What does antibiotic history tell you about antibiotic resistance? – the relationship between prior macrolide and fluoroquinolone use and resistance in *S. pneumoniae*

#4423

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Abstract

Background: Prior exposure to antibiotics (ABs) is an important predictor of resistance (AR)for many pathogens. We explored the relationship between the timing and duration of prior AB use and resistance for SPN.
Methods: TIBDN has performed population based surveillance for invasive pneumococcal disease (IPD) in Toronto/Peel since 1995; and surveillance for SPN from sputum/BAL since 2002. AB histories are obtained by chart review, patient and MD interview
Results: Between 2000-2010, TIBDN identified 4440 episodes of IPD, and collected 3875 sputum/BAL isolates. 7388 (89%) of cases were adults, 907 (12%) were nosocomial, 323 (4.5%) were nursing home acquired. 7198 isolates were available, 185 (2.6%) were R (MIC ⩾4) to cipro (FQR), 137 (2%) to levo, 1444 (20%) to erythro. FQR is associated with respiratory isolates vs IPD (P<.001), nosocomial (P=0.002) & LTC acquired cases (P<.001), older age (P<.001). The relationship between the category of prior use of and resistance to fluoroquinolones (FQs) and macrolides (MLs) is shown below. Relationships were independent of other FQR risk factors.

No. (%) FQR*								
	Fail < 48h	Fail =>48h	Fail + Prior Rx	Relapse	Prior Rx <15d	Prior Rx 15-29d	Prior Rx 30-59d	Prior Rx 60-100d
Any FQ	5/36 (14)	30/73 (41)	12/28 (43)	5/54 (7)	7/78 (9)	8/111 (7)	13/203 (6)	7/127 (6)
Moxi	1/9 (11)	4/5 (80)	2/3 (40)	3/17 (18)	0/3	2/30 (7)	2/42 (5)	0/27
Levo	1/12 (8)	10/28 (34)	4/11 (36)	3/28 (11)	1/23 (4.3)	2/44 (5)	5/64 (8)	3/38 (8)
Cipro	3/7 (30)	9/14 (39)	9/14 (39)	0/12	6/39 (15)	2/22 (9)	3/49 (6)	2/50 (4)
No. (%) ERY R*								
	Fail < 48h	Fail =>48h	Fail + Prior Rx	Relapse	Prior Rx <15d	Prior Rx 15-44d	Prior Rx 45-59d	Prior Rx 60-100d
Any ML	58/84 (69)	73/93 (78)	12/16 (75)	22/30 (73)	17/32 (53)	39/98 (35)	14/40 (35)	21/81 (26)
Azi	23/33 (70)	28/40 (70)	4/6 (67)	13/17 (76)	7/10 (70)	19/28 (68)	10/21 (48)	13/40 (33)
Clari	33/46 (72)	36/43 (84)	6/7 (86)	8/9 (89)	7/13 (54)	17/58/ (29)	4/17 (24)	7/32 (22)
Ery	1/2 (50)	6/7 (86)	-	-	1/7 (14)	0/5	0/1	1/5 (17)

*numbers may not match; some prior Rx included >1 ML or FQ.

Conclusion: Prior ML and FQ increases ABR within class. With ML, resistance is high for all failures/relapses, and decreases significantly by time from most recent use, declining more slowly after azi than clari/ery use. FQR is highest in persons failing longer courses prior to diagnosis, and risk declines more slowly over time.

Introduction

Antibiotic use is the primary cause of antimicrobial resistance and individual antibiotic use has been shown to increase the risk of resistance to antibiotics in subsequent infections.

We have previously shown that, in patients presenting with invasive pneumococcal disease, use of fluoroquinolones and macrolides in the previous three months is associated with substantial increases in the rate of resistance to fluoroquinolones and macrolides in the infecting isolate (Vanderkooi, CID 2005).

In this study, we asked how the timing of prior fluoroquinolone and macrolide therapy affected the risk of resistance in infecting pneumococci.

Methods

The Toronto Invasive Bacterial Diseases Network (TIBDN) has performed population-based surveillance for invasive pneumococcal disease in metropolitan Toronto and Peel region (pop. 4M) since January 1, 1995. From 2002 to 2009, all respiratory site isolates from hospital laboratories were also collected. Broth microdilution antimicrobial susceptibility testing was performed to CLSI standards.

Demographic and clinical data are collected from review of health records and interviews with patients and attending physicians. Details of previous antibiotic treatment have been collected since 2000. Patients are asked if they had received any antibiotics in the previous 3 months and if they had received treatment for the current infection prior to the diagnostic specimen that was positive for *S. pneumonaie*.

Definitions

Failure: patients currently on antimicrobials or within 48 hours of completion of a course of antibiotics when the culture yielding pneumococci was obtained.
Relapse: patients who were treated for the current infection and completed a course of antibiotics from 3-14 days before the culture yielding pneumococci was obtained.
Prior therapy: patient was treated for an unrelated episode of infection in the previous three months

Results

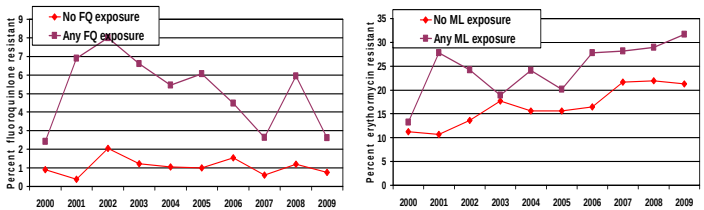
From 1/1/2000 and 31/12/2009, there were 4440 episodes of invasive pneumococcal disease (e.g. bacteremia, meningitis, empyema) and 3875 patients with respiratory isolates of *S. pneumoniae.*

Fluroquinolone resistance was more common in isolates from the respiratory tract, older patients, and in episodes of disease acquired in hospitals and nursing homes. Overall fluoroquinolone resistance decreased over the 8 years of surveillance (Table 1, Figure 1). Macrolide resistance was more common in isolates from the respiratory tract, from children, and in episodes of disease acquired in hospitals and nursing homes. Macrolide resistance increased steadily during the surveillance period..

Table 1. Non-antibiotic factors associated with fluoroquinolone and macrolide resistance in respiratory and sterile site isolates of *S. pneumoniae*

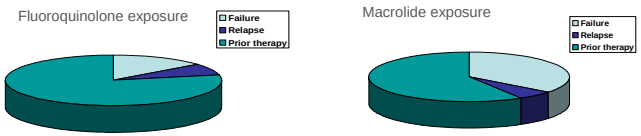
	FQR (Ciprofloxacin MIC>4µg/ml)		Erythromycin Resistance	
Isolate Type:				
Sterile site	56/4288 (1.3%)		779/4289 (18.2%)	
Respiratory	143/3479 (4.1%)	p<0.0001	817/3479 (23.5%)	p<0.0001
Age group:				
<=16	0/897		242/897 (27%)	
17-65	76/3664 (2.1%)		732/3664 (20%)	
>65y	123/3206 (3.8%)	p<0.0001	622/3207 (19.4%)	p=0.0002
Source of infection				
Community	127/5882 (2.2%)		1170/5882 (19.9%)	
Hospital	29/842 (3.4%)		199/643 (23.6%)	
Nursing home	25/307 (8.1%)	p<0.0001	69/307 (22.5%)	p<0.0001
Year				
2000-2003	61/2005 (3.0%)		325/2005 (16.2%)	
2004-2006	73/2529 (2.9%)		474/2529 (18.7%)	
2007-2009	51/2666 (1.9%)	p=.01	655/2666 (24.5%)	p<.0001

Figure 1. Fluoroquinolone and erythromycin resistance in patients with and without recent exposure to antibiotics of the same class, TIBDN, 2000-2009.



Antibiotic histories were available for 5806 (70%) of episodes of disease: 1067 patients (18%) had been exposed to fluoroquinolones in the previous three months, while 762 patients (13%) had been exposed to macrolide antibiotics. Patients exposed to macrolide antibiotics were more likely to be failing therapy at presentation (Figure 2)

Figure 2. Differences in the distribution of prior use of fluoroquinolones and macrolides in patients presenting with pneumococcal infection, TIBDN, 2000-2009



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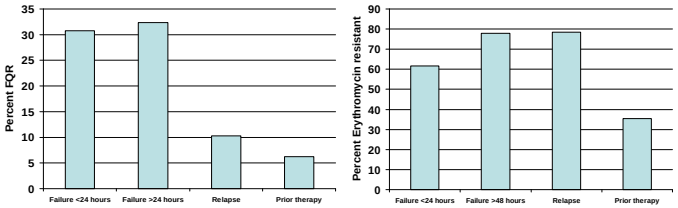
Results cont.

Patients who were failing therapy with macrolides or fluoroquinolones were much more likely than other patients to have pneumococcal isolates resistant to the class of antibiotics they were failing (Figure 3). Resistance rates were substantial even in patients who had received only one or two doses of the antibiotic (i.e. <24 hours of therapy).

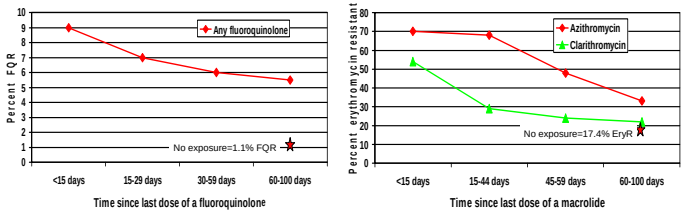
Resistance was class-specific; patients failing fluoroquinolone therapy were no more likely to have a macrolide resistant isolate than other patients (23.2% versus 20.2%, p=.45), and those failing macrolide therapy were no more likely to have a fluoroquinolone resistant isolate than others (1.7% versus 2.6%, p=.63). Patients failing macrolide therapy were more likely to have a ceftriaxone non-susceptible (9.6% vs 2.8%, p<.001) or amoxicillin resistant (5.1% vs 1.3%, p<.001) isolate; however, those failing fluoroquinolone therapy were not (3.0% ceftriaxone non-susceptible, 1.9% amoxicillin resistant).

Figure 3. Fluoroquinolone and macrolide resistance in pneumococcal isolates from patients with different types of exposure to the same class of antibiotics.



The time course of return to baseline resistance after exposure to antibiotics varied depending on the antibiotic. At 3 months after the last dose of a fluoroquinolone, patients were still significantly more likely to have a fluoroquinolone resistant isolate than other patients. (Rates of fluoroquinolone resistance are too low to identify whether different fluoroquinolone antibiotics are different). At two months after clarithromycin therapy, resistance rates were close to baseline (22% vs. 17% for patients never exposed). In contrast, resistance rates after azithromycin therapy remained significantly elevated at 3 months (Figure 4).

Figure 4. Fluoroquinolone and macrolide resistance in patients with previous exposure to the same class of antibiotics, by time from last dose of prior antibiotics to pneumococcal infection.



Conclusions

- Recent exposure to antibiotics in the same class is an important predictor of macrolide and fluoroquinolone resistance in pneumococci.
- Pneumococci isolated from patients who are failing therapy with an oral macrolide or fluoroquinolone when they are admitted to the hospital are likely to be resistant to the class of antibiotics that they are failing.
  - This is true even if they have taken only 1 or 2 doses of the antibiotic.
- Antibiotic histories may be more useful if they include a longer period of time than 3 months.
  - At 2 months after last exposure to clarithromycin, macrolide resistance has returned to close to baseline;
  - At 3 months, resistance to fluoroquinolones persists.