Risk factors for Antimicrobial Resistance in Invasive Pneumococcal disease (IPD) in Toronto, Canada, 2012-2017

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Abstract (updated):

Background: Several studies have documented factors predictive of antimicrobial resistance (AMR) in invasive pneumococcal disease(IPD). However, the implementation of routine pediatric PCV programs, antimicrobial stewardship, and increasing immunocompromised in populating might be expected to change such factors. We report on predictive factors for AMR in IPD from 2012-2017.
Methods: TIBDN performs population-based surveillance for IPD in Toronto/Peel (pop 4.5M). IPD cases are reported to a central office and one isolate/case is serotyped and has antimicrobial susceptibility testing performed by broth microdilution to CLSI standards.
Results: 2459 cases of IPD were identified from 1/2012 to 12/2017. Overall rates of resistance to penicillin, macrolides, fluoroquinolones, and TMP-SMX were relatively stable over the course were stable over the study. In multivariable analysis risk factors for IPD non-susceptible to penicillin at meningitis breakpoints were current residence at nursing home (odds ratio [OR], 2.9; P =.0008), immune compromised status (OR, 1.5; P = 0.01), and exposure to beta-lactam (OR 1.6, P = 0.03) or macrolide (OR 2.3, P = 0.009). Infection with TMP-SMX–resistant pneumococci was associated with current residence in a nursing home (OR 2.0, P = 0.006), and recent exposure to beta-lactam (OR 1.9, P = 0.0004) or TMP-SMX (OR 3.9, P = <0.0001). Infection with macrolide-resistant isolates was associated with recent exposure to macrolide (OR, 3.1; P < 0.001), or macrolide treatment failure or relapse (OR, 7.9; P < 0.00.1). Infection with ciprofloxacin-resistant pneumococci was associated with HIV infection (OR 17, P = 0.002), current residence in a nursing home (OR, 3.8; P < .035), and fluoroquinolone treatment failure or relapse (OR, 39; P < 0.0001)
Conclusion: Recent same class antibiotic exposure remains a major predictive factor for macrolide non-susceptibility, and also predicts TMP-SMX, and penicillin non-susceptibility. Treatment failure or relapse is a predictive factor for macrolide and fluoroquinolone failure. HIV infection and immune compromise are risk factors for IPD infection with penicillin resistant pneumococci. Hospital acquisition of infection is no longer a risk factor for fluoroquinolone resistance. Nursing home residence is associated with non-susceptibility to fluoroquinolones, penicillin, and TMP-SMX.

Introduction:

Several studies have documented factors predictive of antimicrobial resistance (AMR) in IPD. Previously described risk factors include recent exposure to antimicrobials, immune compromise, and underlying comorbidity have been Fluoroquinolone resistance has been associated with nosocomial and nursing home acquired infections.

We used data from population based surveillance in Ontario, Canada to ask if the introduction of PCV programs and/or changes in antimicrobial use might have altered risk factors for AMR in IPD.

Methods:

The Toronto Invasive Bacterial Diseases Network performs population based surveillance for IPD metropolitan Toronto and the regional municipality of Peel in Ontario, Canada (pop, 4.5 million).

IPD is defined as illness in which S. pneumoniae was isolated from a normally sterile body site. One isolate per case was confirmed as *S. pneumoniae* by standard methodology. Broth microdilution antimicrobial susceptibility testing was performed and interpreted according to CLSI standards. Clinical data was collected from chart review, patients/ families and treating physicians.
Data were analyzed using SAS for PD, V9.4. Logistic regression models were used for multivariable analysis of risk factors for antimicrobial resistance. Variables considered for inclusion in the models were those revealed by univariate analysis and/or previous research to be potentially associated with these outcomes.
Patients were included in the analysis if recent antibiotics were unknown, with the exception unknown history of antibiotic use and macrolides because this groups had a significantly different rate of non-susceptibility.
Definitions: *Relapse*: if a patient completed a course of antibiotics for an illness with the same diagnosis as the current infection and the last dose was taken >48 hours and <14 days prior to the collection of this culture. *Failure*: if a patient was receiving antibiotics (most recent dose ≤48 hours) for the current infection when invasive culture was obtained. *Recent Antibiotics:* Antibiotics given for a separate infection in the last 3 month.

Results:

Data: 2459 cases of IPD were included in the study from the years 2012-2017. Of these, 69% were pneumonia or empyema, 17% primary bacteremia, and 6% meningitis. The overall incidence of IPD was 13.7 per 100,000 and declined from 16.3 (2012) to 11.6 (2017). Rates of resistance were stable over the study period (Figure 1). Isolates remained susceptible to moxifloxacin (overall, 2/2139 isolates resistant), and to penicillin at non-meningitis doses (5/2138 isolates resistant).

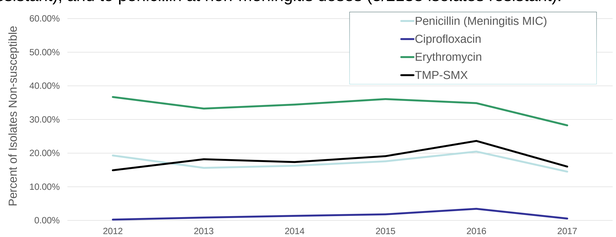

Figure 1: Overall rates of antibiotic non-susceptibility in IPD to penicillin, ciprofloxacin, erythromycin, and trimethoprim-sulfamethoxazole (TMP-SMX) from 2012-2017.

Previous Antibiotic exposure: Details of antibiotics received in the 90 days prior to infection were available for 1466 of 2106 cases from the years 2012-2016. The prevalence of non-susceptibility by category of exposure to antibiotics of the same class is shown for fluoroquinolones, macrolides, and beta-lactams in Figures 2, 3, 4 respectively.
Patient Characteristics: In univariable and multivariable analysis, we considered the potential impact of time of infection (2012-2016), age, gender, underlying illnesses, institutional exposure (hospital, nursing home, daycare), pneumococcal vaccine and the class and category of antibiotic use in the 90 days before infection. Factors associated with non-susceptibility to fluoroquinolones (ciprofloxacin), macrolide, erythromycin, beta-lactams (meningitis doses of penicillin), and trimethoprim-sulfamethoxazole are shown in Tables 1-4. Non-susceptibility to both levofloxacin and ciprofloxacin were associated with the same patient characteristics as ciprofloxacin (Data for levofloxacin not shown).

Ciprofloxacin

Characteristic	Characteristic present Non-Susceptible / Total (%)	Characteristic Absent Non-Susceptible / Total (%)	Univariable Analysis OR; (95% CL)	*P* Value*	Multivariable Analysis OR; (95% CL)	*P* value*
Underlying Illness:						
Lung Disease	8/290 (2.8)	17/1375 (1.2)	2.3 (.97,5.3)	0.06	-	-
Cancer	10/318 (3.1)	15/1347 (1.1)	2.9 (1.3,6.5)	0.02	3.1 (1.2,7,8)	0.02
Immune Suppression	10/383 (2.6)	17/1423 (1.2)	2.2 (1.0,4.9)	0.06	-	-
HIV	3/47 (6.4)	22/1681 (1,4)	4.9 (1.4,17)	0.03	17 (3.9,78)	0.0002
NH Acquired	6/76 (7.9)	21/1730 (1.2)	7.0(2.7,18)	0.0007	3.8 (1.1,13)	0.035
Failure or Relapse on FQ Therapy	5/18 (28)	22/1788 (1.1)	31 (7.9,102)	<.0001	39 (10,143)	<.0001

Table 1: Abbreviations: NH (Nursing Home), HIV (Human Immunodeficiency Virus), FQ (Fluoroquinolone).
Non-susceptibility to ciprofloxacin was significantly associated with history of HIV infection or cancer, residing in a nursing home, and failure or relapse of therapy with a fluoroquinolone. Non-susceptibility to Ciprofloxacin was not associated in univariate or multivariate analysis with nosocomial acquired infection. Cancer and HIV were associated significantly with non-susceptibility to ciprofloxacin. Not presented here is levofloxacin non-susceptibility for which the same factors in multivariable analysis were associated with non-susceptibility.

Results: (cont'd)

Erythromycin

Characteristic	Characteristic present Non-Susceptible / Total (%)	Characteristic Absent Non-Susceptible / Total (%)	Univariable Analysis OR; (95% CL)	*P* Value*	Multivariable Analysis OR; (95% CL)	*P* value*
Failure or Relapse on ML Therapy	57/68 (83.8)	418/1260 (33.2)	6.0 (3.4,11)	<.0001	6.5 (3.7,11)	<.0001
Recent ML	46/78 (59.0)	429/1250 (34.3)	3.1 (1.9,5.2)	<.0001	3.1 (1.9, 4.7)	<.0001

Table 2: Abbreviations: ML (Macrolide). Non-susceptibility to erythromycin was associated with failure of therapy with macrolides or recent exposure to macrolides.

Penicillin (Meningitis MIC Breakpoint)

Characteristic	Characteristic present Non-Susceptible / Total (%)	Characteristic Absent Non-Susceptible / Total (%)	Univariable Analysis OR; (95% CL)	*P* Value*	Multivariable Analysis OR; (95% CL)	*P* value*
Underlying Illness:						
Immune Suppression	84/383 (22)	239/1423 (17)	1.4 (1.1,1.8)	0.02	1.5 (1.1,2.1)	0.01
HIV	84/383 (22)	239/1423 (17)	1.4 (1.1,1.8)	0.02	1.5 (1.1,2.1)	0.01
Cancer	69/249 (22)	233/1347 (17)	1.3 (0.98,1.8)	0.07	-	-
Received PPV23 Vaccine	111/561 (20)	116/741 (16)	1.3 (1.0,1.8)	0.055	-	-
NH Acquired	27/76 (36)	296/1730 (17)	2.7 (1.6,4.3)	0.0002	2.9 (1.5,5.3)	0.0008
Recent Macrolide	43/178(24)	271/1578 (17)	1.5 (1.0,2.2)	0.03	1.6 (1.0,2.3)	0.03
Recent Beta-Lactam	23/78 (29)	294/1691 (17)	2.0 (1.1,3.3)	0.007	2.3 (1.2,4.4)	0.009

Table 3: -Abbreviations: NH (Nursing Home Resident), PPV23 (23-valent polysaccharide pneumococcal vaccine). Non-susceptibility to penicillin associated with nursing home residents, immune suppression, HIV, and recent beta-lactam or macrolide antibiotics.

Trimethoprim-Sulfamethoxazole

Characteristic	Characteristic present Non-Susceptible / Total (%)	Characteristic Absent Non-Susceptible / Total (%)	Univariable Analysis OR; (95% CL)	*P* Value*	Multivariable Analysis OR; (95% CL)	*P* value*
Underlying Illness:						
Immune Suppression	87/383 (23)	247/1423(17)	1.4 (1.1,1.8)	0.02	-	-
HIV	18/47 (38)	291/1618 (18)	2.8 (1.6,5.2)	0.002	-	-
NH Acquired	23/26 (30)	311/1730 (18)	2.0 (1.2,3.3)	0.01	2.0 (1.2,3.5)	0.006
Child (<15)	60/234 (26)	274-1572 (17)	1.6 (1.2,2.3)	0.004	-	-
Received PPV23 Vaccine	118/561 (21)	128/741 (-17)	1.3 (.96,1.7)	0.09	-	-
Recent TMP-SMX	18/40 (45)	267/1525(18)	3.9 (2.0,7.3)	<.0001	3.9 (2.1,7.4)	<.0001
Recent Beta-Lactam	50/178 (28)	272/1578 (17)	1.9 (1.3,2.7)	0.0007	1.9 (1.3,2.8)	0.0004

Table 4: - Abbreviations: NH (Nursing Home Resident), PPV23 (23-valent polysaccharide pneumococcal vaccine), TMP-SMX (trimethoprim-sulfamethoxazole). Non-susceptibility to TMP-SMX was associated with nursing home residents, and recent exposure to TMP-SMX or beta-lactams.

Conclusions:

- Treatment failure or relapse with the same class of antibiotics is predictive of macrolide and fluoroquinolone non-susceptibility. Recent exposure to beta-lactams or macrolides is associated with non-susceptibility to penicillin. Recent TMP-SMX or beta-lactams are associated with non-susceptibility to TMP-SMX.
- Nursing home residence is associated with non-susceptibility to ciprofloxacin, TMP-SMX, and penicillin.
- Hospital acquisition of infection is no longer associated with non-susceptibility to ciprofloxacin.
- HIV is associated with non-susceptibility to both ciprofloxacin and penicillin, ciprofloxacin non-susceptibility is associated with a history of cancer, immune suppression is associated with non-susceptibility to penicillin.

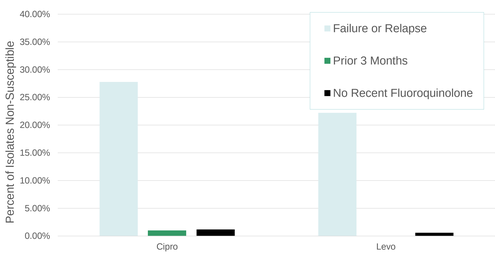

Figure 2: Exposure to Fluoroquinolone Antibiotics and Non-Susceptibility to Ciprofloxacin, Levofloxacin in 2012-2016.

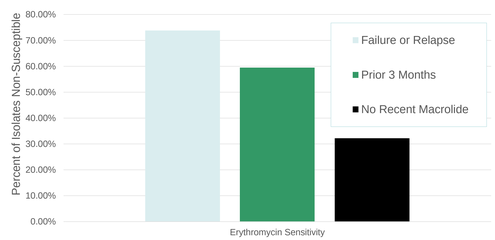

Figure 3. Exposure to Macrolide Antibiotics and Erythromycin Non-Susceptibility 2012-2016.

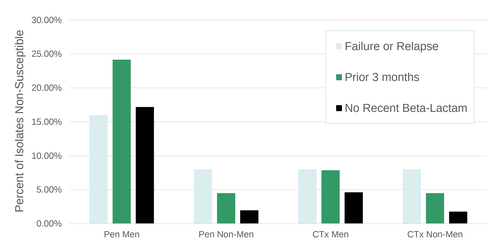

Figure 4: Exposure to Beta-Lactam Antibiotics Non-Susceptibility to Penicillin at Meningitis Breakpoint (Pen Men) and Penicillin at Non-Meningitis (Pen Non-Men), Ceftriaxone at Meningitis Breakpoints (CTx MEN) and Ceftriaxone at Non-Meningitis Breakpoint (CTx NON-Men). Non-Susceptibility 2012-2016.

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