Antimicrobial Resistance and Stewardship

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CFMS Canadian Federation of Medical Students

FEMC Fédération des étudiants et des étudiantes en médecine du Canada

Background

Antimicrobials are a class of drugs designed to destroy or incapacitate infectious microorganisms. Scientists began experimenting with antimicrobials in the nineteenth century, but the discovery of penicillin in 1928 commenced a period of rapid antimicrobial discovery. This momentum continued through to the 1970s, leading to the production of over 20 different classes of new antimicrobials. Over time however, microorganisms that have been targeted by antimicrobial therapy have developed strains that are resistant to the therapy, and thus have become untreatable (1). Common examples of microorganisms that have developed resistance to most or all of their conventional antimicrobial treatments across Canada include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), carbapenem-resistant enterobacteriaceae (CRE) and *Clostridium difficile* (*C. difficile*) (1, 2).

Antimicrobial resistance poses a significant danger to patient populations. In 2013, one in twelve patients were infected with at least one multidrug-resistant microorganism in hospitals across Canada every day, leading to approximately 2,000 deaths per year (3, 4). Furthermore, deaths due to *C. difficile* and its resistant strains have increased four-fold in the past twenty years and show little signs of relenting (5). Canada's aging population has created a greater number of patients with suppressed immune systems due to solid organ and stem cell transplantation, treatment of various cancers, and immune-modifying drugs for inflammatory conditions. Consequently, the susceptibility to resistant infections is projected to increase in the future. In today's health care sector, there is heavy emphasis on infection control, but not antimicrobial stewardship (AS). AS is a coordinated intervention which aims to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy and route of administration. In fact, as late as July 2013, antibiotic resistance was still generally seen as an issue of infection control, rather than one that impacts clinical decision- making (6).

The Impact of the Pharmaceutical Industry

Despite the increasing prevalence of resistant organisms and the associated need for new antimicrobials, there has been noticeable stagnation in the development of new antimicrobials by pharmaceutical companies. This stagnation in research and development has led to the creation of only four new classes of antibiotics since the 1970s (7). There are many proposed reasons for this slowed growth, including the merging of pharmaceutical companies and the low profitability of selling antimicrobials.

Between 1985 and 2005, almost 40 mergers of major pharmaceutical companies occurred; these have led to a decrease in the number of groups searching for new antimicrobials (7). It appears as if only smaller pharmaceutical companies and biotechnology firms (defined as companies with revenues less than $3 billion and/or R&D expenditures less than $500 million) are interested in developing antimicrobials. In 1995, 17 antimicrobials were in development by small companies, while only three antimicrobials were in development by the large pharmaceutical companies. However, the large and newly merged pharmaceutical companies have forced many of these smaller companies out of the market, which has further stunted the development of new antimicrobials (7).

There is a prevalent (albeit erroneous) assumption among North American and European physicians that the discovery of new antimicrobial agents is unnecessary because most normal cases can be

treated with the current slate of drugs (7). It is also assumed that infectious diseases are "less profitable" than other illnesses, and as such, the scarce research and development dollars that exist should be directed to the "more profitable" illnesses, such as chronic heart failure and diabetes. Consequently, there is little incentive for the companies to spend large sums of money on the development of new antimicrobials. However, physicians also reported that they were unable to treat up to 15% of their patients with currently available antimicrobials (7). Antimicrobial development is not seen as a largely profitable opportunity; antimicrobials act fast, are only taken consistently for a limited time, and can become obsolete rapidly and unpredictably due to resistance. Current patent laws further exacerbate the issue of profitability. It has been proposed that antimicrobial resistance tends to rise when the patents on an antimicrobial expires because at this point, generic forms of the drug can be created and sold by other companies at a cheaper price in mass quantities (8). When less expensive generic forms of an antimicrobial enter the market, consumers may avoid the more expensive brand-name antimicrobial.

Since consumers typically choose the less expensive generic brands at this point, the original manufacturers experience a poor return on investment when developing novel antimicrobials, leading to a decrease in their spending on future Research and Development. Consequently, patent laws have increased antimicrobial resistance given the decline in antimicrobial drug development.

Hospital & Patient Care

Many patients are accustomed to receiving an antibiotic, even for viral illnesses unresponsive to antibiotics, such as the common cold. Studies demonstrate that many patients will visit their physician with a preconceived notion of obtaining a prescription (9, 10). However, the following studies demonstrate that patients who are cognizant of what constitutes an appropriate use for antibiotics are amenable to conservative management of viral illnesses. There seems to be immense value in educating patients and physicians. When patients have been educated on the natural course of a disease by their physician, particularly on the negative and positive effects of antimicrobials and the reasons for misuse, patients experienced greater satisfaction; meanwhile physicians reported more time-efficient patient encounters (11). Indeed, patient education about AS has been proven to be effective. In paediatric populations, parents who were provided with a contingency prescription at an initial visit were more satisfied; receiving a prescription at a follow-up appointment related to the initial patient complaint resulted in a significantly lower parental satisfaction (12). These examples highlight the need for medical students to be trained in AS in order to serve the public effectively in the future.

In addition to protecting the public, AS also benefits the health care system. At the Toronto East General Hospital, the antimicrobial costs decreased by half within six months of the implementation of an AS program (13). The pilot study at the Toronto Eastern General Hospital in 2010 allowed an AS team to make recommendations ranging from "optimization of dose for indication" to "discontinuation of therapy". Over the six months during which the AS program was implemented, the antimicrobial costs at the ICU unit decreased by half from $102,000 to $52,637 (13). There are many other successful AS programs in North America; a recent systematic review of AS programs in paediatric settings further substantiates the impact of AS (14). The review of 28 published AS programs has suggested that these programs can decrease antimicrobial utilization, antimicrobial drug costs and even prescribing errors (14). Moreover, further evidence demonstrates that it is the combination of guidelines and AS programs that can change prescribing patterns; after implementation of the 2007 Infectious Diseases Society of America guidelines for developing AS

programs, there was a larger decline in average antibiotic use in the United States (15). Interestingly, this decline was further accentuated in hospitals that had a formalized AS program (15). Taken together, this evidence demonstrates that AS programs are useful in health care at both the patient and system level.

Context

Need for Action

Several groups have identified a need for hospitals to adopt a multidisciplinary, interprofessional AS team. The team is directed or supervised by an infectious disease physician and ideally includes a clinical pharmacist with infectious diseases training, a microbiologist, a hospital epidemiologist, an infection control professional, and an information system specialist with at least one member trained in AS (16). A recent policy paper adopted by the Infectious Diseases Society of America stated that "research on AS is needed to address knowledge gaps in this field, including our understanding of antimicrobial resistance and interventions to limit both the emergence and the transmission of resistance, as well as our ability to measure and monitor resistance and its associated impacts and clinical outcomes (16). For instance, there is currently no universal consensus on the risk factors that promote the unnecessary overuse and abuse of antimicrobial therapy, let alone a standardized definition of what constitutes appropriate or inappropriate antimicrobial use. From a medical anthropology perspective, further research is needed to understand the impact of generic versus branded antimicrobials on how they are used. On the technological side, there is a need to develop and evaluate accurate and rapid point-of-care diagnostic tests in order to correctly identify disease etiology and dispense antibacterial therapy only when appropriate. There is also a palpable absence of randomized multi-centre cluster studies of a robust design that compare stewardship interventions across the spectrum of health care settings, and more importantly, studies that measure the impact of such interventions on epidemic and endemic antimicrobial resistance. Finally, given that only four new classes of antimicrobials have been developed since the 1970s, pharmaceutical companies must be incentivized to research and develop innovative antimicrobials with novel mechanisms of action (17).

Need for Medical Education

Preliminary analysis has shown that formal curriculum pertaining to principles of antimicrobial stewardship has not been widespread in Canadian medical education. Medical schools with such a curriculum include the University of Toronto, the University of Alberta, and Memorial University of Newfoundland.

Action to Date

Britain has already declared that, alongside terrorism and climate change, antimicrobial resistance is a threat to the country's economy and security (18). The World Health Organization (WHO) stated earlier this year in a global surveillance report on antimicrobial resistance that this is "a post-antibiotic era in which common infections and minor injuries can kill; a very real possibility for the 21st century" (19). In September 2014, the President of the United States of America, Barack Obama, signed an Executive Order directing key federal departments and agencies to overcome the rise in antibiotic-resistant bacteria (20). In addition, the United States released its National Strategy on Combating Antibiotic-Resistant Bacteria and announced a $20 million prize to promote the

identification of highly resistant bacterial infections through the development of rapid, point-of-care diagnostic tests (21). As of 2013, Accreditation Canada developed an Antimicrobial Stewardship Program (ASP), which deemed that all acute care hospitals undergoing accreditation must have an AS program in place. At the same time, the Ontario Medical Association (OMA) released a position paper, When Antibiotics Stop Working (22) and called for additional education for medical students and trainees in antimicrobial resistance and stewardship. The American Medical Student Association (AMSA) and the International Federation of Medical Students' Association (IFMSA) have both supported and advocated for legislation and policy to combat antimicrobial resistance through the development of novel antimicrobials and adoption of AS. In November 2014, the federal Canadian government published Antimicrobial Use in Canada: A Federal Framework for Action, which calls for improvements in surveillance, stewardship, and incentivizing innovation across all industries (ex. agriculture, health care) involved in antimicrobial resistance (23). On March 31, 2015, federal Health Minister Rona Ambrose hosted a national roundtable discussion with key leaders representing human and animal health stakeholders, to discuss a national strategy to combat antimicrobial resistance. She also unveiled the government's first-ever integrated surveillance system for antimicrobial resistance, called the Canadian Antimicrobial Resistance Surveillance System (CARSS), and a $250,000 USD investment to support a new study on the economic impacts of antimicrobial resistance (23).

Principles

1. **Antimicrobial resistance is a growing global public health concern that is of great relevance to the CFMS membership and Canadian society**

2. **Antimicrobial resistance caused by inadequate stewardship poses an unacceptable risk to the safety of patients and the public**

3. **Medical education must include relevant training that prepares students for the current, worrying realities of antimicrobial resistance**

4. **CFMS members must be supported in their advocacy efforts to promote antimicrobial stewardship and combat resistance, provided that these efforts are informed by evidence and do not compromise public health and patient safety**

5. **Interprofessional education and approaches to antimicrobial stewardship are required to successfully combat resistance**

Recommendations

1. **Canadian medical schools should adopt administrative capacity to foster antimicrobial stewardship training**
   Physician education in antimicrobial resistance and stewardship has been proven to enable them to prescribe antimicrobials more appropriately. However, formal curriculum at Canadian medical schools regarding these principles is currently not widespread. Antimicrobial resistance and stewardship must be recognized as a priority by all medical schools and should be incorporated into the portfolios of relevant faculty members at every medical school in Canada. Faculty leads of AS should be selected to champion the endeavour. Antimicrobial stewardship

programs should be implemented in both pre-clerkship and clerkship curricula at all Canadian medical schools.

2. **Antimicrobial stewardship must be incorporated into the mandatory requirements for physician training via the Medical Council of Canada (MCC), the Committee on Accreditation of Canadian Medical Schools (CACMS), the Royal College of Physicians and Surgeons of Canada (RCPSC) and the College of Family Physicians of Canada (CFPC)**

   In addition to training and education regarding antimicrobial stewardship and resistance, medical students and trainees must develop and be evaluated on their competencies surrounding this important topic. The MCC must include items related to antimicrobial resistance and stewardship in the MCC Qualifying Examinations written by medical students and residents.

   CACMS must incorporate teaching of antimicrobial stewardship as a mandatory component of the accreditation criteria for pre-clerkship and clerkship curriculum at every Canadian medical school. The Royal College of Physicians and Surgeons of Canada (RCPSC), and the College of Family Physicians of Canada (CFPC) must include knowledge of AS and resistance as a mandatory competency required by residents to graduate from all residency programs in Canada; and incorporate items pertaining to AS and resistance into the licensing examinations for all medical specialties in Canada. This recommendation will ensure that the future generations of health care providers in Canada are sufficiently prepared to tackle the challenges posed by the growing threat of antimicrobial resistance.

3. **All levels of government and partner organizations should explore new policies and incentive programs to enhance Research and Development of novel antimicrobials and improve understanding of resistance and stewardship.**

   We have outlined many significant barriers to the research and development of novel classes of antimicrobials. Currently, pharmaceutical companies are not incentivized to develop new classes of antibiotics, and have instead focused on drugs for more profitable diseases. The Government of Canada must develop policy to incentivize pharmaceutical companies to develop innovative antimicrobials with novel mechanisms of action (ex. re-evaluating patent laws and modifying patent times, development of innovation grants for new antimicrobial development), provided that this does not compromise public health and patient safety. All levels of government must work with health care providers to develop policy that incentivizes providers to promote antimicrobial stewardship in hospitals and clinics. The Canadian Health Care Association (CHA) must also support the establishment of antimicrobial stewardship programs at every hospital in Canada. This will encourage all stakeholders in the health care sector to more readily adopt antimicrobial stewardship practices, which in turn will combat resistance. Finally, the government must engage in research with key leaders including, but not limited to, non-governmental organizations, industry leaders, and university researchers to: 1) prioritize the development of new classes of antibiotics, 2) develop evidence-based prescribing guidelines and 3) assess patterns of resistance. With this knowledge, governments, health care providers, and stakeholders will be able to better understand patterns of resistance and the evidence behind rational prescribing practices, thereby improving Canadian patterns of resistance and the evidence-based prescribing guidelines.

4. **Medical student members should be supported in their endeavours to educate themselves in the principles of antimicrobial stewardship and advocate for changes within education and health policy that combat resistance and promote stewardship of antimicrobials.**
   Changing the culture around prescribing antimicrobials is a critical element of antimicrobial stewardship. Culture change amongst physicians can be more readily achieved if they have been made aware of the principles of antimicrobial resistance and stewardship from the early stages of their training. Consequently, the CFMS recommends all Canadian medical students maintain continued engagement with the issue of antimicrobial resistance and stewardship. Faculties of medicine are also recommended to collaborate with their students to develop antimicrobial stewardship programs, coupled with teaching and evaluation of antimicrobial stewardship principles at every medical school in Canada. Students should also receive support from their faculties and member organizations when they engage with hospitals, levels of government, and other relevant stakeholders to promote antimicrobial stewardship and prevent resistance. Finally, a key component of successful antimicrobial stewardship is an interprofessional approach. The CFMS therefore recommends medical students collaborate with their colleagues in other health professional faculties at the local level, and the National Health Sciences Students' Association (NaHSSA), in order to develop and promote interprofessional education and approaches to learning and promoting antimicrobial stewardship principles.

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