THE HONG KONG COLLEGE OF PATHOLOGISTS
SCIENTIA ILLUMINAT MEDICINAM
香港病理學專科學院

Topical Update – The Hong Kong College of Pathologists

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

Volume 3, Issue 3 **December 2008**

Editorial note:

In this issue of Topical Update, Dr. Margaret IP discusses the current problem of antimicrobial resistance in both the global and local perspective. We welcome any feedback or suggestions. Please direct them to Dr. Janice Lo (e-mail: janicelo@dh.gov.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Antimicrobial Resistance – The Challenge Ahead

IP, Margaret
Professor, Department of Microbiology, The Chinese University of Hong Kong

Introduction - Global Concerns and Challenges

Throughout the world, healthcare professionals are concerned at the growing problem of antimicrobial resistance and the global emergence of multi-drug-resistant organisms (MDROs) in the healthcare setting and in the community. The use of penicillin in early 1940s on a wider scale, and the subsequent newly-introduced antimicrobials, was soon followed by the emergence of resistant microbes. Some of these resistant organisms in relation to the introduction of antimicrobial agents are listed in Table 1. The prevalence of MDROs has increased dramatically worldwide during the last decades [1]. Most alarmingly are in infections caused by MDROs whereby resistance has developed for virtually all currently available drugs and no effective therapies are available. This is compromised by the lack of new discovery of potent classes of antimicrobials in recent time, with shortfalls in funding for the development of new drugs which often relies on interests and support from pharmaceutical industries.

In a wider context, this threat to treatment and control of infectious diseases ranges beyond that of common bacterial pathogens. Drug resistance to infectious agents causing tuberculosis, malaria, pandemics of HIV, and influenza including H5N1, is also increasingly recognized, affecting treatment and hampering their containment. Antimicrobial resistance makes infections more difficult to treat; prolongs duration and increases severity of illness. This lengthens the period of infectivity, enhances spread and poses the added challenge to infection control. In effect, this translates to increases in direct and indirect healthcare costs and a higher morbidity and mortality.

To combat the emerging resistance problem, organizations including the Centers for Disease Control and Prevention, US, and the UK Department of Health, in the late 1990s have published recommendations and guidelines for the management of antimicrobial resistance [2, 3]. In 2001, the World Health Organization (WHO) launched the first global strategy for combating problems caused by the emergence and spread of antimicrobial resistance [4]. Six key interventions have been suggested; namely, reducing the disease burden and prevention of spread, access to appropriate antimicrobials and appropriate use, improvement of surveillance systems, application of relevant regulations and legislation, and development of appropriate new antimicrobials and vaccines [4]. The strategy recognizes that antimicrobial resistance is a global problem that must be addressed in all countries. The stakeholders include all whose practices and behaviours contribute to resistance and where changes are judged likely to have a significant impact at both national and international levels. These include consumers, prescribers and dispensers, veterinarians, managers of hospitals and diagnostic laboratories as well as national governments, the pharmaceutical industry, professional societies, and international agencies.

It is well recognized from findings on the resistance rates for many bacterial species in countries in the Western Pacific region that these are among the highest in the world [5-12]. Examples include that of methicillin-resistant *Staphylococcus aureus* in hospitals in the Asia-Pacific [5, 6], and fluoroquinolone- and penicillin-resistant *Streptococcus pneumoniae* in Hong Kong [7]. Fluoroquinolone-resistant *E. coli* was reported at 64.9% [8], whilst the incidence of extended-spectrum beta-lactamase (ESBL) production among *Escherichia coli* isolates was up to 35% in a report from China [9]. One study reported a 68% prevalence of ESBL phenotypes among *E. coli* and *Klebsiella pneumoniae* from the Indian subcontinent [10]. Outbreaks due to MDROs such as pandrug-resistant *Acinetobacter baumanii* are also increasingly reported in hospitals from Thailand [11] and Taiwan [12]. Sadly, despite WHO recommendation to call for implementation of evidence-based containment strategies in 2001, up until 2005, many member states have not yet established comprehensive national antimicrobial resistance surveillance programmes [13].

Local Efforts

In Hong Kong, the establishment of the Centre for Health Protection (CHP) of the Department of Health in Hong Kong [14] in 2004 facilitated the network organization for a comprehensive territorial-wide antimicrobial resistance containment strategy. Under the Infection Control Branch of the CHP**,** a platform for an ongoing antimicrobial resistance surveillance program was formalized, using standardized laboratory testing. Antimicrobial susceptibility rates of a number of common bacterial organisms against set panels of antimicrobials are collected from major public hospital laboratories into a central information technology (IT) system and are monitored real-time. An antibiotic stewardship program (ASP) was instituted in large, public hospitals to review and monitor antimicrobial use, and to implement strategies for improving antimicrobial prescribing practices [15]. Within the hospital, a multidisciplinary antimicrobial management team is established, comprising infectious disease (ID) physicians, clinical microbiologists and pharmacists, who reviews and provides timely feedback on targeted broad spectrum antimicrobial agents [15]. The programme also incorporated a platform that enables real-time monitoring of the utilization of major broad-spectrum antimicrobials according to WHO standardized units of antibiotic consumption in defined daily dose (DDDs)/ 1000 bed days occupied (BDO). This provides a means of benchmarking and quantifying use of different classes of antimicrobials in various specialties within hospitals. Evidence from published studies clearly indicated the positive impact of ASPs [15, 16], although they do not always result in decreased level of resistance. The ASP is still in its infancy, and one awaits the long term effects of its establishment and its sustainability.

At the community level and in the private sector, campaigns and educational activities have been put in place to improve rational use of antibiotics. It is generally believed that the major

consumption of antimicrobials is from the primary healthcare. An Antibiotic Resistance Surveillance on community isolates initiated by the Department of Health since July 1999 and is regularly updated and is published on the website [17]: The local surveillance data on the organisms involved and their susceptibility patterns are essential to guide the best choice of treatment.

The CHP, via its various branches, plays the lead role in achieving the other complementary tasks of improving local infectious disease epidemiology, surveillance, prevention and control, in the combat and containment of spread of antimicrobial resistance.

Future Strategies

Successful implementation of the strategies for antimicrobial resistance containment depends on high-level commitment and sustained support from national ministries of health and ongoing multi-sectoral collaboration.

In Europe, in line with the Council Recommendations on Prudent Use of Antibiotics, a European Antimicrobial Surveillance System (EARSS) [18] was established since 1999, and has become one of the most successful infectious disease surveillance systems in Europe. However, accumulated data brings an important message that antimicrobial resistance is becoming a larger public health problem year after year, and demands further concerted efforts. Besides selective pressure from human consumption, animal husbandry and agriculture are also major target areas for widespread use of antimicrobials in many countries. The data highlights that, in addition to the classical human pathogens, many of the MDROs that are 'environmental' organisms contribute significantly morbidity and mortality of healthcare-associated infections in Europe. Thus, both prudent use of antibiotics and compliance with hand hygiene and infection control measures are pertinent to reduce selection and spread of these MDROs.

These issues are now placed at a high priority at the EU level. A European Antibiotic Awareness Day took placed across Europe on 18th November 2008 (http://antibiotic.ecdc.europa.eu/), and will be an annual recurring event to raise awareness about the risks associated with inappropriate use of antibiotics. Under the Council Recommendation on Patient Safety and Quality of Health Services, national infection control programmes will be strengthened [19]. In April 2009, a conference on the 'Microbial Threat to Patient Safety in Europe', organized by the Czech Presidency of the EU, will be held, followed by the organization by the Swedish Presidency of the EU of a follow-up conference, focusing more specifically on gaps between increasing multidrug resistance, the need for new antibiotics with novel mechanism of action, and incentives for research and development of such antibiotics.

The WHO, at the World Alliance for Patient Safety, will address on Antimicrobial Resistance at the Third Global Safety Challenge to be launched in 2010 [20]. The previous two global challenges encompassed areas on hand hygiene and safe procedures in the prevention of healthcare-associated infections, including safe surgery. Already, core groups met to discuss on the work plan, aiming at quantifying the problem of resistance to antibacterial drugs, its burden of diseases including the financial costs, and focusing on areas for control, research and development.

Hong Kong, after the experience of the SARS outbreak, has taken a major reform in strengthening the structure of Public Health [14]. With its reputation of being in the forefront in medical science and research in many aspects of infectious diseases, it should be well placed and equipped to take on this challenge in the Asia Pacific region.

The development of antimicrobial resistance is inevitable when antimicrobials are used. The aim is to minimize the selective environment for these bacterial pathogens to develop resistance by optimizing the antimicrobial usage and reducing the potential for any genetic variability and spread of these organisms. A concerted effort is vital from all stakeholders in preserving the efficacies of these antimicrobials, once known to us as the 'magic bullets' of the twentieth century.

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Table 1. Emergence of resistant organisms in relation to the introduction of major antimicrobial classes/groups.

Antimicrobial group	Year introduced	Resistant organism	Year appeared
Penicillins (susceptible to β-lactamases) Penicillin Ampicillin	1940s	Penicillin-resistant *Staphylococcus aureus* Penicillin-resistant *Streptococcus pneumoniae* Ampicillin-resistant *Escherichia coli*	1950s 1967 1965
Tetracyclines **Glycylcyclines** Tigecycline	1948 2005	Tetracycline-resistant Group A streptococcus Tigecycline-resistant *E. coli*	1952 2007
Penicillins (β-lactamase-stable) Methicillin	1960	Methicillin-resistant *S. aureus* (MRSA) Community-acquired MRSA (CA-MRSA)	1960s 1999
Cephalosporins Cefazolin **Extended-spectrum cephalosporins** Cefotaxime	1962 Early 1980s	 Extended spectrum beta-lactamase (ESBL)-*Klebsiella pneumoniae*	 1983
Glycopeptides Vancomycin	1956	Vancomycin-resistant enterococci (VRE) Vancomycin-intermediate *S. aureus* (VISA) Vancomycin-resistant *S. aureus* (VRSA)	1988 1997 1998
Carbapenems Imipenem	1975 1986	Imipenem-resistant A*cinetobacter sp.* Imipenem-resistant *Pseudomonas aeruginosa* Imipenem-resistant *E. coli*	1990s 2001
Fluoroquinolones	1982	Ciprofloxacin-resistant *E. coli* Levofloxacin-resistant *S. pneumoniae*	1980s 2002
Oxazolidinones Linezolid	2000	Linezolid-resistant *Enterococcus sp.*	2001
Cyclic lipopeptides Daptomycin	2003	Daptomycin-resistant *Staphylococcus sp.*	2007