Chapter 1

Introduction
The introduction of penicillin in clinical practice dates back to the 1940s, and almost immediately the possibility for micro-organisms to develop resistance to antibiotics was recognised. Some 60 years later, antimicrobial resistance has become a major public health concern and a world-wide problem, requiring international approaches. The world’s leading health authorities, such as the World Health Organisation (WHO) and the Centers for Disease Control and Prevention (CDC), as well as the European Community have recognised the importance to study the emergence and determinants of antimicrobial resistance and launched strategies for its control (1-3).

Antimicrobial resistance makes infections more difficult to treat. It may also increase the length and severity of illness, the period of infectiousness, adverse reactions (due to the need to use less safe alternative drugs), length of hospital admission – and costs (4, 5).

The emergence of resistance represents adaptive selection by micro-organisms which is to some extent an inevitable result of the therapeutic use of antibiotics. Killing or suppressing drug-sensitive organisms allows naturally drug-resistant ones to emerge which can then not only spread but also transfer their resistance to other organisms.

There is an established but complex relation between the consumption of antibiotics and the prevalence of drug resistance in micro-organisms. This problem can not be overcome by continuously developing new drugs, as time needed may come too short. An important complementary step is to avoid further increase in resistance by reducing unnecessary and inappropriate use of antibiotics.

This makes it imperative that measures are taken to slow the emergence and spread of resistance to existing antibiotics and to new ones as they come into use. This chapter provides a brief discussion on the concept of resistance and will illustrate some clinical implications of recalcitrant infections with resistant strains as opposed to infections with susceptible strains.

Mechanisms of resistance

Resistance is considered to be present if a bacterium is not susceptible to a clinically-relevant concentration of an antibiotic and/or when it is possible to demonstrate that the bacterium possesses a mechanism or property which will render the antibiotic ineffective.

Resistance of a bacterium to an antibacterial substance may be:

Inherent: the species is not normally susceptible to a particular drug. This may be due to an inability of the antibacterial to enter the bacterial cell and reach its target site(s), lack of affinity between the antibacterial drug and its target (site of action), or absence of the target in the cell. This is also called intrinsic resistance.

Acquired: the species is normally susceptible to a particular drug but certain strains express drug resistance that may be mediated via a number of mechanisms:

i. destroying enzymatically the antimicrobial agent inside or outside the cell;
ii. lowering the intracellular concentration of an antimicrobial as a result of reduced uptake and/or increased excretion;

iii. altering the target site so that the antimicrobial no longer binds to it;

iv. creating an alternative metabolic pathway that bypasses the target action.

In those strains having an inherent or an acquired mechanism of resistance, minimum inhibitory concentrations (MICs) of the antibiotic may be higher than those which may be achieved for an adequate period at the site of infection and, hence, there is the risk of therapeutic failure. Sometimes two or more mechanisms exist simultaneously in the same organism and may produce an even greater degree of resistance. One single mechanism of resistance may bring about the ability to resist actions of some or all of the drugs of a particular class (cross-resistance). Therefore, exposure of a bacterial population to one single antibiotic may select for organisms that display resistance to a large number of similar agents.

Transfer of resistance

There is a genetic basis for all bacterial resistance to antimicrobial agents. Inherent resistance is determined by the genetic composition of a particular bacterial species. Acquired resistance is brought about either by random mutation of the DNA of the bacterial genome, which is then passed on to offspring, or by the acquisition of DNA containing a gene or genes which code for a mechanism(s) of resistance. DNA may be transmitted to other bacterial cells by three processes: conjugation, transformation and transduction (6).

In conjugative transfer, DNA passes along a tube that links two bacteria, which may occur between bacteria of the same or similar species. Plasmids carrying genes as transposable elements (transposons) may transfer between cells. Those carrying more than one transposon can encode resistance to many, chemically unrelated, antibacterials.

Transformation involves the uptake of DNA from the environment. DNA acquired by this process may come from an unrelated species, and antibacterial resistance may be acquired even from species not usually responsible for causing disease.

Transduction involves the transfer of DNA by a bacteriophage.

Extent of the problem

There is no clear answer to the question of the extent of the resistance problem. In the Netherlands, for example, the ‘Rijksinstituut voor Volksgezondheid en Milieu’ (RIVM, National Institute of Public Health and the Environment) and a number of associated regional laboratories run a resistance monitoring programme. The data can be used in order to formulate antibiotics policy both inside and outside hospitals. However, this concentrates on selected material so that no picture is established of morbidity and mortality in the population as a whole or of financial consequences.
Resistant strains are generally no more virulent than non-resistant ones. However, an infection with a resistant strain can be much more serious because the chance of effective treatment is much lower. Little is known about the frequency of problems of this kind. In addition, it is also possible that patients will remain contagious for longer as a result of inadequate treatment so that an infectious disease can spread more extensively.

Mild infections often improve after treatment using antibiotics to which the pathogen is resistant (7). The reason for this may be that, despite the reduction in susceptibility, enough effective concentrations are still attained at the location of the infection (8, 9). Another possible cause is that the natural course of many of these infections - such as bronchitis, otitis and sinusitis - is also generally positive without antibiotics (7).

**Staphylococcus aureus: resistant (MRSA) or susceptible to methicillin (MSSA)**

In a case-control study, patients infected with MRSA and MSSA in a hospital in the United States were compared with one another (10). Of the *S. aureus* infections, 31% were caused by MRSA. Infection was associated with several prior courses of antibiotics and extension of the period of admission by seven days. There was no increase in mortality. Another study produced a comparable result (11). In some hospital departments, the period of admission was increased by 30 days.

In a retrospective study Crowcroft and Catchpole used death certificates to examine the evidence that mortality due to MRSA and staphylococcal infections in England and Wales is increasing (12). MRSA was mentioned on 20.6% (1387/6723) of death certificates that included an ICD-9 code for staphylococcal infection, gradually increasing from 7.5% in 1993 to 25.0% in 1998. Although recognising limitations of using routine mortality data for monitoring the impact of MRSA, they conclude that infections due to MRSA seem to be an increasing cause of mortality in England and Wales.

It is assumed that there are a number of risk factors for the contraction and selection of MRSA, like frequent and extensive use of wide-spectrum antibiotics, lengthy hospital admission, presence of decubitus ulcers and other pre-existent skin disorders, intravascular endoprotheses, administration systems and indwelling catheters.

Recently a number of reports are published on MRSA strains possessing the Panton Valentine Leukocidin (PVL) gene. The PVL gene encodes a highly potent toxin, which is involved in severe skin infections and necrotising pneumonia. PVL positive MRSA strains have been detected in the Netherlands and have also been reported in France (in healthy individuals), in the United States (in the Los Angeles gay community, and in a large prison), and in Scotland (small outbreaks of skin abscesses in healthcare staff) (13). It has been suggested that the PVL MRSA is acquired in the community (14-16).
**Penicillin-resistant and penicillin-sensitive Streptococcus pneumoniae**

The mechanism for penicillin resistance in pneumococci is comparable to that of MRSA and is based upon the change in the affinity of beta-lactam antibiotics for the penicillin-binding proteins in the bacterial cell wall (6). Penicillin resistance in pneumococci is still only a sporadic phenomenon in the Netherlands (17), but studies in other European countries report resistance rates of 50% or more (18). The fact that the highest MIC value found for pneumococci in European research is 8 mg/l whereas this is normally < 0.1 mg/l shows that resistance is not absolute. That is why, in the treatment of less serious infections with high doses of penicillin or amoxicillin, a beneficial effect is still usually seen. In the case of more complex infections and infections in compartments where the antibiotic penetrates with greater difficulty, as in the case of the central nervous system and pulmonary abscesses in emphysema, therapeutic failure should be kept in mind (8). Penicillin-resistant pneumococci are less susceptible to cephalosporins. Furthermore, a considerable proportion is resistant to other drugs such as the macrolides, quinolones and doxycycline. The diffusion of teicoplanin and clindamycin is poor in cerebrospinal fluid. Susceptibility is universal only in the case of vancomycin.

Complications seen in penicillin resistance have been described in systemic pneumococcal infections with bacteraemia. In a retrospective study in Spain (19), mortality was significantly higher (54%, n=24) in patients with infections involving resistant pneumococci than in patients with susceptible pneumococci (25%, n=48). Patients with resistant pneumococci had often been treated with antibiotics before. They had also suffered from pneumonia more often and more of them were seriously ill. In a later prospective study carried out by the same researchers, no increase in mortality was found after the results had been corrected for other causes of death (20).

**Implications**

Resistance is a problem with logistical and economical implications. This is true in particular of the severe infections that require hospital admission or which arise in hospitals. In the case of multi-resistance, quarantine measures are required which are not only difficult for the patient in psychosocial terms but which are also accompanied by a higher workload for staff. Often, relatively expensive antimicrobial therapies are required. A number of controlled studies have shown that, in patients with both an infection and resistance, length of admission and costs in general are at least doubled (8).

For general practitioners, it is of major importance to follow a restrictive antibiotic policy given the fact that many infections seen in general practice (upper airway infections) are caused by viruses. Antibiotics should only be prescribed upon strict indication. The Standards of the Netherlands Society of General Practitioners, partly available in English, provide guidelines in this respect (21). If an antibiotic is indicated, the classic drugs should be selected first. Where possible, preference will be for drugs with a narrow
spectrum. In addition, reserve drugs should never be prescribed blindly, since this can contribute to the increase of resistance to these drugs. If an antibiotic therapy that has been started fails, resistance should be tested by means of a culture. Subsequent treatment should be based on the result of this test.

For a number of bacterial antigens and clinical situations, it has been demonstrated that resistance to antibiotics is a complicating factor. Resistance constitutes a threat to patients in risk categories such as those with reduced immunity or those who are infected with tuberculosis or salmonella bacteria. Fast treatment that covers the susceptibility spectrum can often save lives here. If the right antibiotic is not prescribed for this patient group given the susceptibility of the bacterium, therapeutic failure with serious consequences is seen more often than if the right choice had been made. Alongside common strains of bacteria such as *Staphylococcus aureus* and enterococci, it is in the nature of things that more resistant strains are found in this situation, examples being *Pseudomonas spp.* and *Serratia spp.* For a few of the species, it has been shown that infections with resistant strains are associated with higher rates of morbidity, mortality and recurrent infections. This applies to the entire range of Gram-positive and -negative species of bacteria that can cause bacteraemia. Not a single one of these species of bacteria is an obligate pathogen; they constitute a part of the indigenous flora or of flora in the environment that colonises the patient. It is only under exceptional circumstances that their pathogenic properties become evident.

In the Netherlands, in October 1996, the Dutch Working Party on Antibiotic Policy (Dutch acronym is SWAB) was established as an initiative of the Society of Infectious Diseases and the professional societies of medical microbiologists and hospital pharmacists (22). The mission of the SWAB is to contribute to the containment of the development of antimicrobial resistance and of the expanding costs of the use of antibiotics. This is achieved by optimising the use of antibiotics by means of guideline development, education and antibiotic resistance surveillance. In December 2000, the Council on Health Research advised the government on antibiotic resistance. The Minister of Health responded in November 2001, stating that she would follow this advice to a large extent. This advice by the Council on Health Research as well as the decision made by the Minister of Health are of great importance to the SWAB, because the SWAB has since then been designated to co-ordinate the surveillance of antibiotic resistance in the Netherlands.

**Background and outline of thesis**

Pathogens have never recognised the ever more fading European frontiers as barriers. There is a clear need for European collaboration to control infectious diseases. The Treaty of Amsterdam makes provision for action directed towards improving public health, preventing human illness and diseases. At the EU conference ‘The Microbial Threat’, held in Copenhagen in 1998, all EU Member States unanimously agreed that antimicrobial
resistance was no longer a national problem, but a major international issue requiring a common strategy at European level (23). One of the recommendations made at this conference was that a European surveillance system of antimicrobial resistance should be set up. In the same year the RIVM (National Institute of Public Health and the Environment) in the Netherlands had taken the initiative and received funding from the European Commission to start with the European Antimicrobial Resistance Surveillance System (EARSS). In 2001, at a follow-up EU-conference in Visby, Sweden, it was concluded that all Member States should join EARSS as a minimum requirement of national surveillance programmes.

Surveillance of antimicrobial resistance is a first step towards containment of the problem and is generally considered to be necessary to provide local data for selection of empirical therapy, to assess the scale of the resistance problem at local, national or international level, to monitor changes in resistance rates, to detect the emergence and spread of new resistances, and to provide a measure of the effectiveness of interventions aimed at reducing resistance. Surveillance can also provide an opportunity to improve the quality of susceptibility testing among participants in the surveillance (24).

This thesis aims to explore ways how to set up and improve European surveillance of antimicrobial resistance as a necessary step in the containment of antimicrobial resistance. Microbiological laboratories are using different diagnostic protocols between and even within countries. Indications for taking clinical samples may vary as well as the choice of antibiotics. Criteria for discriminating resistant isolates from susceptible bacteria are often based on national, and not on international consensus. How to address these problems, aiming to provide reproducible and comparable data from the participating laboratories, is studied and discussed in chapters 2 and 3.

In chapter 4 the question is asked whether laboratories in different countries are able to provide reliable results when it comes to susceptibility testing of the bacterial species under surveillance. For this reason we initiated an external quality exercise to study the comparability of susceptibility test results among participants.

In chapter 5 a survey is described to investigate the European geographical distribution and a trend-analysis of the susceptibility of the community-acquired pathogen *S. pneumoniae* against a number of indicator antibiotics.

In chapter 6 we investigate whether there is a relationship between the level of resistance in a certain country and the level of antimicrobial use. We therefore study the correlation between *S. pneumoniae* resistance rates and the amount of penicillin and macrolides used at country level.

In chapter 7 a survey is described to investigate the European geographical distribution and a trend-analysis of the susceptibility of a common hospital-acquired pathogen *S. aureus* against key indicator antibiotics.
In chapter 8 we aim to provide the larger framework of which EARSS is part. We present the comprehensive Community strategy against antimicrobial resistance with its actions to contain antimicrobial resistance and discuss how these actions are to be co-ordinated. Finally, in chapter 9 we discuss general findings of the studies and provide recommendations specifically for community- and hospital-acquired pathogens.

References


