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

K. Green, A. McGeer, S. Pong-Porter, A. Plevneshi, C. Ma, D.E. Low, Toronto Invasive Bacterial Diseases Network
Mount Sinai Hospital, Toronto, Ontario, Canada

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 4.5m) 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.

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).

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 failure are associated with resistance to macrolides. This suggests that even low level resistance to macrolides is clinically significant.

Acknowledgements

We are grateful to the infection control practitioners, microbiology technologists, public health staff, physicians, patients and families whose contributions make this surveillance possible, and to our TIBDN staff for their continuing enthusiasm and hard work. This work has been supported in part by Bayer Healthcare AG.

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. Both MIC and macrolide resistance testing is performed and interpreted using CLSI standards. Serotyping is performed on all isolates.

Failures of macrolide 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) (<0.0001 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.

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 failure are associated with resistance to macrolides. This suggests that even low level resistance to macrolides is clinically significant.

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