Global Overview of Antimicrobial Resistance : Historical Perspectives

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Introduction

Discovery of antimicrobial agents was the most brilliant achievement of modern medicine in the 20th century. In the "golden age of antibiotics" from 1940s to 1970s, antimicrobial agents have significantly increased human life expectancy by curing previously fatal infectious diseases. At the end of 1960s, some authorities impetuously declared that infectious diseases would have been the history of human life. Currently, however, half a century after the introduction of "miracle drugs", scientific community and public fear the re-emergence of infectious diseases caused by antibiotic-resistant bacteria. Most cardinal infectious diseases which account for more than 85 % of the mortality from infection worldwide such as acute respiratory infections, diarrheal diseases, AIDS, malaria, and tuberculosis have serious problems in the treatment due to widespread emergence of antimicrobial resistance.[1] For example, treatment of acute respiratory infections is complicated by the emergence of pneumococcal resistance to penicillin, macrolides, and fluoroquinolones. Antimicrobial resistance among major human pathogens including bacteria, virus, fungi, and mycobacteria is obviously one of the most serious threat to public health globally in the 21st century.

Antimicrobial resistance results in increased morbidity and mortality from treatment failures and increased health care costs. It is estimated that USD 30 billion is spent on the cumulative effects of antimicrobial resistance each year including multiple drug regimens, extra hospital days, additional medical care and lost productivity. And a recent study showed that multidrug-resistance was associated with increasing incidence of invasive pneumococcal diseases in children younger than 5 years of age.[2] It means that antibiotic resistance directly contributes to increasing incidence of invasive diseases.

Antimicrobial resistance in different settings

Although antimicrobial resistance became a common problem in a global village, specific issues of resistance may be different between community and the hospitals or between developed and developing countries. Among community pathogens, classic resistance had been reported among *Shigella* species, *Hemophilus influenzae, Neisseria gonorrhea,* and *Moraxella* species since the 1960s. Antimicrobial resistance among *Streptococcus pneumoniae* became a global concern since the 1990s. Among nosocomial pathogens, methicillin resistance among staphylococci has been representative since the 1960s. Staphylococcal resistance was further characterized by newly emerging glycopeptide resistance since 1997. Vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing or multidrug-resistant gram-negative bacilli are also common clinical problems since 1990s. In the industrialized countries, these nosocomial pathogens are the major issues of antimicro-

bial resistance, while antimicrobial resistance among community pathogens such as enteric pathogens and gonococci is still dominating in developing countries.[3] Resistance among pneumococci and mycobacteria is a common issue in both industrialized and developing countries.

Historical evolution of antimicrobial resistance by major pathogens

1. Staphylococcal resistance

Methicillin-resistant *S. aureus* (MRSA) was first reported in 1961 and has become endemic in many hospitals in the world in the 1980s. In some Asian countries, 70-80% of *S. aureus* isolates are resistant to methillin. With the widespread emergence of MRSA, glycopeptide antibiotics such as vancomycin or teicoplanin have been more frequently used in the clinical practice. Popular use of these agents has led to the emergence of glycopeptide resistance at the end of the 20th century. In 1997, an isolate of *S. aureus* with reduced susceptibility to vancomycin (MIC $\geq$ 8 μg/mL) was first reported from Japan.[4] Until 2002, a total of 24 cases of VISA infections were reported from 11 countries in the world. In 2002, two strains with high-level resistance to vancomycin (MIC $\geq$ 32 μg/mL) with vanA gene from enterococci were reported in the U.S.[5,6] It is anticipated that glycopeptide resistance will be more frequent within a few years.

2. Pneumococcal resistance

Pneumococcal resistance to penicillin was first reported in 1967. In the 1980s, a few countries such as Spain, Hungary and South Africa were recognized as having significantly high prevalence of penicillin resistance among pneumococci. However, in the 1990s, pneumococcal resistance became a global problem. According to international surveillance studies by ANSORP, Asian countries including Korea, Japan, Hong Kong, Vietnam and Thailand are a major focus of pneumococcal resistance to penicillin, macrolides, fluoroquinolones, and multidrug-resistance in the world.[7] Prevalence of penicillin resistance among invasive pneumococcal pathogens in Vietnam, Hong Kong, and Korea were reported to be higher than 70%.

3. Enterococcal resistance

Enterococcal resistance with therapeutic problems are high-level resistance to aminoglycosides, high-level resistance to ampicillin, and resistance to vancomycin. Of particular concern, vancomycin-resistant enterococci (VRE) have emerged as important nosocomial pathogens since the first description in 1987. Almost all enterococcal blood isolates from the U.S hospitals were susceptible to vancomycin in 1989, but the proportion of resistance strains increased to 25.9% in 2000.[8] Another data from the United States also documented the rapid increase in vancomycin resistance among *E. faecium* isolates from 26% in 1995 to 49% in 1997.

4. Antimicrobial resistance among gram-negative bacilli

Extended-spectrum beta-lactamase (ESBL)-producing strains among Enterobacteriaceae have been rapidly increasing in frequency in some countries. The highest percentage of ESBL phenotype was detected among *K.pneumoniae* strains from Latin America (45%), followed by those from the Western Pacific region (25%) and Europe (23%).[9] ESBL strains usually showed high levels of co-resistance to aminoglycosides, tetracycline, trimethoprim-sulfamethoxazole, and ciprofloxacin, while imipenem still remains highly effective against ESBL strains. In the 1990s, fluoroquinolone resistance became more prominent in some countries such as China, where more than 50% of *E. coli* strains from Shanghai were resistant to ciprofloxacin. Pseudomonas resistance to antimicrobial agents is also an increasing clinical problem with increased rates of mortality and morbidity. *Acinetobacter* species with multiple antimicrobial resistance is a newly emerging problem of nosocomial infection recent years. Acinetobacter strains that were resistant to all available antibiotics (pandrug-resistant) have

rapidly increased from 0% in 1998 to 6.5% in 2000 in a university hospital in Taiwan.[10]

Conclusion

Abuse or misuse of antibiotics in patients and animal husbandry and the spread of resistant clones mainly affects the global emergence of antimicrobial resistance for the past 3 decades. Antimicrobial resistance is not confined to a certain region, but must be an international issue because resistance can spread throughout the world. Given progressive nature of emergence and spread, antimicrobial resistance will be a critical health problem globally in the 21st century. More effective international collaboration against antimicrobial resistance is strongly required.

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