Antimicrobial stewardship at The Toronto Hospital

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Infectious diseases continue to plague humankind, and the treatment of infections continues to consume a significant proportion of health care resources. Although antibiotics have saved countless lives and have transformed the treatment of infectious diseases, increasing levels of antibiotic resistance present a serious emerging public health threat. Antibiotic resistance results in morbidity and mortality from treatment failures and increased health care costs (1). Current costs to treat infections with antibiotic-resistant organisms are estimated by the Centers for Disease Control and Prevention, Atlanta, Georgia to be over $4 billion annually in the United States (2). Increasing resistance raises concerns about the inability to treat certain infections, bringing about the dawn of the 'postantibiotic' era.

Overuse and inappropriate use of antibiotics are widely believed to be responsible for the increasing level of antibiotic resistance (3-5). Although antibiotic resistance is encountered everywhere, particular problems exist in health care institutions. Many of the organisms that are part of the normal flora may pose a significant threat, as an invasive pathogen, to patients whose resistance is lowered by virtue of age, chemotherapy, transplantation or immunosuppression. The hospital milieu, especially in intensive care units, burn units, neonatal units, hematology-oncology units and other special care units, provides an epidemiological pressure cooker for the emergence and dissemination of antibiotic-resistant organisms. The frequent use of antibiotics, high use of invasive devices and frequent hospitalization in these patient populations adds the necessary ingredients to this pressure cooker environment.

Approaches to controlling the development and spread of antibiotic-resistant organisms have been outlined in several documents and reports (2,5-10). Three major strategies are employed to achieve this end: surveillance to identify the trends of resistance, improving appropriate antimicrobial usage (antimicrobial stewardship), and reducing cross transmission of multiresistant organisms through enhanced infection control precautions and reducing environmental contamination. These strategies may be considered in the context of the classic host-microbe-drug relationship as depicted in Figure 1. We describe the approaches to antibiotic stewardship that have been used at The Toronto Hospital (TTH) over the past seven years.

The Toronto Hospital is a 1200-bed tertiary care medical school-affiliated hospital with over 34,000 visits per year. In 1991, the annual expenditure for antimicrobial agents was over $3 million. At this time the Pharmacy and Therapeutics Committee recommended the creation of a new pharmacy position (Drug Utilization Co-ordinator) to monitor drug use with a focus on appropriate antimicrobial prescribing. The An-

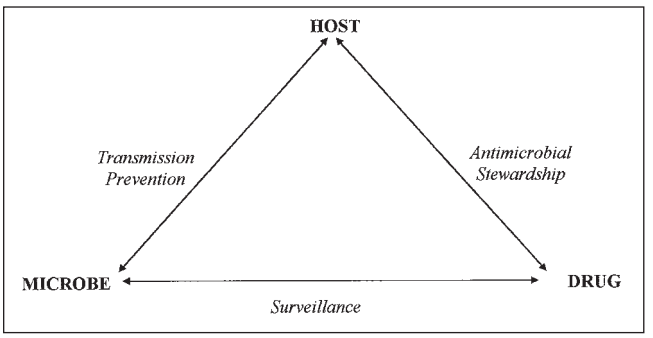

Figure 1) *Controlling antimicrobial resistance in the classic host-microbe-drug paradigm*

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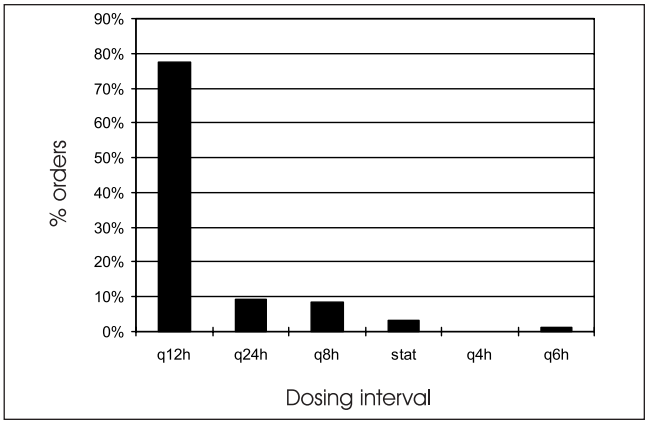

Figure 2) *Dosing interval of cefotaxime 1 g*

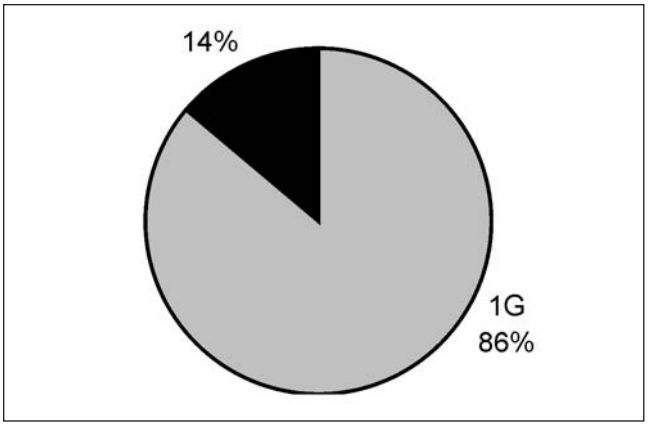

Figure 3) *Cefotaxime 1 g versus 2 g doses*

tibiotic Utilization Subcommittee of the Pharmacy and Therapeutics Committee was revived, and a multistaged, multiyear plan to improve the quality of prescribing and reduce antimicrobial expenditures was formulated. The various components of the plan are described as follows.

Cost awareness: The Antibiotic Subcommittee published annual cost awareness charts outlining the treatment cost of formulary antimicrobials. Hospital acquisition costs as well as administration costs were included in the total daily cost of each treatment regimen. The charts were posted in nursing units and published in the TTH *Guidelines for Antimicrobial Use* . With increased awareness of cost, physicians are in a better position to choose the lower cost treatment option of equally efficacious regimens (ie, cost minimization).

Surgical prophylaxis guidelines: Appropriate antimicrobial prophylaxis has been shown to decrease the incidence of postoperative infection following certain surgical procedures (11). A single dose of antibiotic given preoperatively is sufficient for most surgical procedures. The Antibiotic Subcommittee and the various surgical divisions developed surgical prophylaxis guidelines for the majority of surgical procedures performed at TTH. The TTH guidelines outline the most appropriate choice of antibiotic, the dose, and the timing and duration of prophylaxis based on the surgical procedure. These guidelines are reviewed annually and printed in the TTH *Guidelines for Antimicrobial Use*. Compliance with the guidelines has been excellent as identified by periodic quality assurance audits.

Treatment guidelines: Drug utilization reviews identified several problematic issues related to empirical treatment of specific infectious diseases. The Antibiotic Subcommittee developed treatment guidelines based on the potential pathogens, hospital and community antibiotic resistance patterns, and published treatment guidelines. TTH has treatment guidelines in place for the following conditions: pneumonia, soft tissue infections, urinary tract infections, bacterial meningitis, intestinal protozoa and continuous ambulatory peritoneal dialysis peritonitis. All treatment guidelines are reviewed before each publication of the TTH *Guidelines for Antimicrobial Use*.

Dosage guidelines: The Antibiotic Subcommittee reviewed the dosing of aminoglycosides and cephalosporins to assure that the most cost effective dosage regimens were prescribed. A once-daily dosing program was established for aminoglycosides for most indications. Aminoglycosides exhibit concentration-dependent killing, and this dosage regimen allows for good therapeutic serum levels after the first dose and decreases the need for routine monitoring of serum levels. Traditional dosing is still recommended for a select patient population (ie, patients with febrile neutropenia, dialysis patients, pregnant women and neonates) (12-14).

Dosage recommendations for cephalosporins are based on time above the minimum inhibitory concentration (MIC) of the microorganisms and not peak levels because cephalosporins exhibit time-dependent killing and not concentration-dependent killing. The dosage recommendations took into account dose, half-life and MIC of the organisms (15). Recommendations are made for cefazolin 1 g every 8 h, cefotaxime 1 g every 12 h and ceftazidime 1 g every 8 h. Higher dosages (ie, 2 g doses) are only recommended for infections where drug penetration is of significance (ie, central nervous system) (16). An audit of cefotaxime dosing for the 1997 to 1998 fiscal year indicates that the majority of doses of cefotaxime were given every 12 h and that the majority of the doses were 1 g (Figures 2, 3).

Special programs: A formal Route Conversion Program was established in 1993 to standardize the intravenous to oral conversion of antimicrobials. Many oral antimicrobial agents now have excellent pharmacokinetics and spectra of activity. This allows for early conversion from intravenous to oral for many therapeutic indications. An automatic review of all intravenous orders at 72 h was instituted along with inclusion and exclusion criteria for patient selection. Exclusion criteria are based on disease state and patient ability to tolerate or absorb oral medication. Clinical pharmacists play a key role in the review process and recommendation of oral therapy (17).

A restricted antimicrobial program was established based on the potential for misuse of certain antimicrobial agents and the potential for the development of resistance. Various levels of restrictions are in place on selected antimicrobials from therapeutic indication restriction to mandatory infectious disease consultations. Clinical pharmacists intervene as needed to assure that the program followed.

Education: Several media were used to disseminate informa-

TABLE 1
Summary of cost savings based on usage of antimicrobials at The Toronto Hospital

Fiscal year	Antimicrobial expenditure	Cumulative savings
1991-92	$2,900,000.00	
1992-93	$2,700,000.00	$200,000.00
1993-94	$2,300,000.00	$600,000.00
1994-95	$2,000,000.00	$900,000.00
1995-96	$1,800,000.00	$1,100,000.00
1996-97	$1,700,000.00	$1,200,000.00

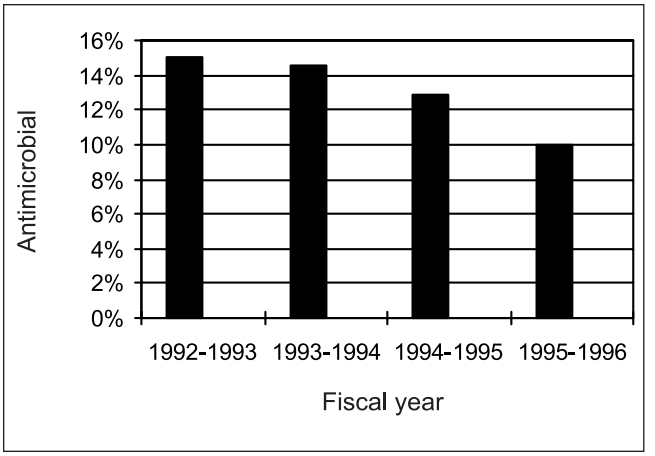

Figure 4) *Antimicrobial percentage of drug expenditure by fiscal year at The Toronto Hospital*

tion on the various components of the program: medical staff bulletins were published with each new recommendation, formal and informal education sessions were given (ie, medical grand rounds or morning report), and the TTH *Guidelines for Antimicrobial* Use was widely distributed. Program implementation was aided by a decentralized pharmacy system where pharmacists were available to deliver point-of-care recommendations for essential components of the program.

Antimicrobial usage patterns and acquisition costs were monitored from year to year. Table 1 summarizes the overall savings based on usage. From 1991 to 1996, the number of hospital beds remained constant (1184 beds from 1991 to 1992, 1167 beds from 1995 to 1996); however, in the 1996 to 1997 fiscal year there was a slight reduction in the number of beds. Antimicrobials accounted for 15% of the total hospital drug expenditure when the program was first initiated; however, this amount decreased over the years to the present figure of 10%.

The need for continued antibiotic stewardship within TTH cannot be overemphasized. With restructuring, an increasing weighted case average reflecting a greater severity of illness in the patient population, and advances in transplantation and cancer chemotherapy it is important to reduce inappropriate prescribing to a minimum. The continuous work of the Antimicrobial Subcommittee, regular updating and publication of guidelines for usage (18) combined with monitoring and feedback on antimicrobial usage will, it is hoped, lead to limited resistance development, improvements in prescribing and reduced health care costs.

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