Antibiotic Use as a Predictor of Antibiotic Resistance

A summary of "Predicting Antimicrobial Resistance in Invasive Pneumococcal Infections" recently published in Clinical Infectious Diseases (Vanderkooi et al. CID 2005:40, 1 May)

While antimicrobial therapy has resulted in decreased morbidity, *Streptococcus pneumoniae* remains the most serious cause of bacterial infections, with an incidence of bacteremic disease of 12-17 cases per 100,000 population. Moreover, antimicrobial resistance among *S. pneumoniae* is increasing, necessitating further research into the causes of resistance. Vanderkooi *et al*. sought to use patient and disease characteristics to identify risk factors for resistance to assist physicians in choosing the most appropriate antimicrobial therapy.

The study included all cases of invasive pneumococcal infections in metropolitan Toronto and Peel Region from 1995-2002, totalling 3339 patients. Laboratory analysis, chart reviews, and patient interviews were used to define variables for statistical testing. These variables included age, sex and site of infection, as well as usage of antimicrobials during the 3 months before infection. Variables included in the study were determined by a univariate analysis, selecting variables that represented independent risks of disease.

Of the 3339 patients identified with *S. pneumoniae*, 19.4% (or 627/3231) died of the disease. Over the 8 year study period, penicillin resistance among the study isolates increased from 0.91% to 6.23%, ceftriaxone resistance increased from 0% to 1.78%, erythromycin resistance increased from 4.6% to 13% and levofloxacin resistance increased from 0.3% to 1.2%. Patients who acquired their infections in a nursing home or hospital were more likely to have a fluoroquinolone-resistant isolate—the only demographic characteristic associated with infection.

Most notably, patients who had received macrolides, TMP-SMX, or fluoroquinolones were at least 4 times more likely to develop an infection that was resistant to treatment from the same antimicrobial class compared to patients without previous antimicrobial use. Besides previous antimicrobial use, less important risk factors for penicillin resistance were year of infection, and an absence of chronic organ system disease.

In the fight against antimicrobial resistance, the study found two important risks factors: antibiotic use in the 3 months before the onset of infection and, for fluoroquinolones, institutional acquisition of infection. The impact of previous antibiotic usage on penicillin and cephalosporin resistance was minimal. Moreover, similar to other research, patient-specific characteristics related to resistance could not be identified. Instead the authors suggest that geography and the clonal dissemination of strains maybe more important factors of penicillin resistance.

Prior use of macrolides was highly predictive of macrolide resistance, although the prevalence of resistance was different for different macrolides. Resistance increased from 9% in patients who had no received any macrolide, to 20-30% in patients who had received clarithromycin or erythromycin, to >50% in patients who had received azithromycin. The authors suggest that resistance may be reduced if shorter-acting macrolides are used.

Patients with community-acquired infections and no history of fluoroquinolones use had isolates that were uniformly susceptible to levofloxacin. In contrast, patients who had recieved any fluoruquinolone in the prior 3 months had levofloxacin resistance rates of 3-4%.; nursing home residents with recent use of fluoroquinolones had 23% rate of resistance to gatifloxacin. While national guidelines still recommend fluoroquinolones for pneumonia acquired in hospitals or nursing homes, the authors suggest this is no longer an optimal therapy.

Knowledge of prior antimicrobial use is crucial for determining appropriate therapy for suspected pneumococcal infection. The most important risk factor for resistance to an antibiotic is previous use of antibiotics of the same class. For patients with a history of recent macrolide use, the risks of macrolide resistance and the desire to preserve fluoroquinolones as a class makes ketolides an attractive option in these patients.

This newsletter is a publication of the Toronto Invasive Bacterial Diseases Network (TIBDN), a collaboration of the microbiology laboratories, infection control practitioners, and public health officials who serve the population of Metropolitan Toronto, Peel, York, Durham, Simcoe, Hamilton, and Halton Regions. For an electronic copy of this newsletter please visit our website at:
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How the Emergence of Antimicrobial Resistance Should be Changing our Practices – Toronto, 2006

Allison McGeer, MD

We have been fortunate in Canada to have seen relatively little antimicrobial resistance in community pathogens. This is in part due to the overall success of physicians in decreasing out-patient antibiotic prescribing. The number of out-patient prescriptions written in Canada has decreased by 25% since 1995, and this decrease is clearly associated with the preservation of antimicrobial susceptibility. Nonetheless, rates of resistance are increasing for some pathogens, and there is enough resistance in some common community pathogens that changes in practice are required. This article summarizes the changes that physicians in Toronto need to consider. Subsequent articles in this newsletter describe recent results of Toronto Invasive Bacterial Diseases Network surveillance that we hope will help with decision making.

Emergence of Community-Acquired MRSA (CA-MRSA)

In the last 18 months, CA-MRSA has started to appear throughout Ontario with increasing frequency.

CA-MRSA strains are different from hospital-acquired strains. They occur in adults and children without any exposure to hospitals or healthcare. While they are sometimes associated with jails, intravenous drug use, and living on the street, they also occur in children and adults without these risk factors. Some cases appear to be associated with travel to areas of the United States where community-acquired MRSA is common (e.g. Texas, southern California). Outbreaks have also been described in sports teams with frequent skin-to-skin contact (e.g. wrestling and football).

Most infections with community acquired MRSA are skin infections. Typically, the infection begins as a small cellulitis with a central necrotic area – people who have been in the southwestern US often think that they have a spider bite. By the time patients are seen, the infection is often a large abscess which may need to be drained.

In some areas, like Victoria, BC, the incidence of CA-MRSA increased very rapidly after initial reports. While we don't know how quickly CA-MRSA will appear, all physicians in southern Ontario should be aware of this potential.

The diagnosis of CA-MRSA should be considered in patients, particularly children and young adults, who have large boils/carbuncles and those whose cellulitis fails to respond to antibiotics. The antimicrobial susceptibility of CA-MRSA is variable – swabs should be sent for culture in patients presenting with skin infections that may be due to CA-MRSA. To date in Toronto, about 70% of CA-MRSA are susceptible to clindamycin, and most are susceptible to mupirocin (only available topically), tetracycline and trimethoprim-sulfamethoxazole.

INSIDE THIS ISSUE

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Macrolide Resistance in Group A Streptococci

Macrolide antibiotics (erythromycin, clarythromycin, azithromycin) are effective second line antibiotics for treating group A streptococcal pharyngitis. In Toronto, the rate of resistance of group A strep to macrolides increased sharply from 1998 to 2002, but has remained stable since then at 12-15%. Since most people with streptococcal sore throat get better by themselves (albeit more slowly), this rate of resistance will not result in many patients returning to the office with failure to resolve. **However, it is important to remember that strep throat should always be treated with penicillin rather than macrolides if possible, and that physicians should be alert to the possibility of macrolide failures.** This is true because macrolide use is continuing to increase in Ontario, and resistance in group A strep may start to increase again at any time.

Macrolide Resistance in *Streptococcus pneumoniae*

The more than 20% decrease in penicillin and cephalosporin use across Canada since 1995 has been associated with a stabilization of resistance to penicillin. **Amoxicillin is now the single most active antibiotic against *S. pneumoniae*** – as active as moxifloxacin, the best of the new quinolones. Because macrolide use has continued to increase, macrolide resistance has increased as well (see Figure).

TIBDN has been working to assist physicians in understanding the implications of macrolide resistance in pneumococcal infections. The next two pages summarize the results of two of these studies. The first (Impact of Macrolide Resistance in Bacteremic Pneumococcal Disease) establishes that macrolide resistance is associated with failure of macrolide therapy, and that this failure results in bacteremia and hospitalization in some cases. The second (Antibiotic Use as a Predictor of Antibiotic Resistance) describes how to avoid macrolide failures: in Toronto, macrolide resistance remains uncommon (<10%) in patients who have not received a macrolide antibiotic in the last 3 months, but very common in patients who have recently received a macrolide, especially azithromycin.

Macrolide therapy is contraindicated in patients who may have a pneumococcal infection (pneumonia, or sinusitis) that is macrolide resistant: the way to identify such patients is to take an antibiotic history. Patient-derived antibiotic histories are adequate: previous TIBDN work has shown that they agree 88% of the time with physician-derived histories.

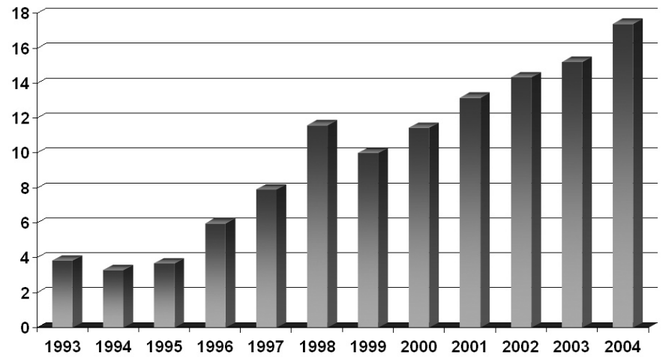
Fluoroquinolone Resistance in Nursing Home Infections

In TIBDN studies of predictors for antibiotic resistance, nursing home residency is a strong predictor of fluoroquinolone resistance in *S. pneumoniae.* In residents of nursing homes, levofloxacin resistance is 5% in those who have not recently received a fluoroquinolone, and 23% in those who hare received any fluoroquinolone antibiotic in the last 3 months. Empiric fluoroquinolone monotherapy is no longer adequate for pneumonia or undifferentiated sepsis in nursing home residents.

Fluoroquinolone resistance is also increasing in *E. coli*, the cause of half of all urinary tract infections. Across Ontario, fluoroquinolone resistance in all *E. coli* increased from 2.7**%** in 2000 to 9.3**%** in 2004. TIBDN does not collect data on fluoroquinolone resistance in *E. coli* from nursing homes. However, in 2005, more than 50% of *E. coli* isolates from nursing home residents presenting to the emergency department at Mount Sinai Hospital were resistant to ciprofloxacin.

Fluoroquinolones have been very useful antibiotics in long term care. However, all physicians who work with nursing home residents should now be conscious of the frequency of resistance to fluoroquinolones in their patients, and the need to develop quinolone sparing policies in nursing homes to preserve the value of this class for these vulnerable patients.

Percentage of *S.pneumoniae* Isolates with Erythromycin Resistance (Ontario 1993-2004)



Source: Toronto Invasive Bacterial Disease Network, Jan 2006

Impact of Macrolide Resistance in Bacteremic Pneumococcal Disease

A summary of data presented at the the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, WASHINGTON, D.C., December 16-19, 2005 (Daneman et al.)

Streptococcus pneumoniae is one of the most common causes of serious bacterial infections in young children and community acquired pneumonia in adults. Macrolide antibiotics are the recommended empiric therapy for patients with suspected pneumococcal infections and are the second most widely prescribed class of antibiotics.

Rates of macrolide resistance in pneumococci are now near 20% in Toronto. Macrolide resistance occurs via one of two mechanisms: methylation of ribosomal macrolide target sites, encoded by the *ermB* gene (high-level resistance), or through drug efflux, encoded by the *mefA* gene (low-level resistance). In Toronto, about 70% of macrolide resistance is mediated by efflux (*mef*A).

Reports of macrolide treatment failure for pneumococcal infections with macrolide resistant isolates have been increasing over the last several years. It is clear that highly resistant strains can lead to clinical failure, but it is unclear whether low level resistance - which is more common in Toronto - also leads to clinical failure.

TIBDN used data from its prospective, population-based surveillance to determine whether macrolide resistance with either or both low and high level macrolide resistance is a cause of failure of macrolide therapy for serious pneumococcal disease. Macrolide treatment failure was defined as the prescription of macrolide antibiotic for the episode of infection, with *S. pneumoniae* isolated from a blood culture taken during this macrolide therapy or within two days of completion of the course of therapy. During the active surveillance period (January 2000 to December 2004), 1696 episodes of community acquired pneumococcal bacteremia were reported (8.5 cases per 100,000 population per year). Of these cases, 60 patients were identified as having failed macrolide treatment therapy. Clinical diagnoses included: pneumonia, primary bacteremia, meningitis, otitis media, and osteomyelitis. Ninety three percent required hospitalization and 15% died.

Thirty six percent of the pneumococcal isolates from macrolide failures were macrolide susceptible and 64% were macrolide resistant. Compared to failures associated with macrolide resistant isolates, failures associated with macrolide susceptible isolates were more likely to be 65 years of age or older (P=0.01), more likely to have cardiac disease (P=0.03), and more likely to be residents of long term care facilities (P=0.008).

The median duration of macrolide therapy prior to presentation with pneumococcal bacteremia was 3 days (range 0-17d).There were significantly more macrolide resistant isolates among cases of macrolide failure than among cases of pneumococcal bacteremia that occurred in the absence of macrolide therapy (37/58 (64%) vs 193/1569 (12%), p<0.001). Significantly more macrolide resistant isolates were also found among cases of macrolide failure than among those failing non-macrolide antibiotics (37/58 (64%) vs 16/74 (22%), p<0.001). Univariate analysis demonstrated that patients failing macrolide therapy were more likely to be children, to have no chronic underlying illness and to have received a macrolide antibiotic for another reason during the previous three months. The multivariate model indicated that patients failing macrolide therapy were more likely to have erythromycin resistance in the infecting isolate, to be older in age, and to be a resident of a long term care facility.

Of the macrolide resistant isolates from macrolide failures, 53% were positive for *mefA*, 44% were positive for *ermB*, and 3% were positive for both *mefA* and *ermB*. *MefA* and *ermB* were both much more common in macrolide failures than in other isolates, demonstrating that both low level and high level resistance to macrolides are associated with macrolide failure.

These results indicate that macrolide resistance contributes significantly to an increased risk of clinical macrolide failure in patients treated for pnemonia. Clinicians should be aware that known macrolide resistance precludes the use of macrolide therapy for pneumococcal pneumonia.

Of course, therapy for pneumonia is almost invariably empiric, and very few patients ever have the etiology and antibiotic susceptibility of their pneumonia diagnosed. Fortunately, it is possible to predict the risk that patients in Toronto will have a macrolide resistant isolate based on an antibiotic history: patients who have not had macrolide antibiotics in the last 3 months can be safely treated with macrolides; patients who have taken a macrolide for any reason in the last 3 months are much more likely to have a macrolide resistant pneumococcal isolate (20-55% chance), and should receive a different class of antibiotics (a ketolide or fluorquinolone).