DECEMBER 2002
VOLUME 3, ISSUE 1

TIBDN
TORONTO INVASIVE BACTERIAL DISEASES NETWORK

INSIDE THIS ISSUE

Does prior antibiotic therapy mean we should change prescribing?

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All of us are aware that the use of antibiotics selects for antibiotic resistance, and that antibiotic resistance is increasing worldwide. However, resistance remains relatively uncommon in Canada, and few of us have seen patients fail therapy because of resistance. When should we choose to change therapy to avoid failures due to resistance?

Pneumococci are the most common cause of otitis media, pneumonia, and community-acquired bacteremia in patients of all ages. Information from the Canadian Bacterial Surveillance Network (CBSN) and TIBDN surveillance suggest that we should now be modifying therapy for suspected pneumococcal infections based on the patient's recent use of antibiotics.

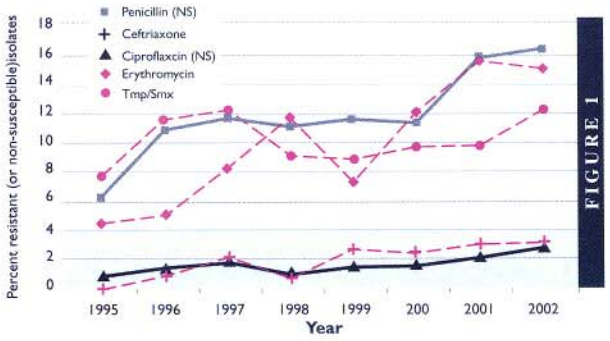

FIGURE 1

Overall rates of antibiotic resistance among isolates of *S. pneumoniae* over time are shown in Figure 1. Antibiotic resistance is increasing for all classes of antibiotics. Most significantly, the percentage of isolates resistant to erythromycin, clarithromycin and azithromycin increased from 4.5% to over 15%. Resistance to flouroquinolones (ciprofloxacin and levofloxacin) remains low: however, this resistance is concentrated in the elderly. In isolates collected in 2002, nearly 5% of strains are not susceptible to levofloxacin.

You may have been asked to provide information about prior antibiotic use for one or more of the 3,161 patients in Toronto and Peel Region who had invasive pneumococcal disease between 1995 and 2001. Of these cases, antibiotic use remains unknown for 1004 (32%) (mostly those without a family physician). Of the remaining patients, 730 (23% overall) had received at least one course of an antibiotic in the three months before their illness, and 1427 (45% overall) had not.

There was no significant difference in antibiotic resistance of the infecting isolate between patients who had received no antibiotics, and those whose antibiotic history was unknown. However, any history of antibiotic use increased the likelihood of antibiotic resistance by a factor of about 2 (range 1.8-3.0 for the different antibiotics). Prior receipt of an antibiotic of the same class (eg. amoxicilin for penicillin, ceftin for cefotaxime) did not make resistance more likely for penicillin or cefotaxime. However, prior use of macrolides (eg. clarithromycin, erythromycin, azithromycin), trimethroprim-sulfamethoxazole or fluoro-quinolones (eg. ciprofloxcin, levofloxacin) very substantially increases the risk of resistance to all antibiotics in the class (Figure 2).

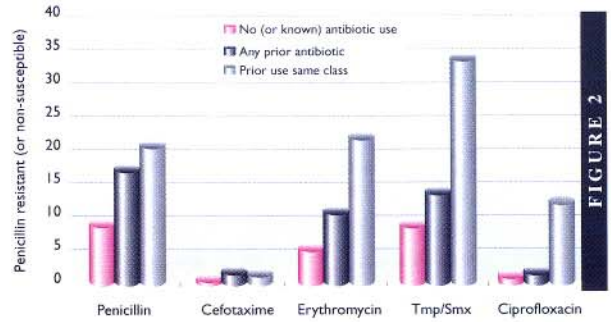

FIGURE 2

Thus, a history of recent antibiotic use is a very important predictive factor for resistance in an infection with *Streptococcus pneumoniae*. In adults aged 50 years and over who have taken ciprofloxacin, levofloxacin or norfloxacin in the past three months, the probability of levaquin resistance in an infecting pneumococcal strain is 12%. Similarly, if a patient has taken any macrolide antibiotic in the past three months, the chance that their pneumococcal isolate is resistant to macrolides is >20%. A history of recent antibiotic use is essential before a macrolide or flouroquinolone is prescribed for any patient with a suspected pneumococcal infection.

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An Outbreak of ESBL *E.coli* in Long Term Care Facilities: An Emerging Clinical and Public Health Challenge

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Background

The emergence of antibiotic resistance in gram positive organisms such as *Enterococcus faecium* (VRE) and *Staphyloccus aureus* (MRSA) are well recognized clinical problems that threaten our ability to treat gram positive infections adequately. Extended-spectrum ß-lactamases (ESBLs) are an emerging cause of antibiotic resistance in *Enterobacteriaceae*, especially *E.coli* and *Klebsiella pneumoniae* that may pose an equivalent challenge in these gram negative bacteria.

ESBLs are enzymes that degrade ß-lactam antibiotics, including the newer cephalosporins antibiotics such as cefotaxime (1). They are frequently encoded on plasmids that can spread rapidly between different bacterial strains (2). ESBL positive (ESBL+) organisms are often resistant to other classes of antibiotics, such as the aminoglycosides and fluoroquinones (2). As a result, organisms such as *E.coli* are becoming increasingly multi-drug resistant (MDR).

We recently reported on an outbreak of MDR, ESBL+ *E.coli* occurring in long term care facilities (LTCF) in the Durham, York and Toronto Regions of Ontario (3). This outbreak is described below as an illustration of several of the critical features of ESBL+ organisms and their potential for dissemination.

The Outbreak

In July 2000, six clinical isolates of ESBL+ *E.coli* were identified over a two week period at a single acute care hospital in Durham Region. The isolates all had identical antibiotic susceptibilities consisting of resistance to penicillins, cephalosporins (including the 3rd and 4th generation cephalosporins), aztreonam, ciprofloxacin and the aminoglycosides. Susceptibility was limited to trimethoprim-sulfamethoxazole and imipenem. Further study using pulsed-field gel electrophoresis demonstrated that all six isolates were clonally related and derived from a common source.

Epidemiological investigation revealed that all six patients had resided at the same LTCF. Investigation at that facility revealed a surprising high level of colonization with the outbreak ESBL+ *E.coli* with over 16% of residents demonstrating gastrointestinal colonization with the organism. An expanded investigation identified over 200 colonized residents at 15 LTCFs and 6 hospitals in Durham Region with evidence of spread to facilities in York and Toronto Region. Although the majority of residents had asymptomatic colonization, 33 had positive clinical isolates and 8 residents died of *E.coli* pneumonia or septicemia since the recognition of the outbreak.

Transmission of the ESBL+ *E.coli* appeared to be due to person to person transmission. Transient colonization with the organism on the hands of healthcare providers and residents was the most likely mechanism of transmission. To limit further spread a number of interventions were employed and included education of residents and staff, infection control audits, enhanced environmental cleaning, closure of common washrooms and increased availability of alcohol handwash. At some facilities antibiotic restriction and unit closure was required. Continued surveillance indicates that these measures have prevented the continued expansion of the outbreak. Unfortunately a large number of residents remain colonized, due to the slow rate of spontaneous clearance of the organisms and to ongoing transmission that continues to occur at several facilities. These individuals represent a reservoir from which resistance could spread to other LTCFs or hospitals.

A final important finding of the outbreak investigation was the identification of a number of ESBL+ bacterial strains in addition to the outbreak strain of ESBL+ *E.coli.* These included other strains of *E.coli* as well as isolates of *Citrobacter freundii*, *Enterobacter cloacae* and *Klebsiella* species. This illustrates the potential for the ESBL resistance plasmid to jump from species to species.

What Can Be Done?

The emergence of ESBL+ *E.coli* and its spread within LTCFs and hospitals in Ontario is concerning and represents both a clinical and a public health challenge.

From a clinical perspective, patients infected with this ESBL+, MDR *E.coli* strain are a challenge to treat due to the limited number of antibiotic options. For severe infections a carbapenem (e.g. imipenem, meropenem) appears to be the only reliable treatment. For patients that are colonized but not infected, antibiotic therapy is not recommended as it appears to be ineffective at eliminating colonization and could lead to resistance to the few remaining antibiotics for which susceptibility is preserved.

Preventing further spread of this organism is a major public health challenge. The prolonged persistence of the organism in the GI tract of asymptomatically colonized individuals means that control attempts are not short term enterprises. Furthermore, the ability of the resistance plasmid to jump from species to species means that surveillance systems must be able to detect increased ESBL mediated resistance in bacteria other than the outbreak organism. Currently, guidelines for the management of ESBL+ organisms in the outbreak (and non-outbreak) situation do not exist. Despite this, some simple measures have been shown to limit the spread of these organisms. Enhanced infection control, including regular handwashing can limit the

transmission of the organism in hospitals and LTCFs (4). In some studies restricting the use of 3rd generation cephalosporins has also been effective (5).

At present, a great deal remains unknown about the potential for ESBL+ organisms to spread, the long term consequences of this spread and the best approaches to prevent it. Research in this area is urgently needed. By limiting the spread of this MDR, ESBL+ *E.coli* strain in Durham Region we hope to prevent this organism from becoming endemic within LTCFs in Ontario.

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Community-Acquired Methicillin Resistant *Staphylococcus aureus* (CAMRSA)

Marie Louie, MD, FRCPC

The last decade has seen the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in Canada, (6.1 cases/ 1000 hospital admission, Canadian Nosocomial Infection Surveillance Program, Health Canada (CNISP), 2000). MRSA has long been considered a hospital-acquired pathogen, with acquisition confined primarily to tertiary care hospitals and long-term care facilities. However, with the emphasis of health care shifting to earlier discharges, and more care being provided in the outpatient setting, the numbers of patients carrying MRSA being discharged from hospitals have increased. In the last several years, there are increasing reports of the emergence of MRSA in the community in individuals with none of the traditional risk factors (prior hospitalization, residence in a nursing home, exposure to known contact with MRSA, prior antibiotic usage) for MRSA acquisition. The CNISP surveillance reports that about 7-8% of all MRSA cases are thought to be community-acquired. Active surveillance of all MRSA cases in the area surrounding Edmonton, Alberta (Capital Health Region, 2001) have found that 9% of all MRSA cases are acquired within the community and are not associated with any known risk factors. Little is known about the epidemiology of community-acquired MRSA and several sources of this emergence have been suggested. These include an increase in community-acquired infections in persons who have acquired their MRSA in hospital but their infection develops at home after discharge; community transmission of MRSA from patients discharged from the hospital and from health care workers, both in households and as a result of community care; and the emergence of "true" community-acquired infections, in which MRSA appears to have arisen in a community with no identifiable contact to, any known risk factors.

Truly *"de novo"* community strains of MRSA tend to be multiply-susceptible to other classes of antibiotics unlike hospital-acquired MRSA strains which tend to be multiply-resistant to other classes of antibiotics other than beta-lactams antibiotics. CAMRSA possess a unique type of mec DNA that is different from the mec DNA of hospital-acquired strains. These "community" strains have been associated mostly with non-invasive skin and soft tissue infections occurring primarily in children. To better understand the epidemiology of CAMRSA and determine the risk factors for CAMRSA, a group of investigators (McGeer, Louie, et al.) will be starting a population-based surveillance and case-control study in southern Ontario, Alberta, and Manitoba. Understanding how and where community-acquired MRSA arises while it is emerging rather than when it has become well established is important. We need to be able to identify those patients at risk of MRSA infection so appropriate empiric antibiotic therapy can be chosen, and appropriate public health responses can be instituted to prevent and control further spread in the community.

Cochlear Implant Recipients may be at Greater Risk for Meningitis

Adapted from Health Canada and CDC information bulletins by Karen Green RN

Health Canada recently circulated information concerning a possible association between cochlear implants and the occurrence of bacterial meningitis. Worldwide, 91 cases of meningitis in patients with one of three FDA approved cochlear implant devices have been reported. A total of 17 deaths have resulted from these meningitis cases. To date, only one case of meningitis (not resulting in death) has been reported in a patient with a cochlear implant in Canada.

Of the 52 patients reported in the U.S., ages ranged from 18 months to 84 years. The majority of cases (33) were under 7 years of age at the time they developed meningitis. U.S. cases had onset of meningitis symptoms from less than 24 hours to greater than 6 years after implant. Thirty-two of the patients developed meningitis within one year post implantation, many within the first few weeks of surgery.

Cerebrospinal fluid (CSF) culture results were available for 23 of the 32 cases. The organisms identified are: *Streptococcus pneumoniae* (pneumococcus) (16), *Haemophilus influenzae* (4), *Streptococcus viridans* (2), and *Escherichia coli* (1). Although vaccination is usually protective against both pneumococcus and *H. influenzae*, 2 cases of pneumococcal meningitis and 2 cases of *H. influenzae* meningitis developed after the patient had received the appropriate vaccine.

Approximately 60,000 cochlear implantations have been performed worldwide as treatment for deafness.

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A small percentage of deaf patients may have congenital abnormalities of the inner ear which predispose them to meningitis even prior to implantation. Other predisposing factors may include otitis media, immunodeficiency status, prior history of meningitis, or neuro-surgical intervention. The cochlear implant, because it is a foreign body, may act as a nidus for infection when patients have bacterial illnesses. In some of the reported cases of meningitis in cochlear implant recipients, patients may have had overt or sub-clinical otitis media prior to surgery or before the meningitis developed. Physicians are encouraged to consider prophylactic antibiotic treatment prior to implantation, as appropriate, and to diagnose and treat otitis media promptly in patients with cochlear implants. A diagnosis of meningitis should be considered in cochlear implant patients when presenting with compatible symptoms such as fever, irritability, lethargy and loss of appetite in infants and young children or headache, stiff neck, photophobia, nausea and vomiting, and confusion or alteration in consciousness in older children and adults.

Cochlear implant candidates, as well as those individuals who have already received the implant, may benefit from immunizations against organisms that commonly cause bacterial meningitis, particularly *Streptococcus pneumoniae*. All candidates for and recipients of cochlear implants should be up-to-date with their immunizations.

The National Advisory Committee on Immunization (NACI) recommends the following:

- Heptavalent pneumococcal conjugate vaccine (PCV7) be routinely given to all children 23 months of age starting at 2 months of age and to all children 24 to 59 months of age at high risk for invasive pneumococcal disease.
- The 23-valent pneumococcal polysaccharide vaccines be given routinely to all adults 65 years of age and older and to persons aged 2 to 64 years at high risk for invasive pneumococcal disease.
- Haemophilus influenzae b conjugate vaccine be routinely given to infants starting at 2 months of age and to children up to 59 months of age.
- Meningococcal C conjugate vaccine be routinely given to infants starting at 2 months of age and be given to children 1 to 4 years, adolescents and adults.
- Quadrivalent (A, C, Y, W135) meningococcal vaccine be given routinely to individuals > 2 years of age at high risk for invasive meningococcal disease.

For more details re: scheduling of doses and risk factor information, please consult the Canadian Immunization Guide, 6th edition, 2002 (www.hc-sc.gc.ca/pphb-dgspsp/publicat/cig-gci/) or your local Medical Officer of Health.

All cases of bacterial meningitis are notifiable and should be promptly reported to your local Medical Officer of Health. Cases of meningitis in cochlear implant recipients should be reported directly to Health Canada/ Health Products and Food Branch Inspectorate 416-973-1466 or fax 416-973-1954

Other useful website links

Canadian Immunization Awareness Program
http://www.immunize.cpha.ca

Health Canada, Population and Public Health Branch
http://www.hc-sc.gc.ca/hpb/lcdc/bid/di/index.html

U.S. Centers for Disease Control and Prevention, National Immunization Program
http://www.cdc.gov/nip/

The National Network for Immunization Information http://www.immunizationinfo.org/

U.K. Public Health Laboratory Service
http://www.immunofacts.com/

Canadian Immunization Guide, 6th edition, 2002
http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/cig-gci/index.html

This newsletter is a publication of the Toronto Invasive Bacterial Diseases Network (TIBDN), a collaboration of the microbiology laboratories and infection control practitioners who serve the population of Metropolitan Toronto and Peel Region.

This newsletter has been generously sponsored by an unrestricted educational grant from:

Pneumococcal Vaccine Recommendations for previously unvaccinated individuals (adapted from Canadian Immunization Guide, 2002, Sixth Edition)

Age at first dose	Recommended groups	Type of vaccine	Dosage/Route	Primary series	Booster
2-6 months	All	Conjugate	0.5 mL. IM	3 doses, 6-8 weeks apart	1 dose at 12-15 months
7-11 months	All	Conjugate	0.5 mL. IM	2 doses, 6-8 week apart	1 dose at 12-15 months
12-23 months	All	Conjugate	0.5 mL. IM	2 doses, 6-8 weeks apart	
24-59 months	Children with sickle cell, asplenia, HIV, CSF leaks, chronic illness or immunocompromising condition	Conjugate	0.5 mL. IM	2 doses, 8 weeks apart	After 3 yrs in children ≤10 yrs old with asplenia, sickle cell, CRF, nephrotic syndrome, HIV, and immunosuppression
	Also consider all other healthy children especially those who attend childcare or live in isolated communities (eg. Aboriginal children)	Conjugate	0.5 mL. IM	1 dose	
>=65 years	All	Polysaccharide	0.5 mL. IM or SC	1 dose	After 5 yrs in persons >10 yrs old with asplenia, sickle cell, CRF, nephrotic syndrome, HIV, and immunosuppression
5-65 years	Persons with asplenia, splenic dysfunction, HIV, CSF leaks, chronic illness or immunocompromising conditions	Polysaccharide	0.5 mL. IM or SC	1 dose	After 3 yrs in children ≤10 yrs old with asplenia, sickle, cell, CRF, nephrotic syndrome, HIV, and immunosuppression