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Antimicrobial Resistance and Judicious Antimicrobial Use in Minnesota

Antimicrobial Resistance in Minnesota and the United States
Problems with antimicrobial resistance in Minnesota and the United States continue to grow. Increasing antimicrobial resistance is being encountered in a variety of organisms; much of this is due to increasing antimicrobial use in human and veterinary medicine.

Nationally, the prevalence of penicillin resistance among *Streptococcus pneumoniae* isolates increased from 1% in 1992 to 16% in 1999.[1] In Minnesota, 24% of invasive pneumococcal isolates submitted to the Minnesota Department of Health (MDH) in 1999 were non-susceptible to penicillin, and 17% were non-susceptible to third-generation cephalosporins.[2] Another concerning aspect of these penicillin/cephalosporin-resistant pneumococcal isolates, especially those with high levels of resistance, is that they often are resistant to other classes of antimicrobials as well.

In Minnesota and elsewhere, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections in patients without traditional risk factors for MRSA are emerging as an important health problem, particularly among pediatric patients.[3,4] The significance of these infections is that MRSA isolates have a gene that makes them intrinsically resistant to all beta-lactam antibiotics, including cephalosporins. This is worrisome, since the empiric treatment of pediatric infections commonly involves the use of beta-lactams.

Another development regarding *S. aureus* is the emergence of "vancomycin-intermediate *S. aureus*" (VISA).[5,6] In the spring of 2000, a Minnesota resident became the fifth person in the U.S. diagnosed with a confirmed VISA infection. This patient was exposed to vancomycin for a total of 18 weeks, and serial isolates from the patient (all of which were an identical strain based on DNA fingerprinting) became progressively less sensitive to vancomycin. This is another example of microbes' ability to adapt rapidly in the face of selective antimicrobial pressure.

Among foodborne pathogens in Minnesota, the prevalence of antimicrobial-resistant isolates of *Shigella*, *Salmonella*, and *Campylobacter* is substantial.[2] For example, 85% of *Shigella* isolates identified in 1999 were non-susceptible to ampicillin, and 25% were non-susceptible to trimethoprim-sulfamethoxazole. These agents have been traditional front-line therapies for *Shigella* infections. Approximately 20% of *Campylobacter jejuni* infections were non-susceptible to ciprofloxacin in 1999. More than 80% of *C. jejuni* infections among persons who recently had returned from foreign travel were resistant to ciprofloxacin. Ciprofloxacin and erythromycin are considered first-line therapies for these infections. Finally, 40% of human *Salmonella typhimurium* isolates now are non-susceptible to ampicillin. Some of these isolates have the "DT 104" phenotype, which has a series of resistance genes that confer resistance to ampicillin, tetracycline, chloramphenicol, sulfamethoxazole, and tetracycline. Between 1995 and 1998, 27% of *S. typhimurium* isolates were resistant to five or more antimicrobials.[7]

The problem of resistant organisms extends to other pathogens as well. Nationally, an increasing percentage of *Mycobacterium tuberculosis* isolates are resistant to one or more antimicrobials that are commonly used to treat tuberculosis.[8] There is also growing resistance of HIV to antiretroviral medications such as AZT.[9] In 2000, a Minnesota resident became the fifth person in the U.S. to be diagnosed with an erythromycin-resistant pertussis infection. Finally, in 2000, MDH reported its first isolate of *Neisseria gonorrhea* that was non-susceptible to ciprofloxacin.

Antimicrobial Prescribing
Over the past two decades, the use of antimicrobials has increased dramatically, particularly among children. Between 1980 and 1992, the rate of outpatient antibiotic prescribing increased approximately 50%.[10] Antimicrobial prescribing is the most important catalyst for the increase in resistant organisms. Recent antimicrobial treatment increases a child's risk of either being colonized[11-13] with or developing an invasive infection[14,15] from resistant pneumococci. Some antimicrobial resistance in humans can be linked primarily to antimicrobial prescribing in food animals. For instance, a study by investigators at MDH demonstrated that a rise in domestically-acquired quinolone-

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resistant *Campylobacter jejuni* infections in Minnesotans was linked to resistant *C. jejuni* strains in chickens, which in turn were associated with the use of quinolones in the poultry industry.[16]

Inappropriate use of antimicrobials can have adverse clinical consequences in addition to drug resistance. Antimicrobial treatment of *Escherichia coli* O157:H7 infections increases the risk of developing hemolytic uremic syndrome.[17] Recent antibiotic use increases patients' risk of acquiring *Salmonella* during outbreak situations,[18] and the treatment of enteric *Salmonella* infections prolongs carriage and shedding of these organisms. Most *Clostridium difficile* infections are associated with recent antibiotic use.[19] Other adverse impacts of antimicrobial treatment include allergic reactions. Finally, antimicrobials contribute substantially to the cost of pharmaceutical benefits for health insurers and health maintenance organizations. Money invested on unnecessary antimicrobials increases cost and decreases access to health care.

Inappropriate Antimicrobial Use and Respiratory Infections: The Core of the Problem

Respiratory infections (including colds, upper respiratory infections, bronchitis, pharyngitis, sinusitis, and otitis media) account for more than 70% of antibiotic prescriptions in the U.S.[10] Data from several studies have demonstrated that 30 to 60% of these prescriptions are inappropriate.[20-22] There is evidence that the problem is similarly pervasive in Minnesota. For example, 53% of Minnesota and Wisconsin residents who reported a non-bacterial infection diagnosis at a recent office visit for a respiratory infection were prescribed antimicrobial agents.[23]

Why is there such widespread and substantially inappropriate antimicrobial prescribing for the treatment of respiratory infections? There are two major factors involved that are clearly related to one another: patient expectation and physician practice. Several studies have shown that a patient's expectation of antimicrobial treatment is strongly associated with receipt of an antimicrobial agent, regardless of diagnosis.[24,25] Data from the Wisconsin Antibiotic Resistance Network (WARN) showed that adults in Minnesota and Wisconsin who expected an antibiotic prior to their clinic visit for a respiratory infection were seven times more likely to receive an antibiotic, regardless of their diagnosis.[23]

Patients' expectations about antimicrobial treatment are partly due to misconceptions about the role of antimicrobials in the treatment of several common medical conditions.[26,27] First, most individuals incorrectly believe that bacteria, not viruses, cause acute bronchitis. In addition, much of the public believes that green or yellow nasal discharge indicates the need for antimicrobial treatment.[23] Improved patient knowledge would lead to decreased prescribing of antimicrobials. WARN data show that Minnesota and Wisconsin residents who were more knowledgeable about appropriate antibiotic use were less likely to think prior to the office visit that an antimicrobial agent was necessary. These more knowledgeable patients were more likely to have been exposed to multiple informational messages about appropriate antimicrobial use and resistant microorganisms; children with more knowledgeable parents were less likely to receive inappropriate antimicrobial treatment.[23]

Public information campaigns have led to reductions in antimicrobial use. Results from a community intervention trial in Wisconsin demonstrated that an intensive informational campaign targeted to the public and physicians reduced the use of both solid and liquid antimicrobials. In this trial, prescribing of solid antimicrobials declined by 19% (compared with an 8% decline in the control area), and prescribing of liquid antimicrobials declined by 11% (compared with an increase of 12% in the control area). A public and physician information campaign in Denver reduced antimicrobial prescribing for acute bronchitis from 74% to 48%, with no change in the rate of prescribing for the control area.[28]

Nationwide interventions focusing primarily on physicians also have reduced antimicrobial use and levels of antimicrobial resistance. In Iceland, rates of penicillin-resistant *S. pneumoniae* (PRSP) rose from 0% in 1988 to 20% in 1993. An information campaign aimed mostly at physicians, coupled with regulatory changes that shifted the cost of prescription drugs to patients, led to declines in antimicrobial use and a subsequent decline in PRSP. This decline was especially marked among children attending daycare, where rates of PRSP declined from 20% in 1992 to 15% in 1995.[29,30] In Finland, macrolide use nearly tripled during the 1980s, and erythromycin resistance among Group A *Streptococcus* rose sharply in the early 1990s. A national campaign among physicians led to a 42% reduction in macrolide use, and erythromycin resistance in Group A *Streptococcus* fell from 17% to 9% between 1992 and 1996.[31]

Guidelines for Appropriate Antibiotic Use in Respiratory Infections

A number of organizations have developed initiatives to clarify appropriate antimicrobial prescribing for respiratory infections. The Centers for Disease Control and Prevention (CDC) and the Minnesota-based Institute for Clinical Systems Improvement (ICSI) have been leaders in this area. CDC recommendations[32] for appropriate antimicrobial prescribing can be summarized as follows:

- **Colds/Upper Respiratory Infections**
  Colds and upper respiratory infections are caused by viruses and should not be treated with antimicrobial agents.

- **Bronchitis**
  Acute bronchitis generally is caused by viral agents and should not be treated with antimicrobial agents. A possible exception is patients with chronic lung disease (excluding asthma), for whom antimicrobial treatment may be of possible benefit.

- **Pharyngitis**
  Antimicrobials are recommended for treatment of pharyngitis caused by Group A *Streptococcus* (GAS). However less than 20% of acute pharyngitis is caused by GAS; viral infections cause most pharyngitis. Antimicrobial treatment for pharyngitis generally should be preceded by either a positive rapid strep test or a GAS-positive throat culture.

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Web Sites: Antimicrobial Resistance and Judicious Antimicrobial Use

- **Site: http://www.health.state.mn.us/divs/dpc/ades/surveillance/table.pdf**
  Minnesota Department of Health tables summarizing antimicrobial susceptibilities of selected reportable pathogens, 1999 and 1998.
- **Site: http://www.wismed.org/warn**
  Wisconsin Antimicrobial Resistance Network (WARN); information, posters, brochures.
- **Site: http://www.cdc.gov/ncidod/dbmd**
  CDC guidelines, rates of pneumococcal resistance for the Active Bacterial Core Surveillance network, slides/brochures/posters about antimicrobial resistance.
- **Site: http://www.cdc.gov/ncidod/hip/SURVEILL/inspear.HTM**
  CDC site for the International Network for the Study and Prevention of Emerging Antimicrobial Resistance (INSPEAR).
- **Site: http://www.healthsci.tufts.edu/apua**
  The Alliance for Prudent Antimicrobial Use (APUA), based at Tufts University, Boston, MA. Current news and events in antimicrobial resistance.
- **Site: http://www.idlinks.com/antimicrobial_resistance.htm**
  Infectious disease organization based in Tacoma, WA. Excellent links to other websites.

- **"Purulent Rhinitis"**
  The common cold and other upper respiratory infections normally are associated with green or yellow nasal discharge, especially after several days of illness. Green or yellow nasal discharge alone is not a reason to prescribe antimicrobials.

- **Sinusitis**
  Sinus abnormalities, such as congestion and discomfort, occur frequently with viral upper respiratory infections. Antimicrobial use generally should be restricted to patients with fever, facial pain, or prolonged symptoms. Of note, the term "acute bacterial rhinosinusitis" sometimes is used to connote bacterial sinusitis.

- **Otitis Media**
  Antimicrobial treatment for otitis media should be limited to acute otitis media. Antimicrobials should not be prescribed for otitis media with effusion (OME); in OME, antibiotics do not hasten symptom improvement or fluid removal from the middle ear.

Future Directions for Combating Antimicrobial Resistance in Minnesota

In Minnesota, initiatives are underway to promote judicious use of antimicrobials. Two groups working on this issue include the Minnesota Medical Association (MMA) Antimicrobial Prescribing Practices Task Force (comprised of representatives from the MMA, the HMO Council of Minnesota, the Minnesota Pharmacy Association, and MDH) and the Twin Cities Antibiotic Resistance Collaborative (comprised of representatives from several HMOs and a health services research company).

In September 2000, the MMA passed a resolution "to develop and implement a statewide public education campaign regarding the appropriate use of antibiotics and the potential dangers of antibiotic resistance."[33] Encouraging efforts to educate the public and improve physician prescribing practices will be the cornerstones for combating antimicrobial resistance now and in the near future. Efforts to study antimicrobial prescribing for respiratory infections will be useful benchmarks for evaluating the quality of care provided by physicians and health care institutions such as HMOs.

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