Previous Antibiotic Exposure and Antimicrobial Resistance in Invasive Pneumococcal Disease: Results From Prospective Surveillance

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Background. Estimating the risk of antibiotic resistance is important in selecting empiric antibiotics. We asked how the timing, number of courses, and duration of antibiotic therapy in the previous 3 months affected antibiotic resistance in isolates causing invasive pneumococcal disease (IPD).

Methods. We conducted prospective surveillance for IPD in Toronto, Canada, from 2002 to 2011. Antimicrobial susceptibility was measured by broth microdilution. Clinical information, including prior antibiotic use, was collected by chart review and interview with patients and prescribers.

Results. Clinical information and antimicrobial susceptibility were available for 4062 (90%) episodes; 1193 (29%) of episodes were associated with receipt of 1782 antibiotic courses in the prior 3 months. Selection for antibiotic resistance was class specific. Time elapsed since most recent antibiotic was inversely associated with resistance (cephalosporins: adjusted odds ratio [OR] per day, 0.98; 95% confidence interval [CI], .96–1.00; P = .02; macrolides: OR, 0.98; 95% CI, .96–.99; P = .005; penicillins: OR [log(days)], 0.62; 95% CI, .44–.89; P = .009; fluoroquinolones: profile penalized-likelihood OR [log(days)], 0.62; 95% CI, .39–1.04; P = .07). Risk of resistance after exposure declined most rapidly for fluoroquinolones and penicillins and reached baseline in 2–3 months. The decline in resistance was slowest for macrolides, and in particular for azithromycin. There was no significant association between duration of therapy and resistance for any antibiotic class. Too few patients received multiple courses of the same antibiotic class to assess the significance of repeat courses.

Conclusions. Time elapsed since last exposure to a class of antibiotics is the most important factor predicting antimicrobial resistance in pneumococci. The duration of effect is longer for macrolides than other classes.

Keywords. antibiotic use; fluoroquinolone; resistance; S. pneumoniae.
between antibiotic exposure and infection remains unclear [11]. Insights into the clinical significance of these variables are of value to clinicians in identifying those patients with previous antibiotic exposure who are at highest risk for infection with a resistant strain of *S. pneumoniae*.

The objectives of this study were to determine the extent to which cumulative prior antibiotic exposure, number of treatment courses, and timing of prior antibiotic treatment predict antimicrobial resistance in isolates of *S. pneumoniae* causing invasive disease.

**MATERIALS AND METHODS**

**Population-Based Surveillance for Invasive Pneumococcal Infections**

The Toronto Invasive Bacterial Diseases Network (TIBDN) is a collaboration of all hospitals, microbiology laboratories, infection control practitioners, physicians, and public health units serving the population of metropolitan Toronto and the Regional Municipality of Peel (population 4.1 million in 2012) that performs population-based surveillance for selected serious bacterial and viral infections [4, 8, 12]. All 25 hospitals, 19 laboratories, and 85 long-term-care facilities serving residents of the population area participate in this network. All invasive pneumococcal infections identified by participating laboratories from 1 January 2002 through 31 December 2011 were included in the analyses.

Invasive pneumococcal infection was defined as illness in which *S. pneumoniae* was isolated from a normally sterile body site. Isolates were forwarded to the central laboratory at Mount Sinai Hospital and informed consent was obtained to collect detailed clinical data (including recent antibiotic exposure). Annual audits were conducted in each laboratory to ensure completeness of reporting. For the assessment of 30-day mortality, patients who were cured or improving at discharge before 30 days and not readmitted to the same hospital were assumed to have survived.

Underlying conditions predisposing to invasive pneumococcal disease (IPD) were defined as per the Canadian National Advisory Committee on Immunization [13]. Healthcare-associated infections were defined as those not present or incubating on admission [14].

**Previous Antibiotic Exposure**

We obtained a history of antibiotics received in the 3 months prior to the date of positive culture from patients and/or their next of kin, family physicians, other physicians identified as relevant by patients, and reviews of hospital and emergency department charts. Information obtained included the clinical indication for the antibiotic course, antibiotic name, and start and end dates of antibiotic therapy. Antibiotic exposure was included in analyses if reported by any 1 source. If the same antibiotic was reported by both a physician and a patient, with start dates within 1 week, a single course was assumed using the physician’s reported dates. Where duration of therapy was unavailable, a 5-day course was assumed for azithromycin and a 7-day course for all other antibiotics. Episodes were excluded from class-specific analyses if treatment dates were unavailable for the respective class of antibiotics or if antibiotic class was unknown for any reported course. Only the first episode per individual was included in class-specific analyses. The antibiotics must have been prescribed on an earlier healthcare visit than that at which the culture was obtained. A course of antibiotic was defined as receipt of antibiotics of the same class for an uninterrupted period.

Antibiotic exposure was classified as follows:

1. **Prior**: if the antibiotics were prescribed for a different clinical episode of infection.
2. **Relapse**: if a patient received a course of antibiotics for an illness with the same diagnosis as the current episode of pneumococcal infection and the last dose was taken >48 hours and <14 days prior to the culture yielding *S. pneumoniae*.
3. **Failure**: if a patient was receiving antibiotics (defined as most recent dose <48 hours previously) for the current episode of infection when the culture yielding *S. pneumoniae* was obtained.

**Laboratory Analysis**

Isolates were sent to the central TIBDN laboratory at Mount Sinai Hospital (Toronto, Canada), where they were confirmed as *S. pneumoniae* by standard methodology, including colonial morphology on blood agar, bile solubility, susceptibility to Op-tochin, and AccuProbe (Gen-Probe, San Diego, California). Antimicrobial susceptibility testing was performed using broth microdilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines [15]. European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used for a secondary analysis assessing ciprofloxacin resistance [16]. Serotyping of isolates was performed at the central study laboratory and the National Centre for Streptococcus in Edmonton, Alberta/Winnipeg, Manitoba, according to standard methodology [17]. For these analyses, we defined erythromycin, penicillin, and levofloxacin resistance and ceftriaxone nonsusceptibility in accordance with CLSI guidelines (using meningitis breakpoints for penicillin and ceftriaxone), and fluoroquinolone nonsusceptibility as a ciprofloxacin minimum inhibitory concentration ≥4 mg/L.

**Statistical Analysis**

Data were double-entered and cleaned, then manually inspected for errors and outlying values, which were confirmed or
corrected with original records. Differences in medians were analyzed using the Wilcoxon rank-sum test. Data were analyzed using SAS software version 9.3 (SAS Institute, Cary, North Carolina) and are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Two-sided P values ≤ .05 were considered statistically significant.

Antibiotic class-specific logistic regression models were used to assess the impact of time from end of antibiotic therapy, total duration of antibiotic therapy, and number of antibiotic courses on antibiotic resistance in infecting isolates (due to rare events, for fluoroquinolones, the Firth penalized-likelihood method and profile-likelihood CIs were used). Linearity was evaluated graphically and variables were log-transformed if transformation improved linearity in the logit. We evaluated potential confounders if they were known from previous reports to be associated with resistance to particular antibiotic classes (macrolides; year, age, and human immunodeficiency virus infection; fluoroquinolones: year, immunosuppressive therapy, and hospital or nursing home associated; penicillins: year, age, underlying chronic condition, alcoholism, and hospital or nursing home associated; cephalosporins: year) and were significantly associated with resistance (P ≤ .05) in bivariate analyses in our dataset. Potential confounding by serotype was evaluated in all categories by grouping together 13-valent and 7-valent pneumococcal conjugate vaccine serotypes. Potential confounders were discarded if inclusion increased CIs and did not change primary effect estimates. Because failure of antimicrobial therapy and relapse may be associated with preexisting antibiotic resistance in the infecting isolate, the primary analysis of impact of prior antibiotic therapy was conducted excluding relapsing patients and patients failing antimicrobial therapy. Secondary analyses were conducted including all episodes with antibiotic exposure, including episodes classified as relapses but not those classified as failures, and excluding antibiotic courses whose length was imputed. Likelihood ratio tests of nested models were conducted in SAS using the %VUONG macro [18]. Profile penalized-likelihood P values were calculated in SAS using the %FL macro [19].

Ethics Approval
The study was approved by the research ethics boards at all participating institutions.

RESULTS

During the 10-year period, 4490 episodes of IPD were identified. In children <5 years of age, the incidence of IPD decreased from 34.5 cases per 100 000 in 2002 to 12.4 cases per 100 000 in 2011. Among adults aged ≥65 years, incidence decreased from 2002 to 2005 and then remained stable from 2005 to 2011 (19.9 cases per 100 000 in 2011). In other age groups, the incidence of disease remained stable during the study period, averaging 2.7 cases per 100 000 among children aged 5–14 years and 4.4 cases per 100 000 in adults aged 15–64 years [20].

Detailed clinical information and antimicrobial susceptibility data were available for 4062 (90%) episodes. Median age of patients was 57 years (range, 0–108 years), and 45% (1814/4062) were female. Overall, patients in 31% of episodes (1273/4062) had an immunocompromising condition or were receiving immunosuppressive therapy, and 49% (1990/4062) had a nonimmunosuppressing condition associated with increased risk for IPD. Infection was hospital acquired in 178 of 4062 (4%) episodes and nursing home acquired in 203 of 4062 (5%) episodes. Patients in 88% (3580/4059) of episodes were hospitalized, and 28% (1127/4059) required intensive care unit admission. Among those requiring hospitalization, the 30-day in-hospital mortality rate was 17% (620/3580).

Overall, 21% (845/4062) of isolates were erythromycin resistant, 1% (52/4062) were nonsusceptible to fluoroquinolones (of which 32 [62%] were resistant to levofloxacin), 16% (657/4062) were penicillin resistant, and 6% (243/4062) were nonsusceptible to ceftriaxone. Between 2002 and 2011, resistance to erythromycin increased from 14% to 32% (P < .0001), and resistance to penicillin increased from 15% to 17% (P = .0003), whereas resistance to levofloxacin remained stable.

Figure 1 presents the distribution of IPD episodes according to antibiotic exposure in the prior 3 months. Overall, 1193 (29%) episodes were associated with 1782 prior antibiotic courses (median, 1 [range, 1–13]). These included macrolides (349 courses), fluoroquinolones (436 courses), penicillins (322 courses), cephalosporins (311 courses), other antibiotic classes (292 courses), and 72 courses in which the antibiotic class could not be identified. The 70 (2%) episodes associated with these latter 72 courses were excluded from analyses. Dates of treatment were unavailable for 234 of 1405 (17%) of the remaining macrolide, fluoroquinolone, penicillin, and cephalosporin courses, and the associated episodes were excluded from respective antibiotic exposure analyses. Duration of treatment was imputed for 245 of 1405 (17%) macrolide, fluoroquinolone, penicillin, or cephalosporin courses. The relationships between categories of prior antibiotic exposure and resistance in the infecting isolate are shown in Figure 2.

Table 1 shows the time elapsed since most recent antibiotic course (same class) and cumulative duration of prior antibiotic treatment by antibiotic resistance/nonsusceptibility among those who received antibiotics. Time since most recent antibiotic course was significantly associated with resistance/nonsusceptibility in macrolides, penicillins, and cephalosporins (fluoroquinolones: P = .10). There was no significant association between cumulative days of antibiotic treatment and resistance/nonsusceptibility for any antibiotic class.

Among those with prior antibiotic exposure, the number of courses of cephalosporins was significantly associated with
Figure 1. Flowchart categorizing episodes of invasive pneumococcal disease by antibiotic exposure in the previous 3 months, Toronto Invasive Bacterial Diseases Network, 2002–2011. Antibiotic exposure categories (prior exposure, relapse and failure) are as defined in the “Methods” section. Episodes may have prior exposure to multiple antibiotic classes, so exposure groups are not mutually exclusive.

Figure 2. Antibiotic resistance by antibiotic exposure in the previous 3 months in episodes of invasive pneumococcal disease reported to the Toronto Invasive Bacterial Diseases Network, 2002–2011. Bars represent exposure categories: hatched bars, no prior exposure to antibiotics; solid gray, prior use of different class of antibiotic; diagonal stripes, prior use of same class of antibiotic for a different episode of illness; stippled pattern, relapsed after antibiotic therapy for this episode; and solid black, failing antibiotic therapy. Prior use, relapse, failure, and antimicrobial resistance/nonsusceptibility are as defined in the “Methods” section.
increased risk of resistance/nonsusceptibility. Table 2 displays univariate ORs for antibiotic resistance/nonsusceptibility for time elapsed since most recent antibiotic course and number of antibiotic courses, as well as for other potential risk factors for resistance. In multivariate analyses, more recent antibiotic treatment was significantly associated with risk of resistance/nonsusceptibility in macrolides \((P = .005)\), cefepime \((P = .02)\), and penicillins \((P = .009)\) (fluoroquinolones: \(P = .07\);

Table 3). Secondary analyses including failures and relapses, excluding only failures, and excluding antibiotic courses for which antibiotic resistance/nonsusceptibility in the infecting isolate as per Clinical and Laboratory Standards Institute standards [15], using meningitis breakpoints for penicillin resistance and ceftriaxone nonsusceptibility. Fluoroquinolone nonsusceptibility is defined as a ciprofloxacin minimum inhibitory concentration \(\geq 4\) mg/L.

DISCUSSION

In prospective surveillance of IPD, we were able to confirm the association between prior antibiotic use and pneumococcal resistance. Our results suggest that the time elapsed from most recent treatment and new infection is much more important than cumulative prior antibiotic exposure. For penicillins, cephalosporins, and fluoroquinolones, resistance declines rapidly in the first month after antibiotic exposure, and by 60–90 days after the last dose of antibiotics, the probability of resistance has returned to baseline population levels. For macrolides, the decline in resistance appears to be slower and more continuous.

Although a few prospective studies have examined the relationship between the details of antibiotic exposure and resistance development [21–23], differentiating particular factors related to prior antimicrobial exposure and the development of resistance has been challenging. A recent systematic review by Costelloe et al was unable to detect any studies that
Table 2. Univariate Odds Ratios for the Association Between Antibiotic Resistance in the Infecting Isolate and Antibiotic Treatment and Nonantibiotic Factors in Cases of Invasive Pneumococcal Diseasea With Prior Antibiotic Exposure, Toronto Invasive Bacterial Diseases Network, 2002–2011

<table>
<thead>
<tr>
<th>Variable</th>
<th>Erythromycin Resistanced</th>
<th>Ciprofloxacin Nonsusceptibilityd</th>
<th>Penicillin Resistanced</th>
<th>Ceftriaxone Nonsusceptibilityd</th>
</tr>
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<tbody>
<tr>
<td>Antibiotic treatment in the prior 3 mo</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Days from end of most recent treatment with same antibiotic class</td>
<td><strong>0.98 (.97–.99)</strong></td>
<td><strong>0.59 (.38–.96)</strong></td>
<td><strong>0.63 (.45–.89)</strong></td>
<td><strong>0.98 (.96–1.00)</strong></td>
</tr>
<tr>
<td>No. of courses of same antibiotic class</td>
<td>2.61 (.56–12.15)</td>
<td>2.82 (.96–7.22)</td>
<td>1.26 (.45–3.51)</td>
<td><strong>2.13 (1.07–4.25)</strong></td>
</tr>
<tr>
<td>Cumulative days of treatment with same antibiotic class</td>
<td>0.99 (.94–1.04)</td>
<td>1.02 (.95–1.05)</td>
<td>0.98 (.93–1.04)</td>
<td>1.03 (.99–1.08)</td>
</tr>
<tr>
<td>Nonantibiotic factorsf</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of infection (after 2002)</td>
<td><strong>1.23 (1.08–1.42)</strong></td>
<td>1.18 (.93–1.55)</td>
<td>1.07 (.93–1.23)</td>
<td>0.86 (.72–1.04)</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>0.89 (.78–1.01)</td>
<td>0.91 (.64–1.34)</td>
<td>0.94 (.84–1.05)</td>
<td>0.95 (.82–1.09)</td>
</tr>
<tr>
<td>Any underlying chronic conditiong</td>
<td>0.78 (.38–1.55)</td>
<td>0.75 (.16–7.24)</td>
<td>0.56 (.27–1.11)</td>
<td>2.03 (.65–6.33)</td>
</tr>
<tr>
<td>Immunosuppressive conditionh</td>
<td>0.78 (.48–1.56)</td>
<td>0.64 (.17–2.32)</td>
<td>0.80 (.40–1.62)</td>
<td>1.54 (.62–3.84)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1.07 (.30–3.84)</td>
<td>0.89 (.01–7.67)</td>
<td>0.46 (.06–3.81)</td>
<td>1.29 (.15–11.29)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>0.92 (.30–2.86)</td>
<td>1.96 (.20–9.35)</td>
<td>0.68 (.19–2.49)</td>
<td>1.32 (.36–4.94)</td>
</tr>
<tr>
<td>Hospital/nursing home associated</td>
<td>0.51 (.10–2.56)</td>
<td>1.12 (.21–4.34)</td>
<td>1.63 (.62–4.31)</td>
<td>1.34 (.49–3.70)</td>
</tr>
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Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

a Cases are included if the patient received at least 1 course of antibiotic treatment in the 3 months prior to illness. Cases are excluded if they were classified as failures or relapses, or if the class or dates of prior antibiotic treatment were unavailable. Only the first episode of disease per individual is included.

b Maximum likelihood method and 95% Wald CIs are presented for macrolides, penicillins and cephalosporins. Firth penalized-likelihood method and profile-likelihood 95% CIs presented for fluoroquinolones.

c Bolded values for ORs represent associations with P ≤ .05.

d Antibiotic resistance/nonsusceptibility in the infecting isolate as per Clinical and Laboratory Standards Institute standards [15], using meningitis breakpoints for penicillin resistance and ceftriaxone nonsusceptibility. Fluoroquinolone nonsusceptibility is defined as a ciprofloxacin minimum inhibitory concentration ≥ 4 mg/L.

e OR for log(days).

f Factors associated with resistance to at least 1 specific antibiotic class in previous reports. Variables evaluated as potential confounders in class-specific analyses described in the Methods.

g Presence of ≥ 1 underlying chronic condition predisposing to invasive pneumococcal disease as defined by the Canadian National Advisory Committee on Immunization in 2012 (as per [13], but excluding asthma).

h Presence of ≥ 1 immunosuppressive condition: lymphoma, hematologic malignancy, chronic renal failure, cirrhosis, previous organ transplant, asplenia, sickle cell disease, systemic lupus erythematosus, HIV infection, or those receiving chemotherapy, radiation, prednisone, or other immunosuppressive therapy.

compared the effects of timing of antibiotic treatment, duration of therapy, and number of courses of antibiotics and resistance in pneumococci [11]. In addition, none of the identified studies assessed time from the end of antibiotic therapy as a continuous variable [11].

Guillemot et al, in a study of penicillin resistance in 55 nasopharyngeal isolates of pneumococci in 54 children, only identified resistance in children who had received longer courses and lower doses of antibiotics in the 30 days prior to culture, but the differences between longer and shorter duration and higher and lower doses of antibiotics were not statistically significant [24].

In a retrospective cohort study of factors associated with penicillin resistance in 303 pediatric and adult patients with pneumococcal bacteremia, Ruhe and Hasbun found that longer exposure to β-lactams and >1–2 courses of β-lactams, sulfonamides, and macrolides were associated with penicillin nonsusceptibility in pneumococcal isolates [25]. Neither of these studies assessed time from last antibiotic exposure, and neither had adequate power to permit multivariable analysis.

In studies of bacterial species other than pneumococci, Costelloe et al found that longer duration and multiple courses of antibiotic exposure were generally associated with higher rates of antibiotic resistance, but results were not consistent [23, 26, 27]. The prospective study by Malhotra-Kumar et al demonstrated that azithromycin and clarithromycin resistance in oral streptococci appear to decrease with time from antibiotic exposure over a >6-month period [21], with clarithromycin resistance rates declining more rapidly. In contrast, the study on the effect of amoxicillin exposure on resistance rates in Haemophilus influenzae by Chung et al showed that resistance rates decreased to near baseline within 12 weeks [22]. In another study of amoxicillin and urinary tract infections due to Escherichia coli, Hillier et al found that longer duration, lower dose, and time from most recent antibiotic exposure were all associated with
amoxicillin resistance, with resistance returning to baseline within 1–3 months [27]. These studies suggest that decay in resistance risk after exposure to antibiotics may depend on the particular antibiotic–bacterial species combination being studied. Our results indicate that, for antibiotics other than macrolides, baseline resistance rates can be expected after 90 days from last antibiotic exposure in S. pneumoniae. After exposure to macrolides, particularly azithromycin, resistance rates decrease more slowly. This may be explained by the longer plasma half-life of azithromycin (>60 hours compared with 5–7 hours for clarithromycin, 7 hours for levofloxacin, or 70 minutes for amoxicillin), leading to prolonged subtherapeutic concentrations of azithromycin and ongoing selection of resistance. Resistance may occur because multiple rounds of exposure results in more effective selection for drug-resistant strains than a single, more prolonged exposure. However, as mentioned before, it is also possible that, despite excluding antibiotic failures and relapses, our findings are affected by artifacts of sampling.

Our study has several limitations. Sampling from 10 years in a single geographic area may limit the generalizability of our results to other settings. As discussed above, our results apply to S. pneumoniae and prior antibiotic exposure to macrolides, fluoroquinolones, penicillins, and cephalosporins and may not translate to other bacterial species–antibiotic combinations. We were not able to assess the role of antibiotic dose on development of resistance [33]. Antibiotic resistance rates change over time, as demonstrated for macrolide resistance in our data set. Although our multivariable models found that this did not affect the association between time from end of antibiotic exposure and bacterial resistance, this may not be true in all circumstances [21], and relationships may differ if mechanisms of resistance differ over time, or as the introduction of pneumococcal vaccination programs changes the serotype distribution of pneumococcal infections. Finally, antibiotic exposures were as defined by patients’ reporting having taken them and/or physicians’ reporting having written a prescription; however, not all prescriptions may have been filled, patients’ recall may be subject to bias, and we did not assess compliance with taking antibiotics.

In conclusion, in patients previously exposed to antibiotics who subsequently develop pneumococcal disease, the time elapsed from the last treatment course is of considerable value in predicting antimicrobial resistance and the number of

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Abbreviations: CI, confidence interval; OR, odds ratio.

- Cases are included if the patient received at least 1 course of antibiotic treatment in the 3 months prior to illness. Cases are excluded if they were classified as failures or relapses, or if the class or dates of prior antibiotic treatment were unavailable. Only the first episode of disease per individual is included.
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- Multivariable model for P-value was <0.05.
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Adjusted estimates—antibiotic treatment in the prior 3 mo

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courses may be of value, but cumulative antibiotic exposure is not helpful. Clinicians’ choices of empirical antibiotic therapy for presumptive pneumococcal infections should ideally take into account the shape of declining resistance over time. Further research is needed to define relationships in other bacterial species–antibiotic combinations. Increasing the precision and detail in information collected about antibiotic exposure in studies of antibiotic resistance may help to improve clinician decision making about empiric antibiotic choices in the future.

Notes

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