Antibiotic stewardship: Resistance and strategies at the Vancouver Hospital

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The discovery of antimicrobial compounds and their development over the past 50 years has been perhaps the greatest medical advance of all time and has influenced the health of communities worldwide. During the 1970s and 1980s, pharmaceutical companies produced many new compounds with specific advantages. For example, cefoxitin, a ‘second-generation’ cephalosporin with activity against anaerobic organisms, and ‘third-generation’ cephalosporins with expanded activity against resistant Gram-negative bacilli, including *Pseudomonas aeruginosa*, were developed. Accompanying the advances in antimicrobial development were advances in prosthetics, and new, inert plastics that facilitated development of artificial joints and longer-dwelling intravenous lines. Prophylactic antibiotics could then be used to prevent potential infections from complicated surgical procedures. Although the use of antimicrobials has had many advantages in modern medicine, the steady increase in antimicrobial resistance worldwide is now recognized as a major disadvantage.

During earlier use of antibiotics, bacterial resistance was viewed in the context of hospital-acquired infection, principally occurring as a result of Gram-negative rod infections. The resistance patterns were often hospital- and even unit-specific, and could be eliminated with appropriate infection-control measures when reservoirs were eliminated. In a cross Canada surveillance study of susceptibilities in Gram-negative rods, Bryce et al (1) documented resistance rates in 20 Canadian intensive care units (ICUs). Compared with resistance rates found in a similar hospital-wide study over the same time period from 20 Canadian hospitals (2), Bryce et al (1) found that resistance rates were higher in ICUs. For example, resistance rates were 27%, 20% and 22% for imipenem, cefazidime and ciprofloxacin respectively, compared with 23%, 12%, and 5% in the hospital-wide study. Higher rates of resistance may be associated with ICU patients because they have a higher level of acute illness and a larger number of complicated problems. In general, these severely ill patients have taken up more hospital beds in the 1990s than they did 20 years ago.

In the 1990s it has become apparent that the greatest enemy among resistant bacteria is not Gram-negative rods but rather Gram-positive cocci, including the following: methicillin-resistant *Staphylococcus aureus*, which comprise 2.3% of all hospital *S aureus* isolates (3); and high level penicillin-resistant *Streptococcus pneumoniae*, which comprises as many as 7.1% of clinical isolates in Saskatchewan and 4.4% in a 1996 cross-Canada survey (4). Although vancomycin-resistant enterococci (VRE) have appeared in outbreaks in several large Ontario hospitals (5), further outbreaks have been curtailed by intensive screening of patients admitted with a history of exposure to medical facilities in the United States where VRE prevalence is high. Vancomycin-intermediate *S aureus*, with minimal inhibitory concentrations of 8 mg/L (6), have been reported, and the threat of fully vancomycin-resistant *S aureus* lies ahead.

How have antibiotic-resistant bacterial outbreaks developed, and what can physicians, the major antibiotic prescribers, do to prevent outbreaks? The answer to the first question is indiscriminate overuse of antibiotics, and the answer to the second question is antibiotic stewardship that adopts responsible, discerning practices in prescribing antibiotics and in preventing of bacterial infections.
Can changing the practice of prescribing antibiotics affect antimicrobial resistance? Evidence suggests that changing the practice can. A study of community-based antimicrobial resistance in Finland showed that physician compliance with a nationwide policy of reducing prescriptions for macrolide antibiotics resulted in an impressive 40% drop in erythromycin resistance in Group A streptococci from 1991 to 1996 (7). In hospital environments, the increasing incidence of VRE has been associated with high cephalosporin use (8) and vancomycin use, the latter particularly for *Clostridium difficile*-induced diarrhea (9). Cephalosporins select for enterococci because they are already cephalosporin-resistant. Quale et al. (9) demonstrated a reduction in VRE rates from 49% to 15% by instituting beta-lactam/beta-lactamase inhibitor combinations, including ampicillin-sulbactam and piperacillin/tazobactam, as alternatives to second- and third-generation cephalosporins, together with recommending voluntary vancomycin use reductions in intensive care areas, and infectious disease service approval for vancomycin and clindamycin in the rest of the hospital (9).

At the Vancouver Hospital, the reserved antimicrobial drug (RAD) program (10), which requires a requisition form document the reasons for ordering newer, more expensive, broad spectrum agents, has been instituted. The hospital’s antibiotic utilization subcommittee has listed criteria for antibiotic use on the RAD drug form. Implementation of the RAD program has resulted in use of broad spectrum agents that are more likely to select for highly resistant organisms. In addition, the microbiology laboratory has adopted ‘cascade’ reporting of antimicrobial susceptibility. For example, from the cephalosporin group, only the least expensive, narrowest spectrum antimicrobial to which the organism is susceptible, eg, cefazolin, would be reported, rather than second- or third-generation agents; however, the results of the latter drugs’ susceptibilities are available if necessary. This ‘out of sight, out of mind’ strategy has been adopted at many large hospitals to curtail the prescription of expensive and unnecessarily broad spectrum therapy (11).

Another strategy for reducing antibiotic pressure on the microbial environment is wider use of vaccines. In the case of pneumococcal infection, increased use of pneumococcal vaccine should be undertaken for patients with pre-existing lung and heart disease, and the elderly. Influenza vaccination of the same risk groups will reduce the number of seasonal bacterial pneumonias that result from complicated influenza.

A recent, unique strategy developed by the Canadian Infectious Disease Society under sponsorship of Abbott Laboratories is the ‘explanatory prescription’. It is a prescription form with an explanation that the patient has a viral infection for which antibiotics are not indicated. There is a space for the physician to write additional advice. Patients seem to appreciate the ‘explanatory prescription’, instead of feeling that because they have not received an antibiotic for their infection, the doctor has done nothing for them.

Physicians are essentially the gatekeepers for optimal antibiotic therapy, and must keep up with indications for antimicrobial use as new studies appear in the medical literature. For example, several well controlled trials have shown no benefit of antibiotic use in the patient with acute purulent bronchitis, ie, cough, purulent sputum, fever or no fever and a normal chest x-ray (12). The condition will resolve spontaneously with supportive treatment. Similarly, a recent Dutch study has shown no benefit of antibiotics over placebo in a large community practice-based study of acute maxillary sinusitis (13).

In summary, a crisis for the development of bacterial resistance to many antimicrobial agents is approaching. Education of physicians regarding appropriate prescribing habits needs to be intensified, and patients themselves, especially in the community, need to realize that not all infections require antibiotics.

REFERENCES

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