Emerging and Re-emerging Infectious Diseases*

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1. Infectious Diseases Caused by Antibiotic-Resistant Bacteria and Their Management

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Key words: antimicrobial resistance, bacterial resistance, management of resistance

At the turn of the twentieth century, infectious diseases were the most important cause of illness and death. During the first four to five decades of that century, the frequency of infectious diseases in the developed world decreased because of societal and technological changes, including improved hygiene and sanitation, better housing and nutrition, safer food and water, and introduction of immunization and antimicrobial agents. Today, however, emerging infectious diseases pose important public health problems in both the developed and developing world. Many new or previously unrecognized bacterial, fungal, viral, and parasitic diseases have emerged within the past two decades. At the same time, many once-controlled infections have re-emerged or become resistant to antimicrobial therapy. In particular, organisms that are resistant to various groups of antimicrobials also have increased during the past 10 years. These multi-drug resistant bacteria now cause an increasing number of infections each year, primarily in the intensive care units of hospitals. In some cases, multi-drug- resistant strains of both hospital and community origin have become so prominent that keeping patients with serious infections alive has become a difficult task, just as in the preantibiotic era.

In this article, the author highlights the antimicrobial resistance of bacteria.

Definition of antimicrobial agents and resistant bacteria

Antimicrobial agents

Antimicrobial agents are divided into two main groups. The first is a group of antibiotics produced by microorganisms such as streptomyces spp. The second group of antibiotics is synthetically produced.

Resistant bacteria

Resistant bacteria are organisms harboring escape systems against antibiotics.

Why are resistant bacteria born?

Bacteria, the first life that appeared on earth, was born approximately 3.5 billion years ago. Since then, they have made microcosms in the environment competing with each other. Some bacterial species might evolve so as to produce antibiotics to inhibit the growth of other bacteria around them. Furthermore, it is thought that they simultaneously establish vari-

*Presented at the 98th Annual Scientific Meeting of the Japanese Society of Internal Medicine, April 13, 2001, Tokyo
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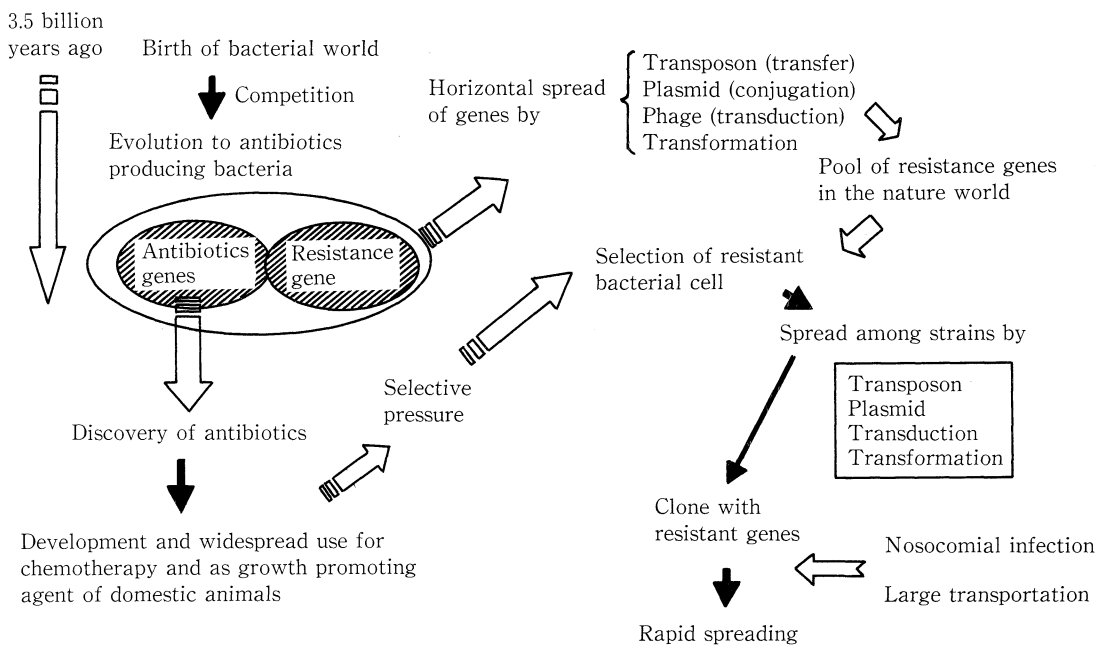


Figure 1. Why does resistance to antibiotics emerge and spread?

ous escape systems against their own antibiotics, which represent the origin of antimicrobial resistance (1). To date, a large variety of antibiotics have been discovered and with clinical use of these agents increasing, resistant genes have also emerged and spread (Fig. 1).

Mechanisms of bacterial resistance to antimicrobial agents

The four fundamental mechanisms of antimicrobial resistance are (1) enzymatic degradation or modification of antibacterial drugs, (2) alteration of bacterial proteins that are antimicrobial targets, (3) prevention of access through permeability barriers, and (4) active efflux pumps (Fig. 2).

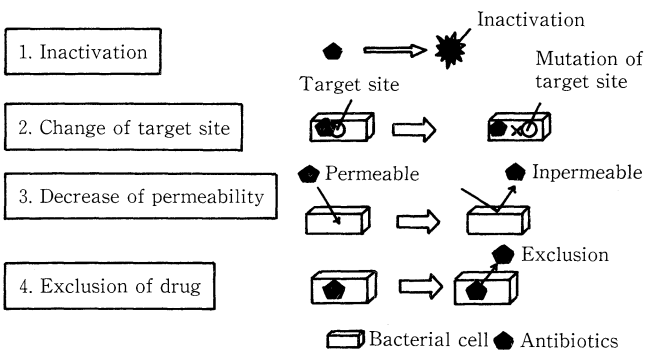


Figure 2. Resistance mechanism of bacteria against antimicrobial agents.

Examples of bacteria currently causing clinical problems because of antimicrobial resistance

Several microorganisms have acquired resistance to antibiotics including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE). Certain strains of these bacteria show multiple resistance, and some of the infections caused by such bacteria is virtually impossible to treat. To date, wide spectrum β-lactamase (ESBL) producing enterobacteriaceae and multi-drug- resistant *Mycobacterium tuberculosis* are a major problem in hospitals and medical institutions around the world (Table 1).

Why does resistance emerge and spread?

Inappropriate use of antimicrobial agents

There are numerous anecdotal examples of the relationship between antibiotic consumption and emergence of resistance (2). Given this fact, it is clear that inappropriate or imprudent use of antimicrobial agents should be discouraged at all cost. Thus, using antimicrobial agents for prophylactic purpose in settings where the likelihood of infection is low should be discouraged. Likewise, the routine use of antimicrobial agents for the treatment of vial upper respiratory tract infections represents another potential source of selective pressure for resistant organisms. On the other hand, the use of antimicrobial agents in animal feed has also led a selective pressure for the development of new breeding grounds for resistant microorganisms (3).

Transfer of exogenous genes

Some of the exogenous resistance genes appear to have originated from other sources. R-plasmids play a major role in the

Table 1. Major Resistant Bacteria Since 1990s

Resistant strain	Target
• Glycopeptide resistant *Enterococci*	Vancomycin Teicoplanin
• MRSA with reduced susceptibility to vancomycin	Vancomycin All β-lactams
• Penicillin-resistant *Pneumococci*	Penicillin Expanded spectrum cephems
• Extended-spectrum β-lactamase producing *Enterobacteriaceae*	Penicillin Expanded spectrum cephems Monobactam (a few) Carbapenem (a few)
• Carbapenem hydrolyzing metallo-β-lactamase producing bacteria	All β-lactams except for monobactam
• β-lactamase non-producing ampicillin resistant *Haemophilus influenzae*	Many β-lactams
• Multi-drug-resistant *Mycobacterium tuberculosis*	Rifamycin Isoniazid Streptomycin

build-up of resistance to many agents, especially because many genes coding for resistance to various agents are easily assembled on plasmids, thanks to the activity of the integron-cassette system. Furthermore, with organisms that are naturally transformed by DNA, "foreign" genes may easily become integrated into the chromosome of the host (4).

Evolution of exogenous genes

Even with some of the most advanced agents, novel, unanticipated types of resistance mechanisms have evolved. An example is the mutation of genes coding TEM or SHV type penicillinase, which are well known as ESBLs (5).

Overexpression of multi-drug efflux pumps

Recent studies have identified the presence of multi-drug efflux pumps in most bacteria. In essence, the efflux pump transports any antibiotic that enters the bacterial cell extracellularly, thus saving the bacteria. Such pumps play a significant role in antibiotic resistance because this mechanism has extremely broad substrate specificity in some pumps, making it almost impossible to design compounds that could withstand such resistance mechanisms.

How could we control and prevent dissemination of antimicrobial resistance?

Appropriate use of antimicrobial agents

Prudent use of antimicrobial agents is our golden goal because the inappropriate use of antimicrobial agents increases the pressure that leads to resistance; this prudent use must extend beyond human medicine to include veterinary, agriculture, and animal husbandry industries.

Development of rapid and sensitive diagnostic tools and surveillance systems

The clinical laboratory plays a major role in successful control of resistance by rapid detection of resistance including new problem resistance. Molecular techniques facilitate the development of rapid and sensitive diagnostic tests. In fact, the past decade has witnessed improvements in laboratory procedures designed for the detection of resistance in several new organisms. On the other hand, the design of new and improved surveillance systems is also needed to prevent nosocomial infections and to control the spread of antimicrobial resistance.

Discovery and development of new antimicrobials

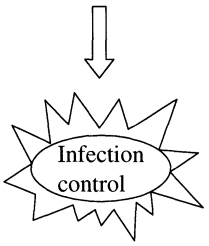
Consequently, there is a clear and urgent need to develop new antimicrobial agents that are effective against most resistant bacteria. At present, scientists at pharmaceutical research facilities are using new tools that enable them to significantly accelerate the drug discovery process. For instance, automation applied in chemistry and biology is allowing the rapid synthesis and screening of thousands of compounds within a short period of time. Advances in structural biology and chemistry make it possible to design more specific and effective inhibitors with great potential in the therapy of infectious diseases (6).

In the last few years, our understanding of the molecular basis of virulence of certain well-studied bacterial pathogens has increased dramatically, which has resulted in the development of genetic techniques for identifying virulent genes. More recently, information about bacterial pathogens has become available from bacterial genome sequencing projects. Many who work in the field hope this new understanding will expand to facilitate the development of new interventions against bacterial infections (Table 2, Fig. 3).

Table 2. How Do We Take Measures Against Resistant Bacteria in 21th Century?

1. Appropriate use of antimicrobial agents
2. (1) Suppression of meaningless and excessive preventive administration
   (2) Shortening of administration period
   (3) Control of excessive use for agriculture or fishing industry
3. Reconsideration of old antibiotics
4. Discovery of effects other than antimicrobial activity
5. Discovery of new target site
6. Control of expression of pathogeneity
7. Application of host defense peptide
8. Development of new vaccine such as DNA vaccine

Chemotherapy
(old paradigm)



(new paradigm)

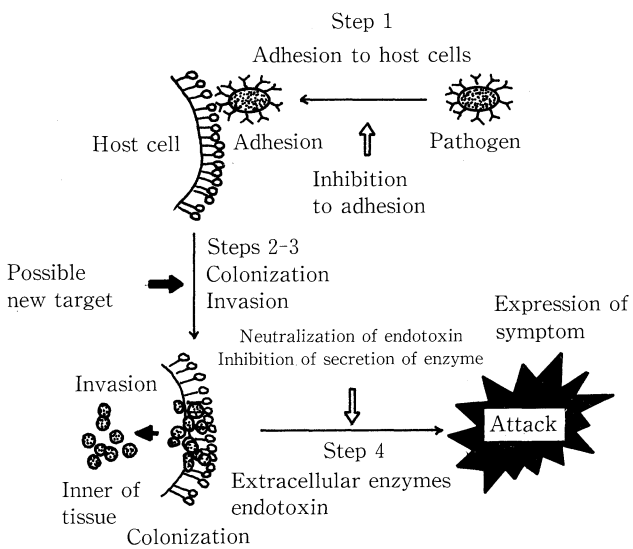


Figure 3. Process of infectious attack and possible new target site of antimicrobial agent.

Conclusions

Microbes are currently winning the race between drug development and bacterial evolution. However, the rapid increase in our understanding of the molecular mechanisms of bacterial pathogenesis should provide an abundance of information for new drug and vaccine discoveries. The next challenge will be to convert this information into practical applications to reduce the burden of bacterial diseases.

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