The Appropriate Use of Antibiotics in Respiratory Tract Infections: Let History Inform Your Prescribing

Dr. Allison McGeer
Dr. James Kellner

Allison McGeer, MD, FRCPC
Director of Infection Control,
Mount Sinai Hospital
Associate Professor,
Department of Pathobiology and
Laboratory Medicine and Public
Health Sciences
University of Toronto
Toronto, Ontario

James Kellner, MD, MSc, FRCPC
Head of Infectious Diseases,
Alberta Children's Hospital
Professor,
Department of Microbiology and
Infectious Disease, and
Department of Pediatrics
University of Calgary
Calgary, Alberta

The broad range of antibiotics currently available can, in theory, treat every pathogen. However, causative pathogens cannot be obtained for many infections, and testing to pinpoint the pathogen causing each individual infection, puts patients at risk of progressive infection while waiting for therapy. As a result, most antibiotic therapy must be empiric. Antibiotic resistance is now eroding the efficacy once associated with empiric therapy. How can we optimize our antibiotic resources to ensure successful therapy while avoiding treatment failures due to resistance?

EXPLORING RISK FACTORS FOR RESISTANCE

Respiratory tract infections (RTIs) provide an ideal working example for examining the issue of response to antibiotic resistance. RTIs account for the majority of physician visits and a significant proportion of antibiotic prescriptions.[1,2] Guidelines including Ontario's Anti-infective Guidelines for Community-acquired Infections (2005) provide first-, second- and third-line recommendations of individual agents from a range of antibiotic classes (penicillins, cephalosporins, fluoroquinolones, macrolides) to assist physicians in utilizing each class and drug to its best advantage.[3]

CLINICAL RESEARCH

Streptococcus pneumoniae is the most common bacterial cause of community-acquired RTIs including bronchitis, sinusitis, and pneumonia. Resistance to all classes of antibiotics among isolates of *S. pneumoniae* continues to increase worldwide. Because most antibiotics are initially prescribed empirically, being able to predict which patient might be at increased risk for infection with a resistant strain of *S. pneumoniae* would have significant clinical value.

To determine whether patient and disease characteristics could be used to predict antimicrobial resistance in isolates of *S. pneumoniae*, the Toronto Invasive Bacterial Diseases Network (TIBDN) conducted in metropolitan Toronto and the regional municipality of Peel, between 1995 and 2002, a prospective cohort study of 3,339 patients with invasive pneumococcal infection.[4] Patient history of antimicrobial therapy in the previous three months was identified.

This study observed that any recent history of antibiotic use increased the likelihood of antibiotic resistance, particularly to antibiotics within a class. In particular, patients who had received macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), or fluoroquinolones in the three months prior to their infection were at least four times as likely to be infected with an isolate that was resistant to the same class. For macrolides, a drug-specific resistance was observed. Patients exposed to azithromycin were much more likely to have a macrolide-resistant isolate causing their infection than patients exposed to erythromycin or clarithromycin.

This effect has also been seen in other population-based studies both in Canada and abroad.[5,6] Regions with high prescription rates for azithromycin have significantly higher rates of macrolide resistance in *S. pneumoniae* than regions with lower rates of azithromycin use.[4,7]

A second surveillance study was conducted by the TIBDN between 2000 and 2004 in the Toronto and Peel region to determine whether macrolide resistance is a cause of failure of macrolide therapy for serious pneumococcal disease.[8] The study first identified macrolide failures resulting in pneumococcal bacteremia and then evaluated the relative proportion of macrolide-resistant isolates. Treatment failure was declared if *S. pneumoniae* was isolated from a blood culture after the initiation of macrolide therapy or within two days of completing therapy. Clinical data including history of antimicrobial therapy in the three months prior to current illness were considered.

Over five years, 60 out of 1,696 identified cases of pneumococcal bacteremia, or 3.5%, represented failures of macrolide therapy. Eighty percent of patients who were failing macrolide therapy had an isolate resistant to macrolides, and 35% of patients who have taken a macrolide for a reason other than the current infection in the past three months had a macrolide resistant isolate. In contrast, only 15% of patients who had not been exposed to any macrolide antibiotics had a resistant isolate.

OPTIMIZE TREATMENT THROUGH PATIENT HISTORY AND ANTIBIOTIC CYCLING

When an antibiotic is clearly indicated, strategies to optimize antibiotic use include targeting the treatment to the pathogen, and factoring antibiotic use in the previous three months into the prescribing decision. Guideline recommendations serve as the starting point, with individual patient history providing the next "layer" of decision making.

The best means of avoiding an antibiotic to which the patient's infection will be resistant, the Ontario Anti-infective Guidelines for Community-acquired Infections recommends:

- reviewing antibiotics prescribed for any type of infection in the previous three months, and selecting an agent from an alternate class if significant exposure has occurred;[3,9]
- avoiding a macrolide antibiotic in a patient who has taken a macrolide for any reason in the last three months and
- avoiding a fluoroquinolone antibiotic in a patient who has taken any fluoroquinolone in the past three months, or in patients who are residents of a nursing home.

Antibiotic cycling or rotation is a strategy designed to optimize patient outcomes while preserving the efficacy of antimicrobials. The key tactic in antibiotic cycling is considering patient history when selecting treatment for a current infection, and utilizing different drug classes over time to maintain efficacy and control resistance. Studies continue to pursue key questions about cycling, including:

1) which antibiotics to cycle for a given condition,
2) the cycle order, and
3) the length of each cycle.[10,11]

In the meantime, however, there are enough data to assist with decision making for out-patient treatment of respiratory tract infections.

Antibiotic resistance represents a challenge to physicians because previously dependable treatments may not deliver the expected results. The strength of our antibiotic resources can be successfully maintained through:

1) continued focus on using antibiotics only when necessary,
2) use of antibiotics with the narrowest possible spectrum when prescribing,
3) taking an antibiotic history before prescribing and
4) awareness of regional resistance rates.

ANTIBIOTIC RESISTANCE IN CHILDREN

Antibiotic resistance is of particular concern in children, as it can limit current and future options for

effective antimicrobial therapy. General guidelines in the Canadian healthcare setting to help maintain antibiotic efficacy include:

- Treating only for bacterial infection, and educating parents who may be looking for immediate relief in the form of an antibiotic;
- follow first-line therapy recommendations for treatment of naïve patients, and preserve "top guns"—second- or third-line therapies—for repeat or resistant infections as recommended in the guidelines and
- educate parents on the importance of compliance with the dose and dosing schedule, and to follow the full schedule of therapy even if the child appears to be improved.

Because some antibiotics are not indicated for use in children, and antibiotic resistance presents a challenge to the effective drugs that are available for pediatric use, it is essential to take steps to ensure that available treatment options are protected. It is important to observe guideline-recommended prescribing strategies for choice of antibiotic class and agent while following general recommendations for the use of antibiotics.

IMPORTANCE OF PATIENT HISTORY IN CHILDREN

S. pneumoniae is the most common pathogen causing acute otitis media (AOM). It is also the most common cause of "typical" community-acquired pneumonia (CAP). Infections caused by *S. pneumoniae*, mostly pneumonia, are responsible for more than 700,000 deaths worldwide each year among children under the age of 5 years.[12]

The TIBDN study showed that antimicrobial use in the three months prior to infection was a leading risk factor for patients presenting with an illness where *S. pneumoniae* was a possible cause. These results, echoed in the Anti-infective Guidelines, determined that recent patient history is crucial in selection of an appropriate therapy. In addition to recent antibiotic use, the other main risk factor in children for aquisition and disease with antibiotic resistant *S. pneumoniae* is daycare-centre attendance.[13,14]

The TIBDN study observed not only class specificity but also drug specificity for macrolide-resistant *S. pneumoniae*. In regions of high prescribing of azithromycin, a correspondingly high incidence of macrolide resistance was observed; erythromycin resistance in *S. pneumoniae* was almost twice as high with use of azithromycin versus clarithromycin in the previous three months.[4] Increasing resistance of *S. pneumoniae* to macrolides is a serious concern because this class is among the most common drugs used to treat community-acquired RTIs.[15]

Despite pneumococcal resistance rates in excess of 25%, macrolides continue to be used first-line for CAP. In children 5 years of age and over, a macrolide is the recommended first-line treatment for CAP because *Mycoplasma pneumoniae* is the most prevalent pathogen in this age group, unlike younger children where *S. pneumoniae* is the most prevalent bacterial pathogen.[16] However, the TIBDN's second surveillance study (between 2000 and 2004 in Toronto and area) showed that patients for whom macrolide therapy failed were more likely to be under the age of 15 years, otherwise healthy and to have been treated with a macrolide in the previous three months.[8] This highlights the concern that for school-aged children and adolescents with CAP, *S. pneumoniae* must still be considered, perhaps moreso in children with more significant clinical features, and/or with radiographic consolidation on the chest x-ray (CXR). In such children, as with adults, macrolides should not be used alone if the child has received them within the previous 3 months.[17,18]

CHOOSING ANTIBIOTICS FOR CHIDLREN

The main strategy to reduce antibiotic resistance in children has been to encourage reduced and more appropriate use of antibiotics. In children in Canada, oral antibiotic prescribing has declined sharply in recent years.[19,20] As a result, antibiotic resistance rates for bacterial infections in children are generally quite low in Canada compared to other countries.

However, when antibiotic resistance is suspected (*e.g.,* in a child with a history of recent antibiotic use or who attends a daycare facility), appropriate selection of second- or third-line agents must be considered to effectively treat such infections.

Maintaining the effectiveness of antibiotics for pediatric RTIs can be supported by observing guideline recommendations for RTIs of bacterial origin and especially by careful prescribing that takes into account recent patient history and knowledge of regional resistance patterns.

COMBAT RESISTANCE BY REDUCING THE RISK OF RTIS

The first approach to combat antibiotic resistance is to ensure that clinical practice reduces the risk of RTIs to the lowest possible level. Your recommendations about two important interventions—vaccination and hand hygiene—can help patients protect themselves and their children. During the winter season, influenza vaccine has been shown to reduce the risk of RTI in adults by 35% to 45%.[21] Similar reductions in otitis media in children have been documented.[22] In older adults, and those with underlying chronic illnesses, pneumococcal vaccine has been shown to reduce the risk of pneumococcal bacteremia by 50% to 60%.[23]

Good hand hygiene—hand washing five times per day in the community—has been shown to be associated with a 30% to 40% reduction in all respiratory and gastrointestinal illnesses during winter seasons.[24,25]

Ensuring that our patients are well-educated is key: arming patients with the facts about vaccination and hand hygiene is a critical element in the fight against resistance.

REFERENCES:

1 Chan BTB and Schultz SE. Supply and utilization of general practitioner and family physician services in Ontario. ICES Investigative Report. Toronto: Institute for Clinical Evaluative Sciences; 2005.

2 Thacker SB and Berkelman RL. Public health surveillance in the United States. Epidemiol Rev 1988; 10:164-90.

3 Rosser WW, Pennie RA, Pilla NJ and the Anti-infective Review Panel. Anti-infective guidelines for community-acquired infections. Toronto:MUMS Guideline Clearinghouse; 2005.

4 Vanderkooi OG, Low DE, Green K, et al, for the Toronto Invasive Bacterial Disease Network. Predicting antimicrobial resistance in invasive pneumococcal infections. Clinical Infectious Diseases 2005; 40(9):1288-97.

5 Blondeau JM. Update on the use of the macrolides for community-acquired respiratory tract infections. Therapy 2006; 3(5):619-50.

6 Bergman M, Huikko S, Huovinen P, et al. and the Finnish Study Group for Antimicrobial Resistance (FiRe) Network. Macrolide and azithromycin use are linked to increased macrolide resistance in *streptococcus pneumoniae*. Antimicrob Agents Chemother 2006;50(11):3646-50.

7 Davidson R, Chan C, Doern G, et al. Poster: Macrolide-resistant *Streptococcus pneumoniae* in Canada: correlation with azithromycin use. Poster, CCAMID 2003.

8 Daneman H, McGeer A, Green K et al. for the Toronto Invasive Bacterial Diseases Network. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. Clinical Infectious Diseases 2006; 43:432-8.

9 Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clinical Infectious Disease 2003; 37(11):1405-33.

10 Dubberke ER and Fraser VJ. Cycling and other strategies to slow and reverse antibiotic resistance. Infect Med 2004;21(11):544-56.

11 Gruson D, Hilbert G, Vargas F, et al. Strategy of antibiotic rotation: long-term effect on incidence and susceptibilities responsible of gram-negative bacilli for ventilator-associated pneumonia. Crit Care Med 2003; 31(7):1908-14.

12 Anon. Vaccine-preventable deaths and the global immunization vision and strategy, 2006-2015. MMWR Morb Mortal Wkly Rep 2006; 55(18):511-5.

13 Regev-Yochay G, Raz M, Shainberg B, et al. Independent risk factors for carriage of penicillin-non-susceptible *Streptococcus pneumoniae*. Scan J Infect Dis 2003; 35;219-22.

14 Levine OS, Farley M, Harrison LH, et al. Risk factors for invasive pneumococcal disease in children: a population-based case control study in North America. Pediatrics 1999;103(3):e28.

15 Nuermberger E and Bishai WR. The Clinical Significance of Macrolide-Resistant *Streptococcus pneumoniae*: It's all relative. Clinical Infectious Diseases 2004;38:99-103.

16 British Thoracic Society Guidelines for the Management of Community Acquired Pneumonia in Childhood. British Thoracic Society of Standards of Care Committee. Thorax 2002;57(Suppl 1);1-24.

17 Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163;1730-54

18 Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Disease Society of America. Clin Infect Dis 2000; 31(2):347-82.

19 Kozyrskyj AL, Carrie AG, Mazowita GB, et al. Decrease in antibiotic use among children in the 1990s: not all antibiotics, not all children. CMAJ 2004;171(2):133-8.

20 Marra F, Patrick DM, Chong M, et al. Antibiotic use among children in British Columbia, Canada. J Antimicrob Chemother 2006; 58(4):830-9.

21 Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995;333(14):889-93.

22 Heikkinen T, Ruuskanen O, Waris M, et al. Influenza vaccination in the prevention of acute otitis media in children. Am J Dis Child 1991; 145(4):445-8.

23 Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. JAMA 1993; 270:1826-31.

24 Meadows E and Le Saux N. A systematic review of the effectiveness of antimicrobial rinse-free hand sanitizers for prevention of illness-related absenteeism in elementary school children. BMC Public Health 2004;4:50.

25 Sandora TJ, Taveras EM, Shih MC, et al. A randomized, controlled trial of a multifaceted intervention including alcohol-based hand sanitizer and hand-hygiene education to reduce illness transmission in the home. Pediatrics 2005;116(3):587-94.