Impact of antimicrobial resistance in the 21st century

Jae-Hoon Song
Division of Infectious Diseases, Samsung Medical Center,
Sungkyunkwan University, School of Medicine, Seoul, Korea

Introduction

Antimicrobial resistance has been a well-recognized problem ever since the introduction of penicillin into clinical use. History of antimicrobial development can be categorized based on the major antibiotics that had been developed against emerging resistant pathogens[1]. In the first period from 1940 to 1960, penicillin was a dominating antibiotic called as a "magic bullet", although *S.aureus* armed with penicillinase led antimicrobial era to the second period in 1960s and 1970s. The second stage was characterized by broad-spectrum penicillins and early generation cephalosporins. During this period, nosocomial infections due to gram-negative bacilli became more prevalent, while those caused by *S.aureus* declined. A variety of new antimicrobial agents with distinct mechanism of action including new generation cephalosporins, monobactams, carbapenems, β-lactamase inhibitors, and quinolones characterized the third period from 1980s to 1990s. However, extensive use of wide variety of antibiotics in the community and hospitals has fueled the crisis in emerging antimicrobial resistance. Newly appeared drug-resistant *Streptococcus pneumoniae* (DRSP), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase-producing *Klebsiella*, and VRSA have posed a serious threat in many parts of the world. Given the recent epidemiology of antimicrobial resistance and its clinical impact, there is no greater challenge related to emerging infections than the emergence of antibiotic resistance. Problems of antimicrobial resistance can be amplified by the fact that resistant clones or genes can spread within or between the species as well as to geographically distant areas which leads to a global concern[2]. Antimicrobial resistance is primarily generated and promoted by increased use of antimicrobial agents. Unfortunately, as many as 50 % of prescriptions for antibiotics are reported to be inappropriate[3]. Injudicious use of antibiotics even for viral upper respiratory infections is a universal phenomenon in every part of the world. The use of large quantities of antibiotics in the animal health industry and farming is another major factor contributing to selection of antibiotic resistance. In addition to these background factors, the tremendous increase in the immunocompromised hosts, popular use of invasive medical interventions, and increase in travel and mixing of human populations are contributing to the resurgence and spread of antimicrobial resistance[4].

Antimicrobial resistance has critical impact on modern medicine both in clinical and economic aspect. Patients with previously treatable infections may have fatal outcome due to therapeutic failure that is unusual event no more. The potential economic impact of antimicrobial resistance is actually uncountable. With the increase in the problems of resistant organisms in the 21st century, however, additional health care costs for this problem must be enormously increasing.

Antimicrobial resistance on the horizon

Among many types of antimicrobial resistance not only in antibacterial agents but in antiviral, antifungal, or antimycobacterial agents, several prototypic examples which raised a global concern recent years will be focused in this review.

MRSA and VRSA. Since the first isolation of MRSA in United Kingdom in 1961, soon after the introduction of methicillin, it was recognized as a major outbreak pathogen until the early 1970s when a decline in the frequency of multiply resistant MRSA was noted in western countries. However, the second wave of MRSA emerged mainly from the late 1970s and early 1980s with many reports of hospital and interhospital spread[5]. The prevalence of MRSA

among nosocomial isolates has continued to increase with the varying incidence in different countries. In some countries, the frequency of MRSA increased to more than 60-70 % among *S.aureus* isolates from the inpatients. Moreover, recent increases in community-acquired MRSA infections cast another concern in the medical society. Glycopeptides, including vancomycin and teicoplanin, have been increasingly used for therapy of MRSA infections. However, a tragic event in the history of antimicrobial resistance occurred in 1996 . A strain of vancomycin-resistant S.aureus (VRSA) was found in a Japanese patient[6]. Since the first isolation of VRSA in Japan, a total of 10 isolates of B|VRSA were reported in Japan, USA, France, United Kingdom, Hong Kong, and Korea.

Drug-resistant Streptococcus pneumoniae (DRSP). *S. pneumoniae* has long been one of the most important bacterial pathogens causing pneumonia, meningitis, otitis media, and septicemia. For many years, pneumococci were uniformly susceptible to penicillin until the first report of penicillin resistance from a clinical specimen in 1967[7]. During the recent three decades, however, the resistance of *S. pneumoniae* to penicillin has been rapidly increasing in many parts of the world. Data on the prevalence of pneumococcal resistance to penicillin from some European countries and South Africa, which ranged from 44 to 59 %, have raised a global concern on this problem. Recent study by the Asian Network for Surveillance of Resistant Pathogens (ANSORP) showed that Korea, Japan, Vietnam, and Thailand had alarmingly high rate of penicillin-resistance (> 50 %)[8]. The data certainly suggested the critical situation in some Asian countries and underlined the importance of more thorough epidemiologic investigation of DRSP in this region. Increasing problem of pneumococcal resistance should be the subject of common concern in many countries not only because of high incidences but because of the spread of resistance to geographically distant areas[9].

Vancomycin-resistant enterococci (VRE). Enterococci rank third most common organism of nosocomial infections causing urinary tract infections, intraabdominal infections, and bacteremia. Enterococci are intrinsically resistant to β-lactam agents and aminoglycosides at low-levels. Increasing resistance to penicillin and ampicillin has been observed in recent years, particularly in strains of *E.faecium*. It resulted in the situation that vancomycin was becoming the agent of last resort for the treatment of infections caused by multidrug-resistant *E.faecium*. High-level resistance to aminoglycosides and penicillins of enterococcal species were followed by emergence of VRE in mid-1980s. VRE has become an issue of enormous concern over the past decade not only because it is difficult to treat with current antimicrobial agents but because it can transfer vancomycin resistance to other bacterial species such as *S.aureus* or streptococci. VRSA already became a reality and vancomycin-resistant *Streptococcus bovis* was reported recently[10]. At present, VRE pose significant problem in clinical practice by restricting antibiotic choices and resultant poor clinical outcomes of the patients as well as the problem of infection control due to relentless spread within the hospital once established.

Extended-spectrum β-lactamase (ESBL) producing Klebsiella. Production of β-lactamase is the major mechanism by which gram-negative bacteria become resistant to β-lactam antibiotics. The most common plasmid-mediated β-lactamases are designated TEM-1 and SHV-1. ESBLs are mutant enzymes created primarily by one or more amino acid substitutions in TEM-1 and SHV-1 β-lactamase. ESBLs are characterized by an ability to hydrolyze β-lactamase-resistant oxyimino-β-lactams, which include extended-spectrum cephalosporins and monobactams. At least 30 variants of TEM-1 and 7 variants of SHV-1 have now been described[11]. ESBLs became more frequently found in gram-negative bacilli such as *E.coli* or *K.pneumoniae*. It is clearly related to overall levels of extended-spectrum cephalsporin use, particularly of ceftazidime. Therapeutic options for infection caused by ESBL producers are often limited, while imipenem remains the drug of choicedue to its stability to hydrolysis by ESBLs.

Antimicrobial resistance in the 21st century

Antimicrobial resistance will remain one of the major issues in the modern medicine in the 21st century. As we learn from the history and evolution of antimicrobial resistance in the past 50 years, new type of resistance will emerge and spread in the future. The worst scenario would be a widespread emergence of antimicrobial resistance which makes a medical community return to the pre-antibiotic era. Undoubtedly, antimicrobial resistance costs human lives and money. The development of new drugs can be a temporary solution with eventual emergence of new resistance. To prevent the emerging antimicrobial resistance in the 21st century, strenuous efforts must be implemented at multiple levels - local, national, and global level.

Future strategies for a global crisis should encompass rational use of antimicrobial agents, reduction of the spread of resistance, and implementation of a containment strategy[12]. First of all, improvement of rational use of antibiotics is an essential component of any program to prevent and control of resistance. Indiscriminate use of antibiotics in humans, animals, and farming should be curtailed. Patterns of antibiotic use and consumption should be monitored at local and national levels. Secondly, every effort to reduce the spread of resistant clones or genes should be exerted. To meet this goal, infection control practices in the hospitals should be reinforced. But, ultimately, practical measures to implement various strategies comprehensively is of utmost importance. Implementation can be improved by education, technical developments, surveillance, and regulatory activities. All these activities should affect physicians (prescribers), patients (consumers), pharmacists (dispensers), and pharmaceutical industry (producers). Although it is difficult to implement all these strategies and practical measures, it must be easier to save millions of patients with desperate infections caused by highly resistant strains for which no antibiotics are available and must be cheaper to implement than to develop new antimicrobial agents and health care costs which must be paid for treatment of resistant infections. More importantly, it is the only way we can choose to contain antimicrobial resistance and to revive the antibiotic miracles in the future.

REFERENCES

1. Medeiros AA. Evolution and dissemination of β-lactamases accelerated by generations of β-lactam antibiotics. Clin Infect Dis 1997; 24 (suppl 1): S19-45
2. Levy SB. The challenge of antibiotic resistance. Scientific Am 1998 ; 278 : 46-53
3. Cassell GH. Emergent antibiotic resistance : health risks and economic impact. FEMS Immunol Med Microbiol 1997; 18: 271-274.
4. Neu HC. The crisis in antibiotic resistance. Science 1992 ; 257: 1064-1073
5. Ayliffe GAJ. The progressive intercontinental spread of methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 1997; 24 (suppl 1) : S74-79
6. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother 1997;40:135-136
7. Hansman D, Bullen MM. A resistant pneumococcus. Lancet 1967; 2: 264-5.
8. Song JH and the Asian Network for Surveillance of Resistant Pathogens (ANSORP). Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries. Clin Infect Dis 1999;28;1206-11
9. Munoz R, Coffey TJ, Daniels M, et al. Intercontinental spread of a multiresistant clone of serotype23F *Streptococcus pneumoniae*. J Infect Dis 1991; 164: 302-6.
10. Poyart C, Pierre C, Quesne G, et al. Emergence of vancomycin resistance in the genus Streptococcus : characterization of a vanB transferable determinant in Streptococcus bovis. Antimicrob Agents Chemother 1997; 41: 24-29.
11. Bonafede M, Rice LB. Emerging antibiotic resistance. J Lab Clin Med 1997; 130 :

558-566
12. Williams RJ, Heymann DL. Containment of antibiotic resistance. Science 1998; 279 : 1153-1154
13. Baquero F, Task Force of the General Direction for Health Planning of the Spanish Ministry of Health. Antibiotic resistance in Spain : what can be done ? Clin Infect Dis 1996 ; 23 : 819-823