in whom invasive pneumococcal disease was identified during the study period are shown in table 1. The overall annual incidence of invasive pneumococcal disease was 12.0 cases per 100,000 population. The case-fatality rate was 19.4% (627 of 3231 patients for whom information was available). For 3194 patients (95.7%), S. pneumoniae was isolated from blood cultures; for 112 (3.7%), S. pneumoniae was isolated only from CSF; and for 17 (3.5%), S. pneumoniae was isolated from a specimen taken from another normally sterile site (e.g., pleural fluid and synovial fluid). Data regarding antimicrobial use during the 3 months before infection are shown in figure 1.

Over the 8-year period, the prevalence of penicillin resistance among study isolates increased from 0.91% to 6.23% (P < .001), ceftriaxone resistance increased from 0% to 1.78% (P = .01), erythromycin resistance increased from 4.6% to 13.1% (P < .001), and levofloxacin resistance increased from 0.3% to
Table 1. Demographic and clinical characteristics of patients with invasive pneumococcal infections—Toronto, 1995–2002.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients with characteristic/total no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>767/3339 (23)</td>
</tr>
<tr>
<td>15–64</td>
<td>1208/3339 (36)</td>
</tr>
<tr>
<td>≥65</td>
<td>1364/3339 (41)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1520/3296 (46)</td>
</tr>
<tr>
<td>Institution associated with acquisition</td>
<td></td>
</tr>
<tr>
<td>Nursing home</td>
<td>264/3264 (8.1)</td>
</tr>
<tr>
<td>Hospital</td>
<td>138/3264 (4.2)</td>
</tr>
<tr>
<td>Underlying condition*</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1379/3264 (42)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>609/3264 (19)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>517/3264 (16)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>484/3264 (15)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>431/3264 (13)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>312/3264 (9.6)</td>
</tr>
<tr>
<td>History of previous pneumococcal infection</td>
<td>84/3264 (2.6)</td>
</tr>
<tr>
<td>Clinical syndrome</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2172/3264 (67)</td>
</tr>
<tr>
<td>Bacteremia without focus</td>
<td>621/3264 (19)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>178/3264 (5.5)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>99/3264 (3.0)</td>
</tr>
<tr>
<td>Other</td>
<td>195/3264 (6.0)</td>
</tr>
</tbody>
</table>

NOTE. Denominators differ because information was not complete in all cases.

* The sum of the patients with the individual underlying conditions is >3264 because patients may have had >1 underlying condition.

1.20% (P = .05). There was no change in the prevalence of resistance to trimethoprim-sulfamethoxazole (TMP-SMX; overall rate, 9.96%). Resistance to penicillin, ceftriaxone, erythromycin, and TMP-SMX were highly correlated: of the 114 penicillin-resistant isolates, 49 (43%) were resistant to erythromycin, and 90 (78%) were resistant to TMP-SMX; of the 275 erythromycin-resistant isolates, 49 (18%) were resistant to penicillin, and 102 (37%) were resistant to TMP-SMX; and of the 290 TMP-SMX–resistant isolates, 90 (31%) were resistant to penicillin, and 102 (35%) were resistant to erythromycin (P<.001 for all outcomes). Fluoroquinolone resistance was not associated with resistance to agents from other antibiotic classes (data not shown).

The prevalence of resistance to penicillin, TMP-SMX, or erythromycin among infecting isolates was greater for children (age, <18 years) than for adults, whereas the youngest patient from whom a levofloxacin-resistant isolate was recovered was 51 years of age (P<.001 for all 4 antimicrobials; figure 2A). Trends in resistance over time were similar in all age groups (data not shown). During the 3-month period before infection, use of penicillin and TMP-SMX was more common among children, and quinolone use was more common among older adults (figure 2B).

The presence of any chronic organ system disease was inversely associated with TMP-SMX resistance, according to univariate and multivariable analysis. HIV infection was associated with erythromycin resistance, and chronic corticosteroid use was associated with fluoroquinolone resistance, according to univariate analysis only (tables 2 and 3). Patients whose infection was acquired in a nursing home or hospital were more likely to have a fluoroquinolone-resistant isolate (adjusted ORs, 12.9 [95% CI, 3.95–43.8; P = .001] and 9.94 [95% CI, 2.22–44.6; P = .003], respectively, for levofloxacin resistance in the infecting isolate). No other clinical or demographic characteristics were associated with infection due to an isolate resistant to any class of antimicrobial. After adjustment for previous antibiotic use, chronic illness, and institutional acquisition, the prevalence of resistance to penicillin, ceftriaxone, and erythromycin was not significantly different for patients infected with an isolate resistant to any class of antimicrobial.

Figure 1. History of antimicrobial use during the 3-month period before infection for patients presenting to the hospital with invasive pneumococcal infection—Toronto, 1995–2002. The sum of the number of known antimicrobials used is >563 because 12.0% of patients received >1 agent. The primary analysis of the impact of previous antimicrobial use classified patients for whom we could not determine whether antibiotics had been received in the 3 months before presentation (“antibiotic use not identified,” above) as not having received antibiotics. There were no statistically significant differences between results of the primary analysis and results of a secondary analysis in which patients for whom previous antibiotic use could not be determined were excluded. TMP-SMX, trimethoprim-sulfamethoxazole.
Predicting Pneumococcal Resistance

Patients who had previously received macrolides, TMP-SMX, or fluoroquinolones were at least 4 times as likely to have an infecting isolate that was resistant to agents from the same class of antimicrobials than were patients who had not received such antimicrobials (figures 3 and 4 and table 3). Previous use of TMP-SMX, azithromycin, and penicillin were all associated (but to lesser degree) with infecting isolates that were resistant to agents from the other 2 classes of antibiotics. For macrolides, the particular antibiotic used was important for predicting the susceptibility of the infecting isolate, with azithromycin consistently associated with an increased risk of resistance to agents from all classes of antibiotics except fluoroquinolones (figure 4). No within-class differences were detected for penicillins, cephalosporins, or fluoroquinolones (data not shown).

Overall, the prevalence of penicillin resistance among infecting isolates increased from 2.1% for those recovered from patients with chronic organ system disease who had not recently received penicillins, TMP-SMX, or azithromycin, to 7.1%, 10%, and 9.1% among those recovered from healthy persons who previously used a penicillin, TMP-SMX, or azithromycin, respectively. The prevalence of macrolide resistance among infecting isolates increased from 7%–10% (when no antibiotic, an antibiotic from another class, or erythromycin had previously been used) to 28% and 53% if clarithromycin and azithromycin, respectively, had previously been used. Similarly, the prevalence of levofloxacin, gatifloxacin, and moxifloxacin resistance among pneumococci recovered from adults with community-acquired infection increased from 0.14%, 0.15%, and 0% if no fluoroquinolone had previously been used to 4.1%, 3.1%, and 3.1%, respectively, if a fluoroquinolone had previously been used and to 23%, 23%, and 14%, respectively, if a fluoroquinolone had previously been used and the patient resided in a nursing home.

DISCUSSION

The prevalence of multiantimicrobial resistance among S. pneumoniae continues to increase worldwide. Recognition of risk factors that identify patients with a greater likelihood for infection with a drug-resistant pneumococcal strain may allow clinicians to choose the most appropriate empirical therapy. In this study, we found that the most important risk factors were antibiotic use in the preceding 3 months before infection onset and, for fluoroquinolones only, institutional acquisition of infection. Most other factors associated with antimicrobial resistance in univariate analysis were also associated with antibiotic use and were no longer associated with resistance when analysis correcting for antimicrobial use was performed. Thus, children who presented to the hospital with invasive pneumococcal infections were more likely to have received penicillins, TMP-SMX, or macrolides and to have been infected with isolates resistant to these antibiotics; older adults were more likely to have received fluoroquinolones and to have infecting isolates that were resistant to fluoroquinolones. Patient age was not retained in any multivariate models. In addition, we found that the decision about which antimicrobial should be given to a patient with a previous history of use should depend not only on the antimicrobial class associated with previous treatment, but also, for some classes, on the particular antimicrobial used.

The impact of previous antibiotic use on penicillin and cephalosporin resistance was not substantial. Infecting isolates recovered from persons who had not previously received these antimicrobial agents were 1.5–3 times as likely to be resistant (or nonsusceptible) to penicillin and ceftriaxone than were isolates recovered from persons who were naive to treatment with penicillin but not to TMP-SMX or levofloxacin increased significantly over time (table 3).

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The impact of previous antibiotic use on penicillin and cephalosporin resistance was not substantial. Infecting isolates recovered from persons who had not previously received these antimicrobial agents were 1.5–3 times as likely to be resistant (or nonsusceptible) to penicillin and ceftriaxone than were isolates recovered from persons who were naive to treatment with...
these 3 agents. However, similar to other authors [19, 20], we were not able to identify patient-specific characteristics that were very helpful in defining which patients were infected with a penicillin-resistant isolate, possibly because clonal dissemination of strains may be a more important factor in penicillin resistance than direct selective pressure associated with antibiotic use in an individual. In our area, where there is a relatively low prevalence of penicillin and cephalosporin resistance among pneumococci, nearly all isolates (>99.8%) remain susceptible to amoxicillin and third-generation cephalosporins, and therapy with high-dose amoxicillin or the currently recommended dose of ceftriaxone or cefotaxime [27] will provide adequate treatment for all patients, including those who have recently used any antibiotic. In other geographic areas, the impact of clonal dissemination of penicillin-resistant strains may alter both the overall risk of infection with a penicillin-resistant strain and the association between antibiotic use history and resistance to penicillins and cephalosporins.

Macrolides are not homogeneous with respect to their association with antimicrobial resistance. In univariate and multivariate analysis, previous use of erythromycin was not associated with infecting isolates that were resistant to any antimicrobial class; clarithromycin use was associated with an increased likelihood of erythromycin resistance in infecting strains, and azithromycin use was associated with an increased risk of resistance to macrolides, penicillins, and TMP-SMX in infecting strains. More than one-half of the isolates recovered from patients with invasive pneumococcal disease who received azithromycin during the 3-month period before infection were resistant to erythromycin. These findings are consistent with population-level data: in 3 of 4 studies that examined this issue, use of macrolides with a long half-life was associated with a greater prevalence of macrolide resistance among clinical isolates of pneumococci or group A streptococci [28–31]. The association between the increasing prevalence of macrolide resistance among group A streptococcal and pneumococcal strains and the use of long-acting macrolides in both individual patients and populations suggests that selective pressure for resistance may be reduced if shorter-acting macrolides are used preferentially.

Patients in whom a fluoroquinolone has been used have a substantially increased risk of infection with a fluoroquinolone-resistant isolate. However, in our cohort, the prevalence of fluoroquinolone resistance among isolates from patients with community-acquired infections who had not been recently exposed to fluoroquinolones was so low (<0.5%) that the prevalence of fluoroquinolone resistance among isolates from patients with community-acquired infections who had previously received fluoroquinolones was only 3%–4%. In this circumstance, monotherapy with a respiratory fluoroquinolone may still be a reasonable therapeutic choice. It is important to be aware, however, of the increasing number of reports of levofloxacin-, gatifloxacin-, and moxifloxacin-susceptible isolates with mutations in one of the target sites for these agents (i.e., the parC gene). The prevalence of such mutations may be higher among susceptible isolates from patients who have previously received fluoroquinolones [6, 32–36]. In these circumstances, resistance during therapy may emerge, and either primary therapeutic failure or relapse may be more common [33].

In our cohort, patients who acquired their infection in a hospital or nursing home and had received fluoroquinolones in the past 3 months had isolates with high enough rates of resistance to the most active fluoroquinolones (23% and 14% were resistant to gatifloxacin and moxifloxacin, respectively) that monotherapy for such patients is precluded. One potential explanation for the association between institutionalization and fluoroquinolone resistance is the effect of antibiotics used >3 months before the episode of infection. We
Table 3. Multivariate analysis evaluating risk factors for antimicrobial resistance in cases of invasive pneumococcal disease.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Penicillin-resistant isolate</th>
<th>Ceftriaxone-resistant isolate</th>
<th>TMP-SMX–resistant isolate</th>
<th>Erythromycin-resistant isolate</th>
<th>Levofloxacin-resistant isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Year of infection&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.28 (1.14–1.42)</td>
<td>1.20 (1.04–1.38)</td>
<td>NS</td>
<td>1.11 (1.04–1.86)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic organ system disease</td>
<td>0.58 (0.35–0.94)</td>
<td>...</td>
<td>0.61 (0.45–0.82)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Drug use ≤3 months before infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any penicillin</td>
<td>2.47 (1.36–4.71)</td>
<td>...</td>
<td>1.71 (1.06–2.77)</td>
<td>1.77 (1.07–2.94)</td>
<td>...</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>5.97 (2.71–13.2)</td>
<td>...</td>
<td>4.73 (2.73–8.23)</td>
<td>2.07 (1.04–4.12)</td>
<td>...</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>2.78 (0.98–7.86)</td>
<td>...</td>
<td>3.49 (1.61–7.54)</td>
<td>9.93 (4.85–20.3)</td>
<td>...</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>...</td>
<td>NS</td>
<td>...</td>
<td>3.93 (2.16–7.16)</td>
<td>NS</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>...</td>
<td>NS</td>
<td>...</td>
<td>...</td>
<td>12.1 (4.22–35.4)</td>
</tr>
<tr>
<td>Institution associated with acquisition</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing home</td>
<td>...</td>
<td>NS</td>
<td>...</td>
<td>...</td>
<td>12.9 (3.95–43.8)</td>
</tr>
<tr>
<td>Hospital</td>
<td>...</td>
<td>NS</td>
<td>...</td>
<td>...</td>
<td>9.94 (2.22–44.6)</td>
</tr>
</tbody>
</table>

NOTE. NS, not statistically significant (P > .05); TMP-SMX, trimethoprim-sulfamethoxazole.

* In a multivariate analysis using nonsusceptibility as the outcome, ceftriaxone nonsusceptibility in infecting isolates was associated with date of culture, as well as with previous use of penicillin (OR, 2.38; 95% CI, 1.30–4.38; P = .005), TMP-SMX (OR, 3.57; 95% CI, 1.61–7.92; P = .002), and azithromycin (OR, 2.84; 95% CI, 1.03–7.82; P = .04).

<sup>b</sup> Annual ORs are presented.
Figure 3. Association between use of penicillins (A), cephalosporins (B), trimethoprim-sulfamethoxazole (TMP-SMX) (C), and fluoroquinolones (D) during the 3-month period before invasive pneumococcal infection and the antimicrobial susceptibility of the infecting isolates—Toronto, 1995–2003. *P* > .05 for all within-group comparisons, unless otherwise indicated.

asked about antibiotics used only during the 3-month period before infection, because of concern about the reliability of recall for longer periods. It is possible that patients with institutionally acquired infections are more likely to have used fluoroquinolones in the more distant as well as the recent past. Another possible explanation is the acquisition of fluoroquinolone-resistant pneumococci by transmission from other residents or patients. Several nosocomial and nursing home outbreaks of *S. pneumoniae* infection have been reported, and carriage and transmission of resistant pneumococci within institutions may be more common than is usually recognized [35, 37–40].

For community-acquired pneumonia occurring in nursing home residents or nosocomial pneumonia acquired on a medical ward, the American and Canadian Thoracic Societies guidelines recommend monotherapy with a respiratory fluoroquinolone either as first-line treatment or in combination with a β-lactam and a macrolide or doxycycline [41–43]. The more recent update of the Infectious Diseases Society of America guidelines for the treatment of community-acquired pneumonia incorporates (in a footnote) a recommendation to avoid fluoroquinolones in outpatients and patients hospitalized on medical wards who have recently received a fluoroquinolone; however, respiratory fluoroquinolones remain without qualification the recommended first-line treatment for nursing home residents [44]. Clinicians should be aware that the evolution of antimicrobial resistance to levels important enough to warrant changes in empirical therapy may be rapid, and guidelines updated every 3–5 years may not be able to keep up with these changes. Despite the guidelines, in our geographic area (and possibly in others), monotherapy with respiratory fluoroquinolones is no longer acceptable as routine empirical therapy for pneumonia in residents of long-term care facilities.

In conclusion, knowledge of previous antimicrobial use is cru-
cial for determining appropriate therapy for a patient presenting with an illness for which *S. pneumoniae* is a possible cause. The single most important risk factor for resistance to a particular antimicrobial is previous use of antibiotics from the same class. Nursing home acquisition and nosocomial acquisition also play key roles in fluoroquinolone resistance, but neither age nor underlying illness have a significant impact, except to predict the history of antimicrobial use and thus the increased possibility of resistance. The association between antimicrobial resistance and macrolides is drug specific; that is, compared with the use of erythromycin and clarithromycin, the use of azithromycin preferentially selects for resistance to macrolides.

**TORONTO INVASIVE BACTERIAL DISEASES NETWORK INVESTIGATORS**

Investigators in the Toronto Invasive Bacterial Disease Network are as follows: P. Da Camara and J. Downey, Toronto East General Hospital (Toronto, Canada); H. R. Devlin, St. Michael’s Hospital (Toronto); H. Dick, Vita-Tech Laboratories (Toronto); I. N. Gaid, I. Kitai, and J. L. Platt, Rouge Valley Health System (Toronto); P. Garrod and N. Rau, Halton Healthcare Services (Oakville, Canada); R. Lovinsky, D. Neria, and D. Rose, The Scarborough Hospital (Toronto); F. Jamieson, Ontario Public Health Laboratory (Toronto); R. Grossman, Credit Valley Hospital (Mississauga, Canada); J. Kapala, Gamma Dynacare Laboratories (Toronto); S. Krajden, St. Joseph’s Health Centre (Toronto); K. S. Lee and B. Oliver, Humber River Regional Hospital (Toronto); M. Loeb and F. Smaill, Hamilton Health Sciences Center (Hamilton, Canada); M. Lovgren and G. Tyrrell, National Centre for Streptococcus (Edmonton, Canada); A. G. Matlow, Hospital for Sick Children (Toronto); R. McKweon, Peel Region Health Department (Brampton, Canada); B. Mederski, North York General Hospital (North York, Canada); Z. Moloo, P. O’Brien, and C. Quan, William Osler Health Care Centre (Brampton); M. Naus, British Columbia Centers for Disease Control (Vancouver, Canada); K. Ostrowska and A. Sarabia, Trillium Health Centre (Mississauga); P. Shokry and I. Eptitimios, Markham Stouffville Hospital (Markham, Canada); A. E. Simor and M. Vearncombe, Sunnybrook and Women’s College Health Science Centre (Toronto); D. Sturman, Riverdale Hospital (Toronto); P. Van Nostrand, The Rehabilitation Institute of Toronto (Toronto); S. Walmsley, University Health Network (Toronto); B. Willey, S. Pong-Porter, and A. Plevneshi, Toronto Medical Labs/Mount Sinai Hospital (Toronto); B. Yaffe, City of Toronto Public Health (Toronto); and D. Yamamura, MDS Laboratories (Toronto).

**Acknowledgments**

We are grateful to the infection-control practitioners and microbiology laboratory technologists of The Toronto Invasive Bacterial Disease Network, for their ongoing contribution to surveillance, and we thank the many patients and physicians who have willingly agreed to participate in this study. We also thank Sylvia Pong-Porter, for her tireless efforts associated with the identification and susceptibility testing of all isolates, and Raymond Chow, for his assistance with the creation of the figures.

**Financial support.** Canadian Institutes for Health Research, Ontario Thoracic Society, Abbott Laboratories of Canada, and Bayer Healthcare.
Potential conflicts of interest. D.E.L. and A.M. have received grant support from Bayer Healthcare, Hoffman LaRoche, Abbott Laboratories, Pfizer, and Bristol-Myers Squibb, Canada. All other authors: no conflicts.

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