Risk Factors for Macrolide-Resistance in Pneumococcal Bacteremia in Toronto, Canada

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Abstract (revised)

Background: Macrolide resistance (MLR) continues to increase in *S. pneumoniae* in Canada. We looked at risk factors for MLR in patients with pneumococcal bacteremia (PB) in Toronto, Canada.
Methods: TIBDN has conducted prospective, population-based surveillance for PB in Toronto/Peel, Canada (pop 4M) since 1995. Isolates have susceptibility testing performed to CLSI standards at a central lab. ML failures are cases of PB occurring during or within 48h of completion of therapy (Rx) with ML. Prior use of ML is defined as receipt of ML for another infection in the prior 3m.
Results: From 1/1/2000 to 31/12/2007, 3020 cases of invasive pneumococcal bacteremia were identified with 2864 (95%) isolates available for testing. MLR increased from 12% in 2000 to 20% in 2007. 196 (6.7%) pts received a ML prior to their PB; 80 (2.6%) pts were failing ML Rx, and 115 (3.8%) had received a ML for a prior infection.

	Total Episodes	MLR Episodes	Odds Ratio for MLR (95% CI)	Significance (p-value)
No ML exposure	2570	331	5.29(3.9-7.3)	<0.0001
Any prior ML exposure	196	86		
Failing ML therapy:				
Any ML	80	57	15.6 (9.3-26.4)	<0.0001
Azithromycin	39	28	14.9 (7.1-32.2)	<0.0001
Clarithromcin	34	24	14.0 (6.3-31.5)	<0.0001
ML Prior 3 months:				
Any ML	125	38	2.6 (1.7-3.9)	<0.0001
Azithromycin	46	19	4.0 (2.1-7.6)	<0.0001
Clarithromycin	70	15	1.5 (0.8-2.8)	0.15
Age Group:				
<15	830	174	12.8 (2.2-3.6)	<0.0001
15-65	1043	142	0.8 (0.7-1.0)	0.051
>65	988	123	0. 7(0.6-0.9)	0.002

Failures of ML therapy occurred in 23/2425 (0.9%) episodes with ML susceptible isolates, 49/376 (13.0%) episodes with low level MLR (ery MIC 1-8), and 31/243 (12.8%) episodes with high level MLR (eryMIC>8) (p<.001 MLS vs MLR, P=0.9, low vs. high level MLR).
Conclusions: MLR is increasing, and is associated with ML failure. Failing ML therapy, prior use of azithromycin, and younger age are risk factors for MLR. Reducing azithromycin use might help to preserve ML antibiotics.

Introduction:

From 1995 to 2007, outpatient macrolide use in Ontario has remained stable while macrolide resistance (MLR) has increased significantly prompting us to re-examine risk factors for MLR in patients with pneumococcal bacteremia (PB) in Toronto, Canada.

Methods:

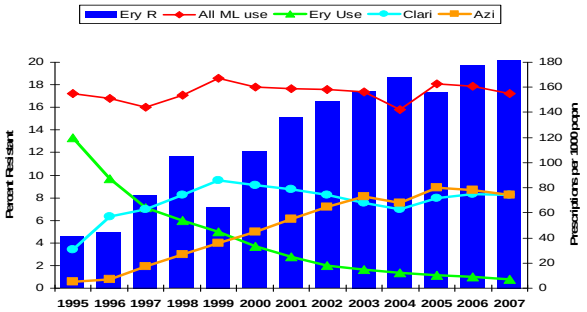
From January 1, 1995 to December 31, 2007, population-based surveillance for invasive pneumococcal infections was conducted in metropolitan Toronto and Peel Region, Ontario. Since 2000, a detailed history of preceding antibiotic therapy was elicited by chart review, and patient and physician interview. Isolates are shipped to the central study laboratory at the Mount Sinai Hospital, where they are confirmed as *S. pneumoniae* and frozen. Broth microdilution susceptibility testing is performed and interpreted using CLSI standards. Serotyping is performed on all isolates.

Failures of macrolide therapy were defined as pneumococcal bacteremia occurring during or within 48 hours of completion of treatment with a macrolide antibiotic. Prior use is defined as the receipt of a macrolide for a previous episode of infection in the 3 months prior to the current pneumococcal infection.

Results

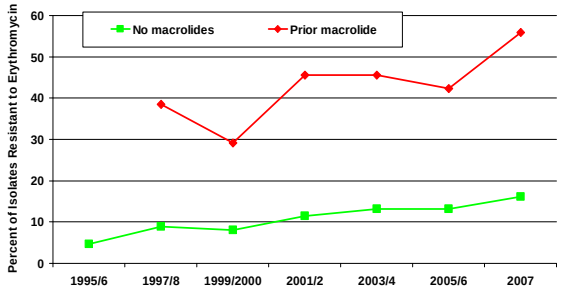
From 2000 to 2007, 3020 episodes of pneumococcal bacteremia were identified, corresponding to a rate of 8.5 cases per 100,000 population per year. 2864 (95%) of these isolates were available for susceptibility testing. Macrolide resistance in pneumococcal bacteremia increased from 12% in 2000 to 20% in 2007.

Figure 1: Outpatient macrolide use and macrolide resistance



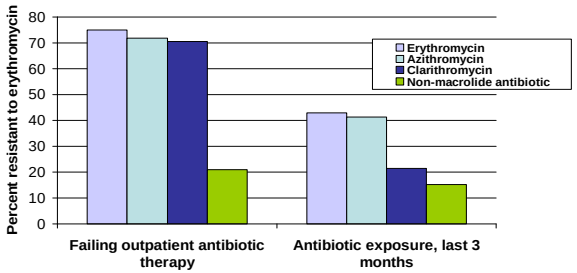
The proportion of patients presenting with pneumococcal bacteremia who have had some exposure to macrolide antibiotics in the three months prior to presenting with pneumococcal bacteremia has remained stable over time at 7% (overall, 203/2864). These patients account for 21% of all MLR isolates: there is a large difference between MLR in those with and without exposure (Figure 2).

Figure 2: Resistance in pneumococcal bacteremia with and without recent exposure to macrolides



Patients who are failing out-patient macrolide therapy with any macrolide are likely to have a macrolide resistance isolate (Figure 3). Prior exposure to azithromycin is much more likely to be associated with resistance to macrolides than prior exposure to clarithromycin (Figure 3).

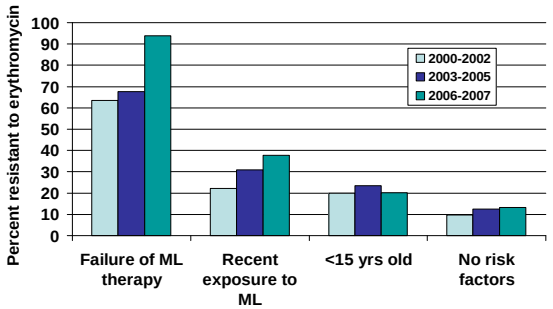
Figure 3: Resistance in PB by exposure to specific macrolides



Results (cont'd)

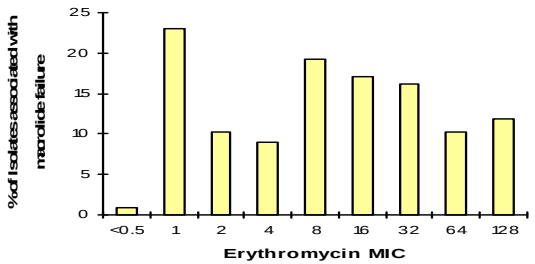
Macrolide resistance has increased proportionately in all risk groups for resistance over time, with the exception of children (Figure 4). The introduction of conjugate pneumococcal vaccine in Ontario has resulted in a temporary stabilization of the rate of macrolide resistance in children.

Figure 4: Erythromycin resistance by risk factors and time



The distribution of erythromycin MICs in erythromycin resistant isolates has remained stable over time, with 65-70% (overall, 300/439 isolates having an erythromycin MIC of >4ug/ml). Erythromycin susceptible isolates are very unlikely (<1%) to be associated with failure of macrolide therapy. Isolates with MICs of 1-4ug/ml, and those with MICs of >=8ug/ml are equally likely to be associated with macrolide failure. This suggests that even low level resistance to macrolides is clinically significant.

Figure 5: Percentage of pneumococcal blood culture isolates associated with failure of outpatient macrolide therapy, by erythromycin MIC



Conclusions:

- In patients with pneumococcal bacteremia, more than 20% of macrolide resistant isolates are associated with an individual history of macrolide exposure. Overall rates of macrolide resistance over-estimate true rates of resistance in macrolide naïve patients
- Azithromycin exerts stronger pressure for resistance than clarithromycin: patients who have recent exposure to azithromycin are significantly more likely to have a macrolide resistant isolate that those with a recent exposure to clarithromycin.
- The fact that the proportion of patients who present failing out-patient macrolide therapy is increased in patients whose isolates have erythromycin MICs of 1-4 as well as those whose isolates have MICs of >=8 suggests that "low-level" macrolide resistance is clinically significant.

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