Confronting antibiotic-resistant organisms – A Canadian perspective

ANTIBIOTIC-RESISTANT ORGANISMS (AROS) AND WITH THEM THE threat of new and reemergent infectious diseases are on the rise worldwide. This rising tide of resistance to antimicrobial drugs has been referred to as a 'worldwide calamity' (1). Since the beginning of this decade, clinicians, microbiologists and public health officials have confronted an unprecedented number of epidemics of 'new' infectious diseases and resurgent 'old' infectious diseases on a truly international scale. Examples are the hantavirus pulmonary syndrome in the United States, human T cell lymphotrophic virus in the Caribbean, Sabia virus in Brazil, Guanarito virus in Venezuela, *Escherichia coli* O157:H7 disease and cryptosporidiosis in the United States, *Vibrio cholerae* 01 in Latin America and 0139 in Asia, Rift Valley fever in Egypt, multidrug-resistant tuberculosis in Asia and the United States, bubonic plague in India, and AROs in Europe, Latin America and the United States (2,3). Of the reemerging infectious diseases, AROs arguably represent the most immediate threat to human health and welfare. The prospect and indeed reality of attempting to treat multiply drug-resistant enterococcal, pneumococcal and tuberculous infections have been brought to the attention of both the scientific community and the lay press (3-5). The most serious threat is the acquisition of resistance to vancomycin either by methicillin-resistant *Staphylococcus aureus* or by macrolide penicillin-resistant *Streptococcus pneumoniae*, which could create invasive clones for which there are few or no easily available therapeutic agents. The successful transfer and expression of vancomycin-resistant genes to *S*

aureus have been demonstrated in vitro (6). The emergence of vancomycin-resistant strains of *S aureus* in clinical strains was considered to be only a matter of time and there are now reports of such strains in Venezuela (7).

There are many specific examples of AROs and the most commonly encountered organisms include multiply drug-resistant *Mycobacterium tuberculosis* (8,9), methicillin-resistant *S aureus* (10), vancomycin-resistant enterococci (11), penicillin-resistant pneumococci (12,13), multiply resistant *Shigella* species and *Salmonella typhi* (14,15), extended spectrum beta-lactam (including third-generation cephalosporin resistance) resistant enteric Gram-negative bacilli such as *Klebsiella-Enterobacter* species (16) and multiply resistant *Acinetobacter* species (17).

There are many reasons for the emergence of AROs, but clearly the remarkable and extraordinary capacity for microorganisms to adapt to their changing environment is the most important factor. The Darwinian theory of evolution with respect to 'survival of the fittest' may be no more aptly applied than in the setting of microorganisms that are repeatedly exposed to antimicrobial agents. It is widely acknowledged that anti-microbial resistance is spawned in large part by the selective pressures of antibiotic use and abuse (1,18,19). The discovery, overuse and development of resistance to new antimicrobials is a predictable pattern. Worldwide usage of antimicrobials is staggering. In 1990 in the United States antibiotics were the most commonly prescribed category of drugs, and the sales of antibiotics to drugstores and hospitals have amounted to over $5 billion annually since 1991. In third world countries where antimicrobials are available over the counter, there is a great propensity for the development and spread of resistance in the setting of a huge burden of infectious diseases, with poor sanitation, overcrowding and inappropriate usage. An expanding population of very old and very young individuals who may be particularly susceptible to infectious diseases, a growing population of individuals with immunodeficiency (AIDS), immunosuppression (cancer chemotherapy, transplantation), societal behavioural changes (public demand for antimicrobials, increased use of daycare, sexual promiscuity) and technological advances are all contributing factors to the spread of AROs. The contribution of antimicrobial usage in agriculture has been speculated as another factor contributing to the development and spread of AROs, but it is probably minor in comparison with human antimicrobial usage (20).

The spread of AROs is a complex and dynamic process and we do not fully understand the complexities of this spread. Throughout the world, there may be high rates of AROs within one region or country and little to no resistance in adjoining regions or countries. For example, Portugal is relatively free from penicillin-resistant pneumococci whereas Spain has rates exceeding 50% (21). Similarly the United States has major problems with methicillin-resistant *S aureus,* vancomycin-resistant enterococci, multidrug-resistant *M tuberculosis* and penicillin-resistant pneumococci, whereas in Canada there is very little resistance to any of these organisms. A collation of regional data (personal communication) suggests that the frequency of isolation of methicillin-resistant *S aureus* is less than 2%, isolation of vancomycin-resistant enterococci is extraordinarily rare (22) and high level resistance to *S pneumoniae* is reported as 1.9% in a nationwide survey (23).

The reasons for these differences are unclear, but antibiotic control, considered a cornerstone of dealing with multiresistant organisms (1,24,25), particularly in the hospital setting may offer some explanation. Surveys of hospital pharmacies in Canada and the United States indicate that 75% of Canadian but only 34% of American hospital formularies used prescribing restrictions (personal communication, 26). There may also be differences in infection control practices and fundamental differences in the delivery and access to health care that could also offer an explanation for the differences. Whatever the reasons there should be no complacency with respect to AROs in Canada given the capability for microorganisms to adapt to their surroundings.

The approaches to controlling the development and spread of AROs have been outlined in several documents and reports (3,4,24,27-29) including the Lac Tremblant Declaration of The Canadian Expert Working Group on Emerging Infectious Disease Issues (30). In general, the recommended strategies include surveillance for AROs, improved antimicrobial usage including antibiotic restriction when appropriate, reduced environmental contamination and improving the practices of infection control to reduce potential cross-transmission of microorganisms. The practice of sound infection control techniques need not be applied only to the institutional setting – daycares, hospices and other settings should also be included. Although in Canada, compared with other countries, AROs do not appear to be commonplace at this time, measures to achieve the necessary evolutionary balances between microbe and antimicrobial can, we hope, be achieved with appropriate preventive action.

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