Prior antibiotic use as a risk for pneumococcal infection with resistant strains of *Streptococcus pneumoniae*

Allison McGeer

Patients with serious infections due to *Streptococcus pneumoniae* most often present to emergency departments with community-acquired pneumonia or sepsis without a recognized focus. The prompt administration of antimicrobial therapy that effectively covers the particular infecting organism has been shown to result in significant reductions in morbidity and mortality. Increasing antimicrobial resistance makes it more difficult for clinicians to choose the best initial therapy. The Toronto Invasive Bacterial Diseases Network (TIBDN) has thus been looking at whether it is possible, based on information available to clinicians at the time the patient presents with serious pneumococcal infection, to predict which patients are at increased risk of infection due to a resistant strain of *S. pneumoniae*.

TIBDN has been performing population-based surveillance in Toronto and the regional municipality of Peel since 1995. For each case, data about clinical features of illness, demographics, and medical history are collected by chart review and patient interview. Family and other responsible physicians are asked about prior administration of vaccines, as well as whether the patient has received any antibiotics in the three months prior to the onset of their infection. For the last three years, the patients themselves have been asked about what antibiotics and vaccines they have received.

From 1995 to the end of 2002, 3339 cases of pneumococcal disease associated with the isolation of *S. pneumoniae* from a sterile site were identified. The most common diagnoses were pneumonia (67%), bacteremia without focus (19%), meningitis (5.5%) and otitis media (3.0%). Approximately 25% of patients were children, and 40% were over the age of 65 years. The case fatality rate was 19%. Overall, 35% of patients for whom data were available had received at least one antiobitic in the three months prior to their infection

When data was reviewed to identify risk factors for antimicrobial resistance (as shown in table 1), only three could be defined. Importantly, neither age nor underlying illness was an independent risk factor for resistance. As shown in the Table, resistance to all antibiotics became more common over time (row one, year of infection). For penicillins and cephalosporins, prior use of antibiotics was associated with an increased risk of resistance of about 2 fold. Thus, this risk is not clinically very important. In addition, across Canada, essentially all isolates (>99.8%) remain susceptible to amoxicillin and third-generation cephalosporins. Therapy with high-dose amoxicillin, or the currently recommended dose of ceftriaxone or cefotaxime will provide adequate coverage for all patients, including those who have recently used any antibiotic.

The agents within the macrolide class are not homogeneous with respect to their ability to produce antimicrobial resistance. Prior use of erythromycin was not associated with resistance to any antimicrobial class; clarithromycin use is associated with an increased likelihood of macrolide resistance alone, and azithromycin use is associated with an increased risk of macrolide, penicillin and TMP-SMX resistance (Figure 1). More than half of isolates from patients with invasive pneumococcal disease who have received azithromycin in the prior three months are resistant to erythromycin. These data are consistent with other studies, and are an important reminder that macrolides are not an appropriate therapy for pneumococcal infections in patients who have recently received azithromycin.

Patients in whom a fluoroquinolone has been used, and those who have acquired their infection in a hospital or nursing home have a substantially increased risk of infection with a fluoroquinolone resistant isolate (Table 1, Figure 2). It is not clear why institutional acquisition of infection is so highly associated with fluoroquinolone resistance even after adjustment for recent antibiotic use: the most likely explanations are either that fluoroquinolone use more than 3 months prior to the infection is important, and institutionalized patients are often prescribed fluoroquinolones, or that resistant pneumococci are frequently passed from resident to resident or patient to patient. Whatever the reason, patients who acquired their infection in a hospital or nursing home and had received fluoroquinolones in the past three months had high enough rates of resistance to the most active fluoroquinolones (23% and 14% resistance to gatifloxacin and moxifloxacin, respectively) as to preclude quinolone monotherapy. Despite recommendations from expert bodies that monotherapy with fluoroquinolones is appropriate for nursing home patients, routine empiric fluoroquinolone monotherapy for nursing home pneumonia should not be used in our geographic area.

In sum, an antimicrobial use history is crucial in determining appropriate therapy for a patient presenting with an illness where *S. pneumoniae* is a possible cause. The single most important risk factor driving antimicrobial resistance is specific antimicrobial use. Nursing home and nosocomial acquisition also plays a key role in fluoroquinolone resistance. The association of antimicrobial resistance in macrolides is not class-specific, but drug specific, with the use of azithromycin preferentially selecting for resistance to multiple classes of antimicrobials

Table 1. Risk factors for antimicrobial resistance in patients presenting with invasive pneumococcal disease, Toronto, 1995-2002.

	Odds ratio for resistance (95% confidence limits)			
	Penicillin	Ceftriaxone	Macrolide	Levofloxacin
Year of infection	1.3 (1.2-1.4)	1.2 (1.0-1.4)	1.1 (1.0-1.2)	-
Prior penicillin§	2.5 (1.3-4.8)		2.0 (1.2-3.2)	-
Prior TMP-SMX§	5.2 (2.4-11)		2.2 (1.1-4.3)	-
Prior azithromycin§	2.9 (1.0-8.0)		11 (5.2-22)	-
Prior clarithromycin§	-		3.8 (2.1-6.9)	-
Prior fluoroquinolone§	-		-	12 (4.1-35)
Nursing home residence	-		-	13 (3.9-43)
Hospital-acquired	-		-	9.9 (2.2-45)

§ prior antibiotic refers to an antibiotic received in the three months preceding the patient's presentation

Figure 1. Association between macrolides received in the three months prior to invasive pneumococcal infection on the susceptibility of the infecting isolate, Toronto, 1995-2003. Bars show the percent resistance to the antibiotic noted below them on the x-axis, by prior use of different antibiotics (differently shaded bars). Unlabeled comparisons are not significant (P>0.05).

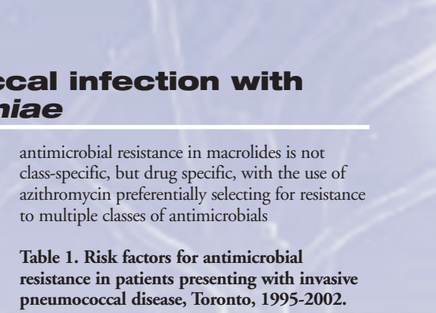
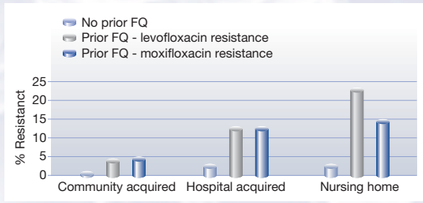


Figure 2: Effect of risk factors on levofloxacin and moxifloxacin resistance of infecting pneumococal isolate in patients with invasive pneumococcal disease, Toronto, 1995-2002.



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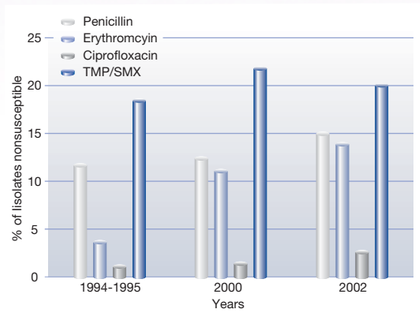
Over Ten Years of Tracking *Streptococcus pneumoniae* in Canada: Maybe Resistance Isn't Futile

Donald E. Low

Streptococcus pneumoniae is the leading cause of bacteremia, meningitis and pneumonia worldwide. It causes significant morbidity and mortality and prior to effective pneumococcal vaccines it affected children and adults in all socioeconomic classes. The annual incidence of invasive pneumococcal disease is 12-17 per 100,000 population in the developed world. In Canada it causes 12,500 cases of pneumonia requiring hospitalization annually. Penicillin resistant *S. pneumoniae* was first reported in 1967. Since then the prevalence of resistance has increased globally, resulting in treatment failures with increased morbidity, mortality and prolonged hospital stays.

The prevalence of resistance has been increasing at different rates, in different geographic regions and demographic groups. The Canadian Bacterial Surveillance Network (CBSN) has been tracking antimicrobial resistance data in Canada since 1993 (Figure 1). CBSN is a volunteer group of private and hospital-affiliated laboratories from across Canada. These centers represent a sample of laboratories providing service to community and tertiary hospitals, as well as community clinics and doctor's offices. Nine provinces and one territory are represented in the sample collection. In addition to *S. pneumoniae,* we have also included clinical isolates of *Staphylococcus aureus, Moraxella catarrhalis, Haemophilus influenzae,* and blood culture isolates of viridans group streptococci. As a result of the collaboration with laboratories across Canada, and financial support from the Canadian Bacterial Diseases Network and the pharmaceutical industry, CBSN has been able to provide not only valuable and unique information for health care providers managing patients with suspect or proven pneumococcal disease, but also has been able to use this information to provide new knowledge regarding the epidemiology, prevalence and mechanisms of resistance and treatment of patients. This has resulted in more then 20 publications in international journals[1-20], including the CBSN's paper on the emergence of quinolone resistance in pneumococci (a citation classic: a publication which has been cited >400 times)[1]. It is the longest running national surveillance program of its kind in the world. During the last decade we have gathered over 27,000 isolates of *S. pneumoniae.*

Figure 1. Nonsusceptibility among S. pneumoniae from 1994 to 1995, 2000, and 2002 to major antimicrobials.



Our latest publication authored by Powis[8] has demonstrated several important points regarding the prevalence of resistance (Figure 1). The prevalence of isolates that were nonsusceptible to penicillin increased to 15.0% in 2002 compared to previously published data from 2000 of 12.4% (P = 0.03). However, penicillin resistance in our sample of isolates has remained stable from 2000 to 2002 (6.5% versus 5.8%, $P \geq 0.05$). There was a significant decrease in the proportion of penicillin resistant isolates from children <5 years of age from 34.1% of penicillin-resistant isolates in 2000 to 26.3% in 2002 ($P \leq 0.04$). One explanation for this decrease may be the introduction of the pneumococcal conjugate vaccine in Canada in July 2001. Use of conjugate pneumococcal vaccine in children has been previously demonstrated to reduce the rates of invasive infection from penicillin nonsusceptible isolates in children and, to a lesser extent, in adults. Alternatively, this may be due to clonal dynamics or changes in the utilization of penicillins and aminopenicillin in different age groups. As seen before, penicillin nonsusceptibility was associated with nonsusceptibility to erythromycin, TMP-SMX, and multidrug resistance.

The good news is that despite the increase in nonsusceptibility to penicillin, <2% of our isolates have penicillin MICs of ≥4 µg/ml, suggesting that empirical ß-lactam therapy other than cefuroxime continues to be an acceptable choice for nonmeningeal pneumococcal disease in Canada. The absence of high-level amoxicillin-resistant clones and continuing low levels of nonsusceptibility make amoxicillin an acceptable option as an antipneumococcal therapy in Canada. Ceftiaxone continues to have excellent activity against penicillin non-susceptible and resistant pneumococci. Only 1.5% of isolates were Ceftiaxone resistant.

The rate of macrolide nonsusceptibility increased from 3.7% in 1994 and 1995 to 11.1% in 2000 and to 13.9% in 2002. In the United States the prevalence of macrolide

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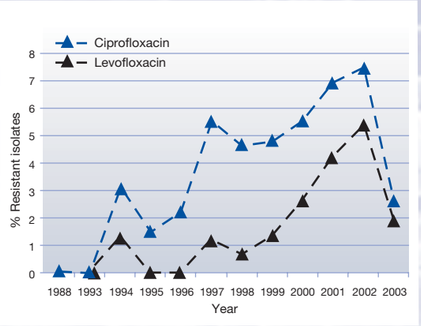
nonsusceptibility ranges from 28% to 30%, whereas in some Asian countries the resistance rates are up to 92%. Despite the increasing nonsusceptibility to macrolides, the ketolides maintain in vitro activity with an MIC50 and an MIC90 of ≤0.015 and 0.03 µg/ml, respectively. The activity of ketolides against macrolide-nonsusceptible strains was maintained whether they demonstrated the M or MLSB phenotype. The telithromycin MIC50 of macrolide-nonsusceptible isolates was, however, higher than the MIC50 of macrolide-susceptible isolates.

Of the isolates tested in our study, 2.7% demonstrated a ciprofloxacin MIC of ≥4 µg/ml. This prevalence is a significant increase from the 1.4% ciprofloxacin nonsusceptibility reported in 2000 ($P \leq 0.005$). This increase is almost exclusively in adults older than 18 years, with the greatest increase in individuals older than 65 years. In this age group there was a marked increase from 0.7% ciprofloxacin nonsusceptibility in 1994 to 3.8% in 2000 and to 5.7% in our study from 2002. The prevalence of ciprofloxacin nonsusceptibility in individuals older than 65 years has been demonstrated previously and is not surprising since this demographic group has the highest proportion of risk factors for fluoroquinolone nonsusceptibility, such as chronic lung disease and institutionalization.

One new important finding that has only recently come to light, is the observation that fluoroquinolone resistance in pneumococci is decreasing (Figure 2). This reduction in resistance rates is statistically different. Although there are several possible explanations for this, the most plausible one appears to be the better use of fluoroquinolones for the treatment of respiratory infections. It is clear that our early studies demonstrating the rise of resistance was associated with the use of fluoroquinolones with marginal activity against pneumococci, the question remains if this decrease is due to the use of fluoroquinolones with greater pneumococcal activity which not only are not selecting for resistance, but killing the less susceptible strains with first step mutations.

In conclusion, rates of nonsusceptibility to most antimicrobials continue to increase in Canadian isolates of *S. pneumoniae*. However, some older antimicrobials (amoxicillin and ceftriaxone), as well as newer agents (ketolides and respiratory fluoroquinolones) remain active against virtually all isolates and can continue to be recommended for empirical treatment of suspected pneumococcal infections. Finally, if we continue to see the lower rates of fluoroquinolone resistance noted in 2003, we may have the first example of how the appropriate use of an antimicrobial may be able to turn back the tide of resistance. Maybe resistance is not futile [21].

Figure 2. Fluoroquinolone-resistant pneumococci in respiratory isolates from older adults (>=65) in Canada, Canadian Bacterial Surveillance Network 1993-2003.



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Clostridium difficile colitis: the return of an old acquaintance.

Louis Valiquette and Allison McGeer

Clostridium difficile associated diarrhea (CDAD) is well known as the most frequent cause of nosocomial diarrhea, and often considered a "normal" consequence of antibiotics. Toxigenic *C.difficile* strains produce two different cytotoxins (toxin A and B) causing increased vascular permeability and inducing local cytokine production which account for the pathogenesis of CDAD. Diagnosis testing is most of the time performed using commercially-available enzyme immunoassays (toxin A, B or both) and cell cytotoxicity assay (toxin B). Traditionally, cessation of the offending antibiotic(s), supportive treatment and 10-14 days of metronidazole for the more severe cases were effective options to control this infection.

Recently, a prolonged outbreak of *C difficile* disease in Calgary, and astonishing increases in CDAD incidence and case-fatality rates in Quebec, the United Kingdom and some hospitals in the United States have substantially modified our appreciation of this disease. In July and August 2004, reports to the Canadian Medical Association Journal (CMAJ) defined the problem in Quebec[1, 2].

Key points:

• In 2003, annual population rates of 160 cases per 100,000 inhabitants in Sherbrooke, Quebec, with rates of 866.5 cases per 100,000 in inhabitants of more than 65 year-old and 1681/100,000 among those aged >80 (almost 2% of Sherbrooke residents over 80 yrs old developed CDAD in 2003)[1].

Did you know?
A nationwide survey conducted in Sweden in 1995, reported an incidence rate of 58 cases per 100,000 inhabitants with rates of 121/100,000 for inhabitants aged 60-79 and 315/100,000 among those 80-89[3].

• For the actual outbreak, most cases occurred in hospitals. In Montreal hospitals, the mean number of CDAD cases per 1000 admissions was 25.1 (14-40)[4].

Did you know?
In 1997, the Canadian Nosocomial Infection Surveillance Program (CNISP) estimated that the mean incidence of *C. difficile* infections in large (>500 beds) hospitals was 5.9 per 1000 admissions[5].

• One characteristic of the Quebec outbreak is the increase in severity and case-fatality rate. Pepin *et al*. reported 30 day all cause mortality rate of 13.8% in 2003 (vs. 8.6% in 2002). 23% of CDAD patients died, developed toxic megacolon or, colonic perforation or required use of vasopressor or colectomy[1].

Did you know?
The CNISP reported that, in Canadian hospitals in 1997, case-fatality and severe CDAD rates were 1.5% and 8%, respectively[5, 6].

• Certain classes of antibiotics may carry a higher risk for CDAD. In Sherbrooke, 2nd and 3rd generation cephalosporins, macrolides, clindamycin and quinolones were associated with a higher risk[1].

Table 1 – Incidence of hospital-acquired CDAD per 1000 patient-days of use of various classes of antibiotics at the Centre Hospitalier Universitaire de Sherbrooke

	1999-2000	2001-02	2003
Narrow spectrum penicillins	1.4	1.2	4.9
-lactam/ -lactamase inhibitors	1.0	1.3	5.0
1st generation cephalosporins	2.3	2.6	8.8
2nd generation cephalosporins	3.7	2.8	16.3
3rd generation cephalosporins	2.7	4.6	19.5
Carbapenems	2.7	6.7	7.4
Aminoglycosides	2.4	2.2	6.5
Quinolones	1.6	1.2	9.9
Clindamycin	4.9	3.1	11.7
Macrolides	1.9	4.3	20.0
Metronidazole	2.0	1.8	5.0
Vancomycin	2.5	2.4	5.2
Cotrimoxazole	0.2	0.2	0.5

Did you know?
Traditionally, clindamycin, cephalosporins and penicillins have been reported most often as the most frequent antibiotics associated with CDAD[7].

• Risk factors for severe CDAD in Sherbrooke were: age > 65 years, immunosuppression, leucocytosis (>20,000/mm3), increased creatinine (>120 mmol/L), and tube feeding[1]. Recently, Dial *et al*, reported interesting data supporting the hypothesis than therapy with proton pump inhibitors (PPIs) may also contribute to the risk of developing *C.difficile* colitis[2].

Did you know?
Proton pump inhibiters (PPI) are one of the most frequent drugs prescribed in primary care settings and hospitals. In Dial *et al* study, almost 50% of the patients were taking PPIs on admission to hospital.

The reasons of this outbreak in Quebec are not well known, but the introduction of a more virulent clone (in one hospital in Montreal, 85% of the strains that underwent typing were clonal) in hospitals suffering from years of under-resourcing are the most likely explanations. Investigations in the United States have revealed that all of the hospital outbreaks of severe disease are associated with the transmission of a single clone of *C. difficile* which is more resistant to antibiotics (particularly fluoroquinolones and macrolide/lincosamides) than other clones of *C. difficile*, and appears to have enhanced virulence: it possesses genes encoding binary toxin CDT (a third cytotoxic toxin produced by some strains of C.difficile) and has a deletion in a toxin repressor gene (*tcdC* deletion), which may be associated with increased toxin production and thus more severe disease[8].

Data from Calgary, Quebec and the U.S. suggest that control of outbreaks of these new virulent clones is very difficult, but critical to patient safety. We have learned from experience with other antibiotic resistance organisms (e.g. MRSA, VRE) that it is much less expensive and more effective to prevent the spread of these organisms with programs that prevent the initial introduction and spread of new clones than it is to attempt to control an established problem.Thus, hospitals all across Canada are looking at what programs and practices need to be in place to protect their patients and staff from outbreaks of *C difficile*. Table 2 summarizes the interventions that have been shown to have an impact that hospitals are considering. These interventions have hospital-wide impacts, but the resource impact is largest for laboratories, pharmacies and infection control programs. These departments will need to work together if we are to be successful in protecting Canadian patients and staff from the substantial morbidity and mortality associated with disease due to these new and virulent clones.

Table 2 – Key interventions to protect patients and staff from Clostridium difficile-associated diarrhea

Surveillance
- Rapidly identify changes in incidence associated with introduction of new strains
- Enable evaluation of intervention programs
- Ensure that diagnostic tests in use are adequate to detect circulating strains
- Ensure early identification of emerging antimicrobial resistance

Prevention of patient-to-patient transmission
- Implement and maintain a multi-disciplinary program to optimize improve hand hygiene; this program should include on-going education and auditing of compliance
- Diagnose *C. difficile*-associated diarrhea promptly
- Use private rooms and contact precautions for patients with suspected or diagnosed *C. difficile*-associated diarrhea; cohort patients if necessary
- Ensure appropriate and adequate cleaning of the hospital environment with agents active against *C. difficile* spores
- Introduce individually assigned thermometers and blood pressure cuffs; ensure that all other equipment that moves from patient to patient is adequately disinfected
- Incorporate infection control expertise from the earliest stages of planning for new building and renovation in health care

Provide prompt and adequate therapy for infection
- Consider diagnosis, order cytotoxin assay of stool samples and provide results of testing promptly
- Introduce and implement guidelines for empirical treatment of diarrhea pending results of cytotoxin assay or endoscopy

Reduce antibiotic use
- Minimize use of clindamycin for all indications
- Ensure that surgical prophylaxis guidelines are followed, including that doses of prophylactic antibiotics beyond recommendations are not given, and that effective antibiotics with the narrowest spectrum are used
- Implement an active, multidisciplinary hospital antibiotic utilization program to ensure patient safety while minimizing overall antibiotic use, and using antibiotics less likely to put patients at risk for *C. difficile*

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