Rational use of antibiotics

Dijkmans, A.C.

Author: Dijkmans, A.C.
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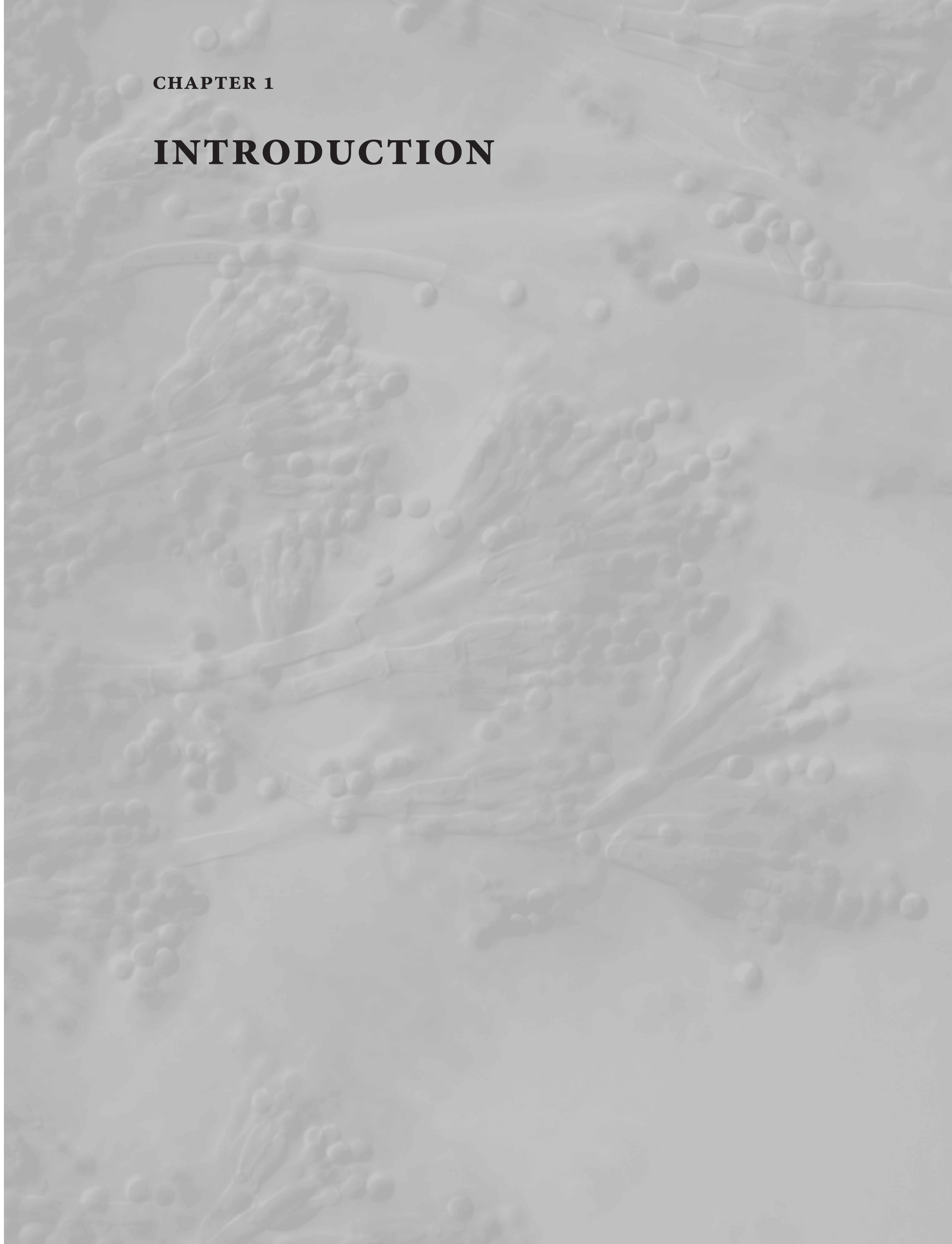
CHAPTER 1

INTRODUCTION



INTRODUCTION

Infectious diseases are much older than mankind and when *Homo sapiens* arrived by evolutionary descent, they were vulnerable for infections. However, the existence, causes and mechanisms of diseases due to microscopically small organisms remained obscure for many centuries and it became clear only since the second part of the nineteenth century. The transport of 'contagious material' was suggested by Ignaz Semmelweis, who was convinced that transfer of the putrefying organic materials from a sick woman resulted in puerperal fever in a healthy woman,[1] without recognizing the relationship of microorganisms to disease. Although the existence of microorganisms had already been revealed as a result of van Leeuwenhoek's development of the microscope, it took two additional centuries to recognise that microorganisms could be the cause of diseases, that at least some of them were pathogenic to man. Experiments to proof that a microorganism could cause a specific disease were performed by Robert Koch in 1877 with his experiments with *Bacillus anthracis*.[2] The next step in Koch's work was to define the conditions in which a specific microorganism could cause a specific disease, i.e. Koch's postulates.[3] With the application of these postulates a connection was made between clinical manifestations of a disease and microorganisms observed under the microscope, establishing the causative role of specific microorganisms for specific diseases as tuberculosis, anthrax and cholera.

Antibacterial agents

HEAVY METALS

In the early sixteenth century heavy metals such as gold and mercury were considered as an elixir of life by Paracelsus. In 1908 Paul Ehrlich pioneered the use of arsenic and 25 years he discovered that arsenical compounds had activity against syphilis, and discovered that compound 606 (Salvarsan; 'beneficial arsenic') was amazingly active against such infection.

Koch reported the *in vitro* inhibition of tubercle bacilli growth by gold cyanide and in 1894 a mixture of gold and magnesium was used to treat tuberculosis. Many publications were written about chrysotherapy for tuberculosis. Believing that tuberculosis and rheumatoid arthritis (RA) had a common infectious aetiology, Forester applied gold for the treatment of RA.[4] Despite the fact that RA turned out not to be directly caused by microorganisms, chrysotherapy proved to be rather effective and became an established drug in the treatment of RA.

CHEMOTHERAPEUTICS

Based on the idea's and work of Paul Ehrlich, Mietzsch and Klarer had synthesized Prontosil in 1932. Prontosil was not active against bacteria *in vitro*, but was quite active in experimentally infected animals. The explanation for this discrepancy was that Prontosil is a pro-drug metabolized by the recipient to the active agent

sulphanilamide. The sulpha drugs were the first chemical substances that made a real difference in the treatment of bacterial infections in particular infections caused by streptococcal species. The historical importance of sulpha drugs is great, and even to date have wide usage in the treatment of systemic or localized infections.

ANTIBIOTICS

During the time that sulphonamides were available another important development took place when Sir Alexander Fleming did his historical discovery of penicillin in 1928.[5] While studying a staphylococcal variant, he found one of the culture plates contaminated with a fungus which destroyed the surrounding staphylococcal colonies. This accidental rediscovery of the long-known ability of Penicillium fungi to suppress the growth of bacterial cultures spurred additional research. Fleming investigated the properties of 'mould broth filtrates' which he named penicillin for brevity. He described penicillin as an antiseptic 'more powerful than phenol', and the name 'penicillin' has since been applied to pure antibiotic substances. After this first historic observation it took a decade before penicillin could be sufficiently purified and produced on an industrial scale. Indeed, only after the successful purification and concentration by Chain and Florey in 1940, it became possible to demonstrate the importance of penicillin by a clinical trial in 1941. Thereafter, in the course of the 20th century numerous new antibiotics were discovered and developed and introduced in daily practice.

Antibiotics are unique among all other medical drugs. They are the only class of medicines, whose primary target is present in bacterial cells but absent in human cells, i.e. they are highly selective for bacterial cells. Although the value of hygiene measures cannot be underestimated, antibiotics have revolutionized human healthcare in a way that only a few other scientific discoveries have. Antibiotics have not only enabled us to overcome 'the captain of the men of death' by saving lives of patients with serious infections, these drugs have also played a pivotal role in major advances in medicine and surgery, a role which is less often highlighted and yet has paramount significance.[6]

On the other hand, antibiotics disturb natural ecological niches by exerting selective evolutionary pressure on bacteria present in the niches were they are applied, both in the human, the animal and agricultural domains of society as well as in the innate environment. As a consequence of exposure to antibiotics the less susceptible and fully resistant mutants of susceptible species survive as do the intrinsically resistant (see below) species; these surviving cells may subsequently greatly expand their niche. We currently face an era of serious threats to human and animal health due to the world wide emergence of multi-drug resistant bacteria. This threat was always on the horizon. As early as 1943, Sir Alexander Fleming noted that microbes can be 'educated to resist penicillin'.[7] Notwithstanding this early observation, only little has been done to prevent the emergence of drug resistance.[6,7]

ANTIBIOTIC RESISTANCE

Antibiotic resistance is recognised as one of the most serious threats to the treatment of infectious diseases globally. Already in 1993 Calvin M Kunin, an infectious diseases specialist in the USA, wrote a perspective in the Annals of Internal Medicine warning against a worldwide calamity due to the global emergence of antimicrobial resistance.[38] However, only in 2004 this emerging threat finally prompted the World Health Organisation (WHO) to issue a warning that antibiotic resistance would seriously impact the opportunities to treat infectious diseases in the future.[7] In 2015 the WHO published its Global Action Plan on Antimicrobial Resistance, outlining the way for all nations to combat the emergence of resistance, a worldwide effort that is currently being implemented in many countries. The awareness posed by the threat of emerging antimicrobial resistance is now greater than ever.

Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), multiple resistant (MR) enteric gram negative bacilli (*Escherichia coli*, Klebsiella species, Enterobacter species) and penicillin-resistant *Streptococcus pneumoniae* (PRSP) are prime examples of common pathogenic microorganisms with increasing rates of resistance to commonly used antimicrobials. The degree of resistance varies worldwide and depends highly on the availability of antibiotics for the population and national policies regarding antibiotic use. Countries with easy access to antibiotics, even without prescription, have a higher degree of antibiotic resistance than countries with a stricter regimen. Nordic European countries including the Netherlands have a strict regimen and as a consequence have lower resistance compared to the South-European countries.[8] In low and middle income countries antimicrobial resistance is higher due to routine over the counter availability and misuse of antibiotics.

TYPES OF RESISTANCE

Resistance to antibiotics is commonly divided in two different classes: primary (intrinsic) and secondary (acquired) resistance. Primary resistance refers to resistance that a bacterium has naturally – i.e. without manipulations such as exposure to antibiotics – against the activity of an antibiotic compound. This resistance is considered to reflect genomic information of a bacterium. Secondary resistance is the acquired capacity of a bacterium to resist the activity of an antibiotic compound to which it was previously susceptible by acquisition of additional genomic information. This renders the bacterium resistant to an antibiotic compound to which it was naturally susceptible. It is particularly the increase in secondary resistances that causes world-wide concern. Bacteria have become more and more adapted due to the long-term massive usage of antibiotics in human, animal and agricultural sectors of society. The global resistance emergence is further aggravated by the fact that resistant organisms selected in one sector of society may contaminate the innate environment and spread to other sectors of society via the environment and via travel of people and animals, and through the transport of agricultural produce and other goods.

Biochemically, several types of resistance mechanisms are observed including antibiotic inactivation, target modification, altered permeability and 'bypass' metabolic pathways.[9] It can be stated that resistance emergence is due to a combination of two groups of factors:

1. Selection of resistant clones as a direct consequence of exposure to antibiotics favouring:
   - intrinsically resistant bacterial species
   - variants of originally susceptible bacteria that have acquired resistance traits by spontaneous mutations in their genome or by acquisitions of resistance genes through horizontal gene transfer from other bacteria in their vicinity
2. Expansion and the spread of resistant strains from their place of emergence to other sites, resulting in outbreaks, epidemics and pandemics of resistant clones.

Resistance thus seems an inevitable consequence of the evolution of microorganisms under antibiotic pressure and their ability to spread globally. Moreover, it is difficult to unravel the separate contribution of each of the factors leading to resistance problems. Although appropriate use of antibiotics essentially exerts the same selective effect favouring the emergence of resistance, it is the inappropriate use of antibiotics that can and should be targeted in the combat against the emergence of antibiotic resistance. Inappropriate usage is still highly prevalent and there are several types of inappropriate use of antibiotics (*table 1*).[10,11]

The contribution of the different types of inappropriate use of antibiotics to acquired resistance is difficult to estimate. However, correlation between antibiotic prescriptions and resistance is well described.[12,13] In primary care antibiotic exposure is associated with a subsequent twofold risk of antibiotic resistance in respiratory and urinary bacteria.[14] In hospitals antibiotic prescribing selects for resistant bacteria both at patient level and at the level of institutions.[15] An almost twofold risk of increase in emergence of MRSA was observed in patients exposed to antibiotics.[16] The risk of mortality from infection in patients harbouring resistant microorganisms in prescribing ineffective antibiotics for patients harbouring resistant organisms was associated with an 1.6-fold increased risk.[17]

With regard to the section 'overuse' (*table 1*) general practitioners are the most involved group of physicians. Apart from clinical experience to discriminate a bacterial infection from other infections modern techniques are helpful as shown in as the use of biomarkers such as C-reactive protein to guide antibiotic prescribing in COPD.[18,19] Continuous medical education is required in the awareness of overuse and underuse by general practitioners and hospital doctors. In 2015 poor knowledge and confidence amongst final year medical students in Australia were observed.[20] In 2004 in a survey amongst doctors in a teaching hospital in the USA it was seen that only 21% of doctors feel confident that they were using antibiotics optimally and 90% of doctors prefer more education about antibiotic use.[21]

A recent publication shed light on a separate problem, the (re)filling of an antibiotic prescription over time: the probability of filling an antibiotic prescription in 62 million enrolees in health insurance plans was 62% over 4 years.[22]

Next to this, a substantial component, perhaps the most influencing factor, for inappropriate use is the influence of the pharmaceutical industry. The publication of Podolsky gives impressive information about aggressive pharmaceutical marketing.[23]

Combating Resistance

Cornerstones of an effective strategy to respond to antibiotic resistance include refining stewardship of existing antimicrobials, re-introducing old antibiotics within the framework of antimicrobial stewardship, and introducing new agents.

ANTIBIOTIC STEWARDSHIP

It is likely that the real change in combatting antimicrobial resistance can only be achieved by rational and restricted or controlled use of antimicrobials. The change in attitude and behaviour towards antibiotics is the goal of so called antibiotic stewardship programs. Antibiotic stewardship is essential for the human, animal and agricultural sectors of society in a coordinated attempt to stop the emergence of antimicrobial resistance and even to redress the degree of multi resistant microorganisms.[24] Essential is that the rules of antibiotic stewardship hold for all antibiotics, the existing ones and also for the new and renewed ones.

Since the relationship between antibiotic prescription and resistance is recognised[12] measures for appropriate prescription have been taken, which are bundled as antibiotic stewardship.[31] Antibiotic stewardship has three primary goals:

- Ensure effective treatment and prevention of bacterial infection[32]
- Reduce unnecessary antibiotic use and costs
- Minimise collateral damage

At patient level, stewardship has been defined as 'the optimal selection, dosage and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal effect on subsequent resistance.[6] The Infectious Diseases Society of America together with the Society of Health Care Epidemiology of America was the first to publish an extensive guideline on Antibiotic Stewardship in 2007.[33] The purpose of these guidelines was to improve the use of antimicrobial agents in hospitals and to prevent antimicrobial resistance in hospitals. Next to this the guidelines were aimed to provide evidence-based recommendations for developing a program to enhance antimicrobial stewardship in the hospital setting to improve the quality of care. The first Dutch guideline on this topic by Stichting Werkgroep Antibioticabeleid (SWAB) was largely based on this example. Stewardship has led to interventions to monitor and direct antimicrobial use. For new drugs and old revisited drugs the antibiotic vigilance, as incorporated in guidelines for promoting antibiotic stewardship should be as strict or even stricter to avoid resistance against these last resort drugs.

In The Netherlands so called A-teams including at least an infectiologist, a clinical microbiologist and a pharmacist have been established. During their regular (weekly) meeting they discuss patients with infections. The use of last resort antibiotics is restricted and specific care is taken to switch as soon as possible from intravenous to oral therapy. Additionally, an Antibiotic Stewardship Committee is in charge of the standard antibiotic treatments and provides alternatives in case of an allergy or adverse effect.

Education in the hospital to medical doctors/pharmacists and for general practitioners plays a major role in restriction of antibiotics.

Re-introducing old antibiotics As one of the possible solutions for the low number of effective antibiotic compounds, it has been suggested to re-introduce antibiotics that have been used previously but currently are no longer in use in clinical setting. These older drugs were for some reason, deleted from antibiotic guidelines and formularies, and, therefore, disappeared from the standard of care. For this re-evaluation it is important to first focus on the reasons why these drugs were removed from the market. In this respect, the fate of colistin, a prototypical polymyxin, may serve as an example. In its handbook 'The use of antibiotics' (third edition, 1979) Kucers states that '"*The polymyxins" are not absorbed from the gastrointestinal tract and, therefore, are administered intramuscularly or intravenously for treatment of systemic infections'* (page 534). *'Patients with renal failure: the polymyxins accumulate in these patients, so a modified dosage schedule with serum level monitoring is necessary'* (page 535). *'The polymyxins frequently cause side effects', 'untoward effects were observed in 25.1 percent'* (page 539). Due to these warnings regarding adverse effects, and due the concurrent development of several aminoglycosides (without these side effects), colistin became a second choice antibiotic and finally disappeared from daily practice. However, the current situation with many strains of multi-drug resistant Gram-negative bacteria causing serious infections in health care setting across the globe prompted a re-evaluation of the polymyxin class of antimicrobial agents. Another antibiotic that was not used for decades, is fosfomycin which was already discovered in 1969.[30] It was not even mentioned in the 1982 edition of Kucers handbook, suggesting it was not clinically relevant at that time. A genuine interest in this antibiotic only arose in the first decade of the 21st century.

NEW ANTIBIOTICS

When the number of effective antibiotics decreases over time, development of new antibiotics becomes crucial.[24] Indeed, several new compounds of known classes of antibiotics and a small number of new classes of agents have been developed and introduced into clinical practice to overcome existing and emerging antimicrobial resistances. However, the number of new antibiotics in the pipeline is currently low, with only two novel classes discovered in the last 20 years.[25–27] In part this is an economic issue since for many manufactures it has been and still is much more profitable to invest in medicines for prevalent chronic illnesses such as cardiovascular and rheumatic diseases, rather than in medicines that are predominantly prescribed as short courses in selected individuals which actually lead to a rapid cure obviating the need for further treatment as is the case with most infections.[6] In 2012 the Infectious Diseases Society of America has proposed an alternative antibacterial drug approval pathway which would accept smaller and less expensive clinical trials.[28] As possible a result of this action, in 2019 studies with new antimicrobial drugs have been published.[24,29] The increased activity in the discovery and development of new drugs is shown by – for example – the next generation aminoglycoside,[29] plazomicin,. Although this development possibly marks the beginning of a new era, it can only be part of the solution to overcome resistance to antibiotics. In case these few new antimicrobials are used in the same way as antibiotics were used the past, resistance for these compounds will occur sooner or later. It is also hard to imagine that a new antibiotic compound (for example a second generation aminoglycoside) will drastically change the treatment landscape, as new antibiotics will not be introduced as first line agents in standard care. Rather, they will only be used as second line or as a last resort antimicrobial agents.

Scope of this thesis

The aim of this thesis was to stimulate rational and effective use of antimicrobials, by addressing the first two cornerstones: (1) refining stewardship of existing antimicrobials and (2) re-introducing old antibiotics within the framework of antimicrobial stewardship.

The overall aim is to contribute to antimicrobial stewardship and to explore the value of the re-introduction of old antibiotics that are currently scarcely used. The basic step is the *in vitro* relationship expressed as minimal inhibitory concentration (MIC) for a given bacteria for a given antibiotic. The next step is the *in vivo* situation. This thesis concentrates on the *in vivo* situation.

OUTLINE OF THIS THESIS

Refining stewardship of existing antimicrobials (chapters 2-5)

Chapter 2 and **chapter 3** describe studies on the proper use of the small spectrum oral antibiotic, flucloxacillin, which is known to have variable absorption. Flucloxacillin, first described in 1970,[34] is used to treat infections caused by *Staphylococcus (S.) aureus* strains. It is used empirically for presumed staphylococcal infection in countries, including the Netherlands, that have documented low rates of methicillin-resistant *S. aureus* (MRSA) strain.[35] In case of severe systemic staphylococcal infections flucloxacillin treatment is usually started intravenously, followed by prolonged oral administration. Since absorption of orally administered flucloxacillin is variable and unpredictable, absorption tests have been recommended. For this purpose we designed a simplified absorption test. This new test was compared with the original absorption test (**chapter 2**) and the next step was to validate the new test in a much larger patient population (**chapter 3**).

Chapter 4 describes studies on the absorption of orally administered penicillin, another small spectrum agent with a highly variable and unpredictable absorption profile.

Chapter 5 describes a new method for simplified therapeutic drug monitoring (TDM) for the long-term oral use of rifampin. Rifampin is notorious because it quickly develops resistance as a result of many factors, including underdosing. Universal testing to assess the absorption of oral rifampin seems to be necessary but remains elusive in many low to middle income settings where most new cases of tuberculosis occur. However, the simplified absorption test may be of value in such settings as well as in developed countries including the Netherlands.

Re-introducing old antibiotics within the framework of antimicrobial stewardship (chapters 6-10)

Chapter 6 presents a detailed review of the old polymyxin class drug colistin. In brief, colistin was isolated in 1949 from the *Bacillus polymyxa 'colistinus'* and became available for clinical use in 1959, but was largely replaced by other agents after only two decades. The increasing resistance to antibiotics led clinical investigators to reconsider the position of colistin, with emphasis on the impact of the reported adverse events and strategies against colistin resistance.[36-37]

Chapter 7 describes the results of a study on the chemical stability of colistin over time, which is relevant for long term infusion therapy at home, e.g., for cystic fibrosis patients with chronic pulmonal infections, especially with *Pseudomonas aeruginosa*.

Chapter 8 is a review about fosfomycin, which was discovered in 1969.[30] Fosfomycin has a broad spectrum of activity, including multi-drug resistant bacteria. In the Netherlands, fosfomycin has long been registered as an oral formulation prescribed for the treatment of uncomplicated urinary tract infection, while intravenous administration was only recently approved.

Chapter 9 evaluates different fosfomycin dosing regimens for the treatment of systemic infections. In this chapter a new pharmacokinetic model for dosing of fosfomycin is described.

Chapter 10 describes a study on the kinetics of fosfomycin after an oral and intravenous dose of 3 gram in patients suffering from urine tract infections with multi-drug resistant strains of the species *Escherichia coli*.

Chapter 11 provides a summary and general discussion of the findings and implications of the studies described in this thesis, as well as some suggestions for antibiotic stewardship and future research.

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TABLE 1 Examples of inappropriate use of antibiotics.*

Type	Example
Overuse	• Prescribing antibiotics for viral infections • Prescribing antibiotics for non-infectious processes (eg febrile patient with pancreatitis) • Treating minor bacterial infections that do not require antibiotics (eg small skin abscesses that resolve with incision and drainage) • Treating bacterial colonisation (eg positive catheter urine culture from an asymptomatic older patient) • Prescribing prolonged treatment courses (eg >24 hours for low-risk surgical prophylaxis)
Misuse	• Use of broad-spectrum antibiotics effective against multidrug-resistant organisms in a patient with a community-acquired infection • Failure to de-escalate broad-spectrum antibiotics according to culture results • Failure to adjust antibiotic prescription according to culture results when the isolated organism is resistant to initial therapy
Underuse	• Inadequate dosing of antibiotics • Premature discontinuation of antibiotics • Delay to prompt treatment of severe sepsis • Failure to prescribe an antibiotic regimen with an adequate spectrum of activity in a patient with a life-threatening infection
Abuse	• Prescribing antibiotics for financial incentive • Prescribing particular antibiotics as a result of pressure from a pharmaceutical industry representative

** Hand K., Antibiotic stewardship, Clin Med 2013, vol 13,499-503*

TABLE 2 Examples of hospital antibiotic stewardship interventions.*

Type of intervention	Example
Governance structures	• Organisational strategy for antibiotic stewardship • Antibiotic prescribing policy (statement of principles of responsible prescribing and expected quality standards), which may include: – 48-hour review – intravenous-to-oral switch – automatic stop orders (termination of prescriptions after a specified interval unless authorisation to continue obtained) – compulsory order forms (prescribers required to complete a form with clinical details to justify use of restricted antibiotics) – expert approval (prescriptions for restricted antibiotics authorised by infection specialist or head of department) – dedicated antibiotic prescription chart – removal by restriction (restrictive policy imposed in target wards, units or operating theatres – eg by removing restricted antibiotics from drug cupboards) – therapeutic substitution (pharmacists authorised to substitute alternative antibiotics) – antibiotic cycling and rotation policy – mixing, diversity and heterogeneous prescribing policy • Antibiotic stewardship committee (including medical microbiologist or infectious diseases physician, specialist pharmacist and information analyst)
Operational delivery	• Antibiotic formulary – may incorporate limited list of antibiotics subject to prescribing restrictions such as requirement for preauthorisation • Guidelines for initial treatment of common infections (evidence based, peer reviewed and informed by local resistance data where possible) • Guidelines for perioperative prophylaxis for common surgical procedures • Reminder systems (eg preprinted adhesive labels for medical case notes) • Computerised physician order entry (electronic prescribing) – may incorporate computerised decision-support systems • Mobile device software applications for point-of-care information and guidance
Risk management	• Guidelines for management of infection in patients with allergy to antibiotics • Information on safe administration of intravenous antibiotics • Guidelines for dosing and monitoring of serum levels of toxic antibiotics
Clinical microbiology/ infectious disease specialist and laboratory support	• Validation and interpretation of microscopy, culture and susceptibility results for laboratory reporting • Surveillance and reporting of trends in antibiotic resistance • Telephone consultation for advice on infection management • Bacteraemia follow-up service • Antibiotic stewardship ward rounds • Point-of-care rapid tests for bacterial infection • Advanced sepsis biomarkers (eg procalcitonin)
Controls and quality assurance	• Surveillance of antibiotic prescribing trends • Public reporting and benchmarking of antibiotic consumption data (eg World Health Organisation-defined daily doses) • Audit and feedback of adherence to prescribing policy • Audit and feedback of adherence to guidelines
Education and training	• Induction training on antibiotic stewardship • Revalidation training • Distribution of printed educational materials (eg pocket guidelines and patient information leaflet) • Educational meetings • Electronic learning • Antibiotic prescribing competency assessment • Academic detailing or educational outreach (one-on-one educational intervention) • Nominated clinical champions for antibiotic stewardship • Provision of patient information and counselling

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