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Risk factors for invasive infection with fluoroquinolone resistant *S. pneumoniae* and failure of oral outpatient fluoroquinolone therapy

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Abstract (revised)

Background: There is increasing concern about the emergence of fluoroquinolone (FQ) resistance in *S. pneumoniae*. We examined fluoroquinolone resistance rates and risk factors in patients with invasive pneumococcal disease in Toronto, Canada.
Methods: From Jan 2000 until Dec 2004, TIBDN performed population-based surveillance for invasive pneumococcal disease in persons living in Toronto/Peel region, Can. (pop 4M). Invasive disease was defined as illness associated with isolation of *S. pneumoniae* from a sterile site. Patients exposed to fluoroquinolones were classified as: treated for current infection before presenting with disease (outpatient Rx) or received a FQ for another infection in the previous 3 months (prior 3 mths). Failure of treatment was defined as having a positive blood culture for *S. pneumoniae* while on or within 2 days of finishing their fluoroquinolone outpatient Rx.
Results: 1722/1792 (94%) of case isolates were available for susceptibility testing; 27 (1.6%) of which had ciprofloxacin MIC ≥4mg/L (CipR), 20 (1.2%) had levofloxacin MIC ≥8 mg/L (LevR) and 5 (0.3%) had moxifloxacin MIC ≥ 4 mg/L(MoxR). 155 patients received a fluoroquinolone prior to presentation with penumococcal disease; 26 (1.5%) failed their fluoroquinolone outpatient Rx for their current infection while 132 (6.7%) had received a fluoroquinolone in the prior 3 mths. Of the 20 LevR isolates identified, 5(25%) were associated with fluoroquinolone outpatient failure, 9 (45%) were associated with patients from nursing homes, and 7 (35%) were nosocomial infections. Of the 5 patients with MoxR isolates, 1 was failing ciprofloxacin outpatient Rx, 2 had exposure to another fluoroquinolone (1 ciprofloxacin, 1 levofloxacin) in the prior 3 mths, and the 2 with no fluroquinolone exposure were in residents of nursing homes. Fluoroquinolone resistance in these patient groups is shown in the table below.

Patient group	LevR	MoxR	Difference
No FQ exposure/No institutional exposure	1/1379	0/1375	NS
No FQ exposure	8/1532	1/1527	P=0.038
FQ prior 3 mths	12/151	4/151	P=0.04
Failure FQ outpatient Rx	5/24	1/24	NS
Nosocomial	6/90	0/89	P=0.03
Nursing Home	8/110	2/110	P=0.052

Conclusion: Pts who have been receiving a fluoroquinolone for therapy and present in hospital with pneumonia or sepsis should be treated with a different class of antibiotic. FQ-R in invasive pneumococcal disease in Toronto occurs almost exclusively in pts with recent direct exposure to FQs, or recent exposure to a health care institution. In patients with none of these risk factors, all isolates were susceptible to moxifloxacin.

Background

Increasing concern about the emergence of fluoroquinolone resistance in *S. pneumoniae (SPN)* prompted us to examine risk factors and resistance rates in patients with invasive pneumococcal disease (IPD) identified through the Toronto Invasive Bacterial Diseases Network (TIBDN) population-based surveillance in Toronto, Canada (pop 4M). We hypothesized that FQ-resistant isolates would be more common among patients failing FQ outpatient Rx than among other cases of *SPN* bacteremia.

Figure 1: TIBDN population area

Methods

From January 1, 2000 to December 31, 2004, population-based surveillance for community-acquired invasive pneumococcal infections was conducted in metropolitan Toronto and Peel Region, Ontario (Figure 1). Broth microdilution antimicrobial susceptibility testing was performed to CLSI standards. A case of FQ failure was defined as an episode of illness in which a blood culture which yielded *S. pneumoniae* was taken from a patient after the initiation of a course of oral fluoroquinolones, or within 2 days of completion of that course. Controls were defined as all other cases of pneumococcal bacteremia in the population during the study period.

Results

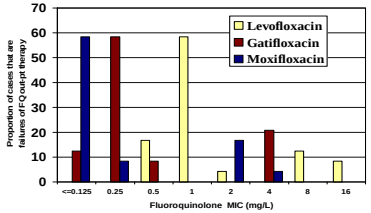
During the 5 year surveillance period there were 1792 cases of pneumococcal bacteremia (9 cases/100,000/yr). 1722 (96%) of the case isolates were available for susceptibility testing.

26 (1%) of cases met our definition for failure of FQ outpatient therapy and 24 (92%) if these were available for susceptibility testing. FQ resistance was more common among isolates from cases failing FQ outpatient therapy (6/24, 25%) than among other cases of pneumococcal bacteremia (21/1693, 1.3%) and cases that had failed therapy with other antibiotics (2/95, 2%), P<0.0001 for both comparisons.

Of the 24 FQ failure isolates tested; 19(79%) were sensitive to levofloxacin (MIC≤4mg/L); 7 of these had received outpatient therapy with levofloxacin, 8 with ciprofloxacin and 1 each with moxifloxacin, gatifloxacin and 2 with norfloxacin. Of the 5 cases with LevR isolates (MIC ≥8mg/L), 3 were treated with levofloxacin, 1 with moxifloxacin and 1 with ciprofloxacin. Neither of the two patients treated with moxifloxacin had a MoxR (MIC ≥4mg/L) isolate. However a MoxR isolate was recovered from one patient treated with ciprofloxacin. Of the 26 outpatient FQ failures 8(30%) had also received a FQ in the 3 months prior to their current infection. Only one of these patients had a FQ-R isolate .

The percentage of FQ failures by individual MIC levels are shown in Table 2.

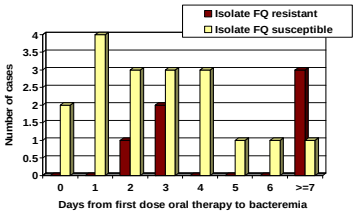
Figure 2. Proportion of FQ outpatient failures by MIC



Results (con't)

The median duration of outpatient FQ therapy prior to presentation with *SPN* bacteremia was 3 days (range 0-14 d)

Figure 3: Time lapse between initiation of FQ therapy and development of pneumococcal bacteremia



Overall, 21/1673 (1.3%) of patients who had not received outpatient Rx with a fluoroquinolone had a levofloxacin resistant isolate compared to 1/10 who received <48 hours of Rx (P=0.12) and 5/14 who received two or more days of FQ Rx (P<0.0001).

Compared to other cases of pneumococcal bacteremia, patients failing FQ therapy were more likely to be adults, to have an underlying disease, to have acquired their infection in a hospital or nursing home or to have been treated with a FQ in the 3 mths prior to their current infection (Table 1).

Table 1: Clinical characteristics of patients with pneumococcal bacteremia that have failed FQ therapy compared with patients with pneumococcal bacteremia in the absence of FQ therapy

Clinical Characteristic	Failed FQ outpatient Rx	Other bacteremias	P-value
Age group (% adult)	26 (100%)	1326 (75%)	0.003
Sex (% female)	14 (54%)	773 (44%)	0.30
Underlying illness	21 (80%)	1011 (58%)	0.02
FQ in prior 3 months	7 (27%)	129 (7.3%)	0.004
FQ resistant organism	6(25%)	21(1.2%)	0.0001
Nosocomial	4 (15.4%)	87 (5%)	0.042
Nursing Home	8 (30%)	109 (6.3%)	0.0002
Death	5 (23%)	342 (19.8%)	0.82

The association between FQ resistance and FQ failure persisted in stratified analysis (Table 2).

Table 2: Increased proportion of FQ-R isolates among patients with pneumococcal bacteremia following failure of FQ therapy

Subgroup		FQ-R among FQ failures	FQ-R among other bacteremias	P-value
Agegroup	Pediatric	1/7(14.3%)	5/698(0.7%)	0.058
	Adult	5/17 (29%)	16/995(1.6%)	<0.0001
Underlying illness	Yes	6/19(31.6%)	17/961 (1.8%)	<0.0001
	No	0/5 (0%)	4/696 (0.6%)	0.86
FQ prior 3 mths	Yes	6/24(25%)	8/127 (6.3%)	0.01
	No	0/0	13/1566 (0.8%)	
Nosocomial	Yes	2/4 (50%)	6/85 (7%)	0.039
	No	4/20 (20%)	15/1570(1%)	<.0001
Nursing Home	Yes	2/7 (28.6%)	9/103(8.7%)	0.144
	No	4/17 (24%)	12/1552 (0.8%)	<0.0001

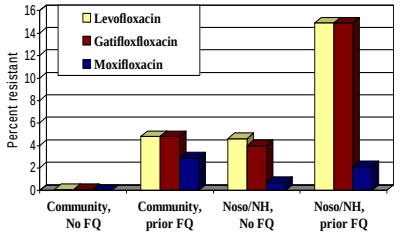
Results (con't)

Tables 3. Factors predicting FQ resistance in infecting isolates in multivariable logistic regression analysis

Risk factor	Odds ratio (95% Confidence Limits)
Nosocomial *SPN* infection	13.2 (4.7-37.2)
Resident of nursing home	12.9 (4.7-37.2)
Exposure to FQ (for this episode or in previous 3 mths)	6.2 (2.7-14.2)

Isolates from patients with community-acquired disease who have not recently been exposed to fluoroquinolones are almost uniformly susceptible to respiratory fluoroquinolones (Figure 4). However patients with institutionally acquired infection (either nosocomial or nursing home), and those with recent exposure to fluoroquinolones (either for the current infection or within the previous 3 months) are more likely to be infected with a FQ resistant organism.

Figure 4. Rates of resistance to respiratory fluoroquinolones in sterile site isolates from population-based surveillance in Toronto.



Conclusions

- FQ resistance among pneumococci may be a cause of clinical failures of outpatient pneumonia therapy.
- Patients failing FQ therapy are more likely to be adults, to have an underlying disease, to have acquired their infection in a hospital or nursing home or to have been treated with a FQ in the 3 mths prior to the current infection
- In our cases of nosocomial or nursing home acquired disease with recent exposure to fluoroquinolones, the rate of FQ resistance is high enough to preclude empiric monotherapy with levofloxacin or gatifloxacin.

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