History of Antimicrobial Agents and Resistant Bacteria

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Abstract

Antimicrobial chemotherapy has conferred huge benefits on human health. A variety of microorganisms were elucidated to cause infectious diseases in the latter half of the 19th century. Thereafter, antimicrobial chemotherapy made remarkable advances during the 20th century, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in response to the development of antimicrobial agents, microorganisms that have acquired resistance to drugs through a variety of mechanisms have emerged and continue to plague human beings. In Japan, as in other countries, infectious diseases caused by drug-resistant bacteria are one of the most important problems in daily clinical practice. In the current situation, where multidrug-resistant bacteria have spread widely, options for treatment with antimicrobial agents are limited, and the number of brand new drugs placed on the market is decreasing. Since drug-resistant bacteria have been selected by the use of antimicrobial drugs, the proper use of currently available antimicrobial drugs, as well as efforts to minimize the transmission and spread of resistant bacteria through appropriate infection control, would be the first step in resolving the issue of resistant organisms.

Key words Antimicrobial agents, Resistant bacteria, History

Introduction

Antimicrobial drugs have caused a dramatic change not only of the treatment of infectious diseases but of a fate of mankind. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered in the near future. However, in reality, emerging and re-emerging infectious diseases have left us facing a countercharge from infections. Infections with drug-resistant organisms remain an important problem in clinical practice that is difficult to solve.

If an improper antimicrobial agent happens to be chosen for the treatment of infection with drug-resistant microorganisms, the therapy may not achieve beneficial effect, and moreover, may lead to a worse prognosis. In addition, in a situation where multidrug-resistant organisms have spread widely, there may be quite a limited choice of agents for antimicrobial therapy. At present, fewer brand new antimicrobial agents are coming onto the market. Considering this situation together with the increasing awareness of drug safety, we are now facing a situation of severely limited options among antimicrobial agents.

This paper provides an outline of the history of antimicrobial agents, and thereafter describes resistant organisms that have emerged in response to antimicrobial agents and discusses practical clues to prevent resistant microorganisms.

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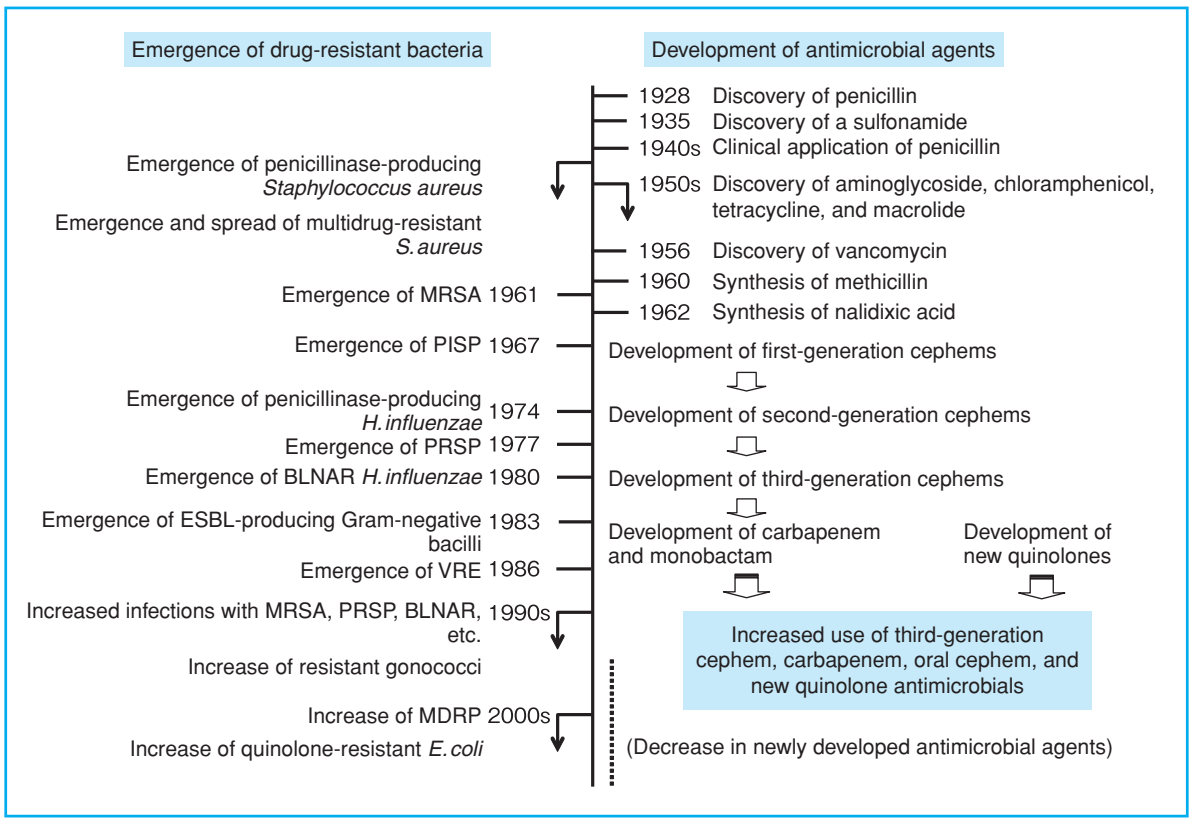

Fig. 1 Trend of development of antimicrobial agents and emergence of drug-resistant bacteria

History of the Development of Antimicrobial Agents[1,2] (Fig. 1)

Looking back on the history of human diseases, infectious diseases have accounted for a very large proportion of diseases as a whole. It was not until the latter half of the 19th century that microorganisms were found to be responsible for a variety of infectious diseases that had been plaguing humanity from ancient days. Accordingly, chemotherapy aimed at the causative organisms was developed as the main therapeutic strategy.

The first antimicrobial agent in the world was salvarsan, a remedy for syphilis that was synthesized by Ehrlich in 1910. In 1935, sulfonamides were developed by Domagk and other researchers. These drugs were synthetic compounds and had limitations in terms of safety and efficacy.

In 1928, Fleming discovered penicillin. He found that the growth of *Staphylococcus aureus* was inhibited in a zone surrounding a contaminated blue mold (a fungus from the *Penicillium* genus) in culture dishes, leading to the finding that a microorganism would produce substances that could inhibit the growth of other microorganisms. The antibiotic was named penicillin, and it came into clinical use in the 1940s. Penicillin, which is an outstanding agent in terms of safety and efficacy, led in the era of antimicrobial chemotherapy by saving the lives of many wounded solders during World War II.

During the subsequent two decades, new classes of antimicrobial agents were developed one after another, leading to a golden age of antimicrobial chemotherapy. In 1944, streptomycin, an aminoglycoside antibiotic, was obtained from the soil bacterium *Streptomyces griseus*. Thereafter, chloramphenicol, tetracycline, macrolide, and glycopeptide (e.g., vancomycin) were discovered from soil bacteria. The synthesized antimicrobial agent nalidixic acid, a quinolone antimicrobial drug, was obtained in 1962.

Improvements in each class of antimicrobial

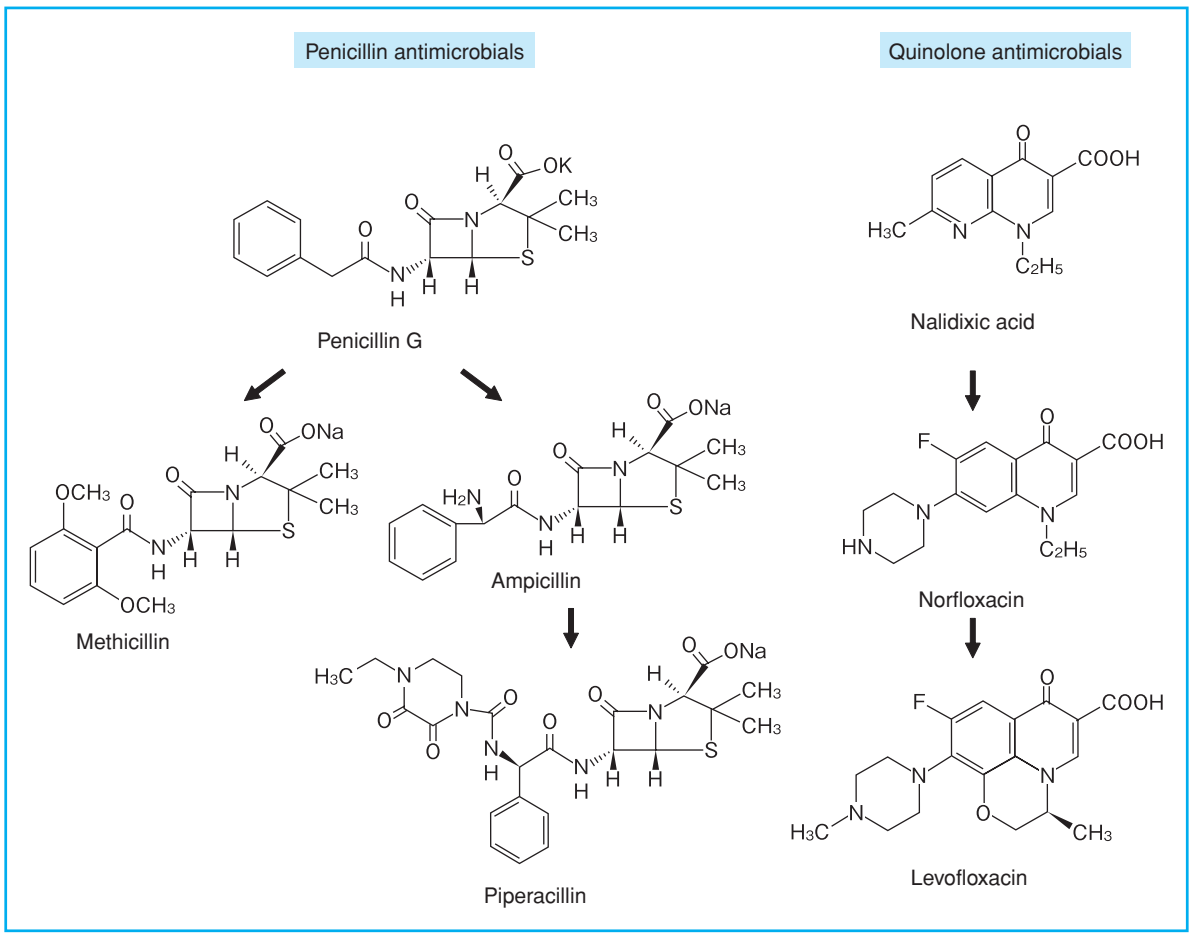

Fig. 2 Evolution of antimicrobial agents (penicillin and quinolone antimicrobials)

agents continued to achieve a broader antimicrobial spectrum and higher antimicrobial activity. β-lactam antibiotics will be described as an example. The β-lactam antibiotics include penicillins (Fig. 2), cephems, carbapenems, and monobactams.

Penicillins were originally effective for Gram-positive organisms such as *S. aureus*. Later, to address penicillin-resistant *S. aureus* which produces the penicillin-hydrolysing enzyme penicillinase, methicillin was developed. On the other hand, attempts to expand the antimicrobial spectrum yielded ampicillin, which is also effective for Gram-negative Enterobacteriaceae, and piperacillin, which is effective even for *Pseudomonas aeruginosa*.

Cephems were developed in the 1960s, and came into widespread use. Cephems are classified into several generations according to their antimicrobial spectra. First-generation cephems (cefazolin, etc.) are effective only for Gram-positive organisms and *Escherichia coli*, although their antimicrobial activity against these organisms is potent. Second-generation cephems (cefotiam, etc.) have an extended antimicrobial spectrum that covers not only Gram-positive but also Gram-negative organisms including other Enterobacteriaceae. Third-generation cephems (ceftazidime, cefotaxime, etc.) have higher efficacy for Gram-negative organisms, and some drugs of this generation are also effective for *P. aeruginosa*, although the antimicrobial activity against Gram-positive organisms is generally lower than that of the first generation.

Carbapenem is an antibiotic class including panipenem, imipenem, and meropenem. These drugs are effective not only for Gram-positive

Table 1 Clinically important drug-resistant bacteria in Japan

Microorganisms	Drugs	Resistant bacteria	Mechanism of resistance
Staphylococcus aureus	β-lactam (methicillin)	MRSA	Production of an additional enzyme that avoids drug binding (PBP2')
	Vancomycin	VISA (VRSA)	Thickening of cell wall Consequent changes in target (*vanA*, *vanB*, etc.)
Enterococcus	Vancomycin	VRE	Consequent changes in target (*vanA*, *vanB*, etc.)
Streptococcus pneumoniae	Penicillin	PISP/PRSP	Mutation in target (PBP)
	Macrolide	Macrolide-resistant *S. pneumoniae*	Modification of target (*erm*) Drug efflux pump (*mef*)
Haemophilus influenzae	Ampicillin	BLNAR	Mutation in target (PBP)
Pseudomonas aeruginosa	Multiple drugs	MDRP	Multiple factors including loss of porin, drug efflux pump, and drug-modifying enzyme
		Metallo-β-lactamase-producing bacteria	Drug-degrading enzyme
Enterobacteriaceae (e.g., *Escherichia coli*)	β-lactam (carbapenem)	ESBL-producing bacteria	Drug-degrading enzyme
	Quinolone	Quinolone-resistant *E. coli*	Mutation in target (*gyrA*, *parC*)
Gonococci	Quinolone	Quinolone-resistant gonococci	Mutation in target (*gyrA*, *parC*)

and Gram-negative bacteria but also anaerobes, and their antimicrobial activity is strong. The monobactam antibiotic aztreonam exerts an antimicrobial effect only on Gram-negative bacteria.

Continuing improvements have been made for antimicrobial agents in various aspects in addition to the antimicrobial spectrum and activity. The drugs have been developed to achieve better pharmacodynamics including the absorption of oral drugs, concentration in the blood, and distribution to the inflammatory focus. In addition, as antimicrobial chemotherapy has been established and matured, more importance has been attached to the drug safety. Antimicrobial agents that are associated with serious side effects have been replaced by other safer drugs.

Quinolone antimicrobials represent an example of drugs with improved pharmacodynamics and safety (Fig. 2). Nalidixic acid, the first drug of this class, was active only against Gram-negative bacteria, and its use was limited to urinary tract infections because it achieves only low blood concentrations and poor tissue distribution, and was metabolized rapidly in the human body. In contrast, norfloxacin, which came to market in 1984, maintains a stable metabolic state and exhibits good tissue distribution. Its antimicrobial spectrum is extensive, covering both Gram-positive and Gram-negative bacteria including *P. aeruginosa*. Quinolone antimicrobials developed after norfloxacin have been called new quinolones, and they have still been key drugs. Levofloxacin is the S-(−) enantiomer of the new quinolone ofloxacin. This enantiomer has higher antimicrobial activity than that of the other R-(+) enantiomer of ofloxacin, and is associated with weaker side effects on the central nervous system, such as restlessness and vertigo.

Although a large number of companies in various countries have competed in the development of newer antimicrobial agents, the number of brand new drugs has been remarkably decreasing in recent years, with few antimicrobial agents of new classes becoming available. In contrast, infectious diseases continue to attack human beings as emerging and re-emerging infectious

diseases, opportunistic infectious diseases, and infection with drug-resistant microorganisms that will be discussed in the next section. Effective utilization of the current limited options is much more important under the dearth of new drugs on the market.

History of the Emergence of Resistant Bacteria

The capacity of microorganisms to acquire resistance to antimicrobial agents has surpassed our imagination. In some cases, antimicrobial agents formerly effective are no longer useful. The history of resistant bacteria will be outlined below and in Table 1.

S. aureus is the resistant bacterium most familiar in the clinical setting. This bacterium rapidly acquired resistance to sulfonamides when they were in use. Penicillin was initially effective to this microorganism, but resistant strains that produce penicillinase increased in the 1950s. Therefore, penicillinase-stable methicillin was developed in 1960, as mentioned previously. However, as early as the following year, 1961, methicillin-resistant *S. aureus* (MRSA) was isolated in the UK.[3]

Since around 1990, nosocomial infection with MRSA became a social problem. During this period, the target of new antimicrobial agents including second- and third-generation cephems, shifted from Gram-positive to Gram-negative bacteria, and agents with wide spectra but weaker activity against Gram-positive bacteria were widely used (Fig. 1). MRSA acquires resistance to most β-lactam antibiotics through its acquisition of the penicillin-binding protein (PBP) 2' gene; PBP2' is an enzyme involved in cell wall synthesis that has low binding affinity for β-lactam antibiotics. In genetic lineage analysis of nosocomial MRSA strains, major nosocomial clones throughout the world would converge on only seven types.[4] On the other hand, community-associated methicillin-resistant *S. aureus* (CA-MRSA), which was noticed in the US around 1997, is of a different type from nosocomial MRSA.

Fortunately, MRSA so far in Japan have responded to glycopeptide antibiotics such as vancomycin. However, in the latter half of the 1990s, vancomycin-intermediate *S. aureus* (VISA) was reported in this country. It is thought that thickening of the cell wall contributes to decreased sensitivity to this drug. On the other hand, vancomycin-resistant *S. aureus* (VRSA) reported in the US seemed to acquire the resistance genes horizontally from vancomycin-resistant enterococci (VRE).[5] In Japan, there have been no reports of VRSA strains so far, partially at least, due to lower detection rates of VRE than those in Western countries.

Although *S. pneumoniae* was originally susceptible to penicillin, penicillin-intermediate *S. pneumoniae* (PISP) strains were found in the latter half of the 1960s, and penicillin-resistant *S. pneumoniae* (PRSP) strains in the latter half of the 1970s. In Japan, PRSP was found in the 1980s, and the detection of PRSP strains began to increase around 1990. Frequent use of oral cephem antibiotics seems to be responsible for this increase in PRSP. There has also been a remarkable increase in macrolide resistance in this species, which seems also due to the frequent use of macrolides in this country.

Ampicillin was initially effective for *Haemophilus influenzae*. However, in the 1980s, some of this species were found to produce β-lactamase, thereby becoming resistant to ampicillin. In the 1990s, such β-lactamase-producing strains decreased in Japan, however, strains that acquired highly resistance to β-lactam through mutations in PBP genes, increased instead. These are called as β-lactamase-negative ampicillin-resistant (BLNAR) strains, and they are more common in Japan than in other Western countries. It has been speculated that increased use of oral cephem antibiotics is also responsible, similar to the situation with PRSP.

Although *P. aeruginosa* are intrinsically resistant to many antimicrobial agents, the emergence of *P. aeruginosa* strains resistant to all of three classes of antimicrobials, i.e., carbapenems, quinolones, and aminoglycosides is a recent concern. These multidrug resistant *P. aeruginosa* (MDRP) sometimes seems to cause an outbreak in some institutions. MDRP has complex mechanisms of drug resistance, including reduced membrane permeability due to decreased outer membrane protein (D2 porin), overexpression of efflux pump, mutation of the quinolone target (DNA gyrase), production of aminoglycoside modification enzyme, and production of metallo-β-lactamase (carbapenem-hydrolysing enzyme). Some resistance genes are horizontally trans-

ferred by conjugative plasmids.

Gonococci used to be susceptible to penicillin and quinolone, but currently they are resistant to both agents in Japan. In particular, quinolone had been the first-choice drug for gonococcal infection in the 1980s because of the potential advantage in the case of co-infection with Chlamydophila. However, since almost all the strains have become resistant to quinolones, the 1999 guidelines declared against the use of quinolone for gonococcal infection.[6]

Conclusion

In summary, it is clear that the use of antimicrobial agents resulted in the selection of resistant bacteria. Since the advent of new mighty drugs is highly difficult, the proper use of currently available antimicrobial agents as well as efforts to minimize the spread of resistant bacteria through appropriate infection control would be quite important, and may represent a first step in solving the issue of resistant microorganisms.[7]

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