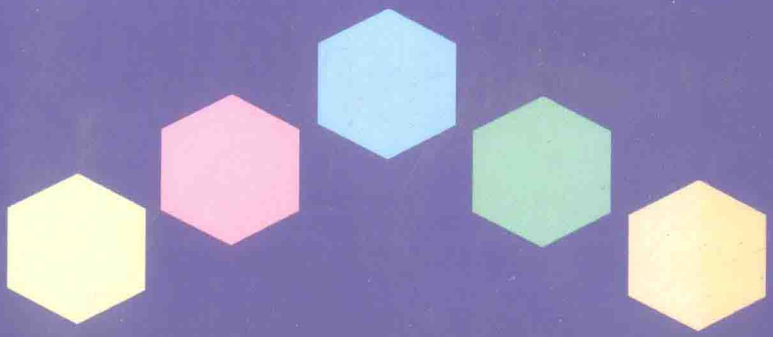
WHO MODEL PRESCRIBING INFORMATION

DRUGS USED IN BACTERIAL INFECTIONS



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WHO Model Prescribing Information

Drugs used in Bacterial Infections

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Preface

WHO's revised drug strategy, as adopted in resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information which is being developed to complement WHO's Model List of Essential Drugs.[1] The objective is to provide up-to-date source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.[2]

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO's Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

This volume has been reviewed by internationally accredited experts and by certain nongovernmental organizations in official relations with WHO, including the International Federation of Pharmaceutical Manufacturers Associations, the International League of Infectious Diseases and the International Society of Chemotherapy.

[1] *The use of essential drugs. Ninth report of the WHO Expert Committee (including the revised Model List of Essential Drugs).* Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 895).

[2] For details of volumes already published, see inside back cover.

Drug dosage

Most drug doses are given per kilogram of body weight or as fixed doses calculated for adults of 60 kg.

Storage conditions

Readers are referred to *The International Pharmacopoeia*, 3rd edition, Vol. 4 (Geneva, World Health Organization, 1994) for definitions concerning containers for drugs.

Abbreviations used

i.m. intramuscularly
i.v. intravenously

Introduction

Although many communicable diseases have been effectively contained, bacterial infections remain a major cause of morbidity and mortality, particularly in developing countries. Moreover, in both developed and developing countries, the risk of some serious bacterial infections has increased because of treatments such as chemotherapy for cancer and the emergence of diseases such as human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS), which impair the patient's defences against infection.

Antimicrobials have reduced the morbidity and improved the survival of patients with bacterial infections and remain essential for the treatment of many kinds of bacterial disease. However, the increasing prevalence of strains of common pathogenic bacteria resistant to widely available, affordable antimicrobials is, in many cases, dangerously eroding their effectiveness. It is hoped that by encouraging the appropriate use of antimicrobials, the emergence and spread of antimicrobial resistance may be delayed.

Resistance to antimicrobials

The prevalence of antimicrobial resistance among pathogenic bacteria is increasing both among hospital patients and in the community. The emergence of such resistance may in part depend on the acquisition of new mechanisms of interference with antimicrobial activity and on the spread of resistant isolates between patients.

Selection of resistant bacteria

Resistance may be due to the following mechanisms:

- *Transfer of genes containing DNA coding for antimicrobial resistance located either on plasmids or on transposons.* Enteric bacteria are a common source of such genes, which have appeared in many species, including *Neisseria gonorrhoeae* and *Haemophilus influenzae.*

- *Spontaneous mutation of bacteria.* Selection of resistant variants allows a pre-existing resistant strain to emerge following treatment with an antimicrobial agent acting against susceptible organisms. For example, patients with staphylococcal infections treated with rifampicin alone often develop resistant staphylococcal isolates within a few days. A minor proportion of enteric bacteria may be resistant strains capable of producing high-level β-lactamases which are readily selected by cefalosporins, broad-spectrum penicillins and monobactams. Some bacterial species are heterogeneously resistant to fluoroquinolones and can, consequently, be selected by the drugs.
- *Antimicrobial-induced effects on the normal microflora.* Treatment with antimicrobials results in susceptible species becoming less common and naturally resistant species more frequent. Genes responsible for such resistance among species of the normal flora can be transferred to pathogens causing infections. It is thought that penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci arose by such a transformation.

The selection of resistant bacteria is minimized by adherence to a few basic principles:

— use antimicrobials that are most appropriate for the cause of infection and the prevalence of local resistance;
— use adequate doses;
— ensure that the treatment course is completed.

For most bacterial infections a single antimicrobial is all that is required. However, in some circumstances combination therapy with two or more agents with different mechanisms of activity may be needed to minimize the emergence of resistance among certain species — for example in the treatment of infections caused by *Mycobacterium tuberculosis.*

Spread of resistant bacteria

The spread of antimicrobial-resistant bacteria was once considered to be mainly a problem associated with poor hygiene in hospitals. Poor hygiene contributes to the spread of resistant strains of bacteria, as has been demonstrated by reports of hospital-acquired (nosocomial) infections over recent years.

The introduction of a number of hygienic measures, including improved facilities for hand-washing, isolation of patients with multiresistant bacteria and improved aseptic techniques for invasive procedures has reduced the spread of pathogenic bacteria in hospitals.

The spread of antimicrobial-resistant strains in the community has presented problems in the treatment of infections of the respiratory tract, gastrointestinal tract, urinary tract, skin and soft tissues as well as in the treatment of some sexually transmitted diseases and meningitis. In many communities it is difficult to maintain hygienic procedures. Childhood infections are common in the community because transfer of microorganisms occurs readily. Antimicrobial-resistant bacteria are also readily spread by and between children.

The breakdown of infrastructure that frequently occurs in situations of armed conflict, famine and economic crisis also leads to outbreaks of infection. Such outbreaks are increasingly caused by bacteria with acquired resistance to antimicrobials.

Although hygienic measures are the main method for controlling the spread of antimicrobial-resistant as well as antimicrobial-susceptible bacteria, inappropriate use of antimicrobials also needs to be addressed. Inappropriate uses include the administration of antimicrobials when their use is not indicated and use of antimicrobials to which the pathogens are already resistant. The use of inappropriate antimicrobials, suboptimal doses, the wrong duration of treatment and excessive use of one particular class of drugs will also increase the prevalence of resistance. Problems such as uncontrolled access to antimicrobials and varying quality of some products may also increase the prevalence of resistance.

Role of laboratories in antimicrobial susceptibility testing and reporting of surveillance data

The majority of bacterial infections are treated on the basis of a presumptive etiological diagnosis determined by the clinical history and physical findings. Empirical therapy should be

based on local epidemiological data on likely pathogens and their patterns of antimicrobial susceptibility. For this reason, capacity for testing the antimicrobial susceptibility of priority pathogens, including those causing infection in the community, should preferably be available in several laboratories in different geographical locations in all countries. As a minimum, testing must be carried out in a national reference laboratory. Data should be collected on *Staphylococcus aureus*, *Pseudomonas aeruginosa* and Enterobacteriaceae. Information about community-acquired infections is usually more difficult to obtain, but data should be collected on *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli* and *Salmonella* and *Shigella* spp. A limited range of antimicrobials is important for different organisms. For *Streptococcus pneumoniae*, for example, information on resistance to benzylpenicillin, cefalosporins, sulfamethoxazole + trimethoprim, erythromycin and chloramphenicol has the highest priority. Information on antimicrobial resistance in *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* is also important.

Laboratories should apply internationally recognized methods of antimicrobial susceptibility testing and should ensure that the results are analysed and communicated appropriately in order that empirical treatment guidelines can be updated. There should be a well-functioning system of quality control in place. WHO has a software package (WHONET)[1] available to laboratories on request for epidemiological analysis of antimicrobial susceptibility data and can assist in the provision of laboratory training.

Not all infections require specific antimicrobial treatment and careful clinical judgement is essential to determine whether symptomatic treatment is sufficient. Microbiological investigations should always be carried out before treatment where possible when the etiology is uncertain, in severe infections when patients fail to respond to empirical therapy or develop a new infection during the course of treatment, or for public health purposes. Appropriate specimens for Gram-staining, culture

[1] Available on request from Anti-infective Drug Resistance and Containment, Communicable Disease Surveillance and Response, World Health Organization, 1211 Geneva 27, Switzerland.

and susceptibility testing should be obtained before starting antimicrobial therapy. In many situations microbiological identification of the pathogen is vital to determine the appropriate antimicrobial treatment. In contrast, group A β-haemolytic streptococci are routinely susceptible to benzylpenicillin and phenoxymethylpenicillin, making mandatory susceptibility testing unnecessary.

General principles of antimicrobial prescribing

Spectrum of activity

Ideally, the antimicrobial susceptibility of an organism should be known and the most effective and safe agent targeted to the infection should be used. This reduces the likelihood of selection of resistant microorganisms and superinfection. However, in most cases the suspected organism is assumed to be susceptible to a particular antimicrobial because of its known characteristics from surveillance data.

Pharmacokinetics and pharmacodynamics

The pharmacokinetics and pharmacodynamics of an antimicrobial are determined by three factors: the serum half-life, its distribution in the body tissues and fluids (e.g. cerebrospinal fluid) and its accumulation in phagocytic cells. The dosage should be consistent with the drug's half-life (e.g. a single daily dose for drugs with a serum half-life of 10–20 hours). Drugs that achieve high intracellular levels are necessary for infections with intracellular pathogens such as *Chlamydia* and *Legionella* spp. and *Coxiella burnetti*. For most infections the concentration of drug in the infected site (e.g. interstitial fluid, urine) is a key pharmacokinetic parameter. Binding of a small fraction of the drug to serum proteins contributes to the achievement of high extravascular concentrations; conversely, serum protein binding levels above 80–85% have an impact on passage from the blood to extravascular compartments, but are not per se indicative of tissue concentrations below therapeutic levels. In patients with renal or hepatic impairment, reduction of the dose may be required.

Oral versus parenteral administration

Antimicrobials should be administered by the most appropriate route in an optimum dose, since inadequate plasma levels

may lead to the development of resistance. Some clinical circumstances (e.g. patients who are severely ill or who have collapsed, or those with impaired bowel function) may require the use of parenteral antimicrobials. The excellent absorption of many oral antimicrobials (including β-lactams, chloramphenicol, doxycycline and fluoroquinolones) and the associated cost-benefits make oral administration usually the most appropriate form of antimicrobial therapy.

Adherence and ease of administration

Oral formulations are more convenient, generally cheaper and associated with less adverse effects than parenteral ones. Parenteral formulations also require trained medical staff for their administration and can have specific adverse effects not seen with orally administered drugs. Oral drugs with fewer doses are preferred. The appropriateness of the choice of drug for individual patients also depends on factors such as the patient's age, the presence of underlying disease, renal or liver impairment or allergies, concurrent therapy and whether the patient is pregnant.

Impact on normal microbial flora

If two antimicrobial agents have similar probable cure rates, cost and tolerance in a particular case, the agent having the least deleterious impact on the normal human microbial flora should be chosen. This may reduce or prevent adverse effects such as antimicrobial-associated diarrhoea and vaginal superinfections with *Candida* spp.

Cost of treatment

The drug with the lowest cost is preferred if efficacy, adherence and tolerance are comparable. However, the cost of the total treatment, and not only the unit cost of the drug, must be considered.

Antimicrobial combinations

In certain clinical settings it may be necessary to use two or more antimicrobials to achieve the desired effect. The common indications for combination therapy are:

- to obtain antimicrobial synergy (i.e. an effect unobtainable with either drug alone);

- to delay the development of resistance;
- to broaden the spectrum of antimicrobial activity against an infection of unknown etiology or involving more than one species.

Effect of commercial promotion

Individuals responsible for prescribing drugs and drug committees are commonly subject to commercial promotion in making choices about antimicrobials. Objective data and evidence of clinical efficacy should provide the basis for decisions for including antimicrobials in drug formularies.

Drug formularies

The list of antimicrobials to be included in the drug formulary of an institution should be established by consensus among the users in the institution represented in the drug committee (e.g. physicians, pharmacists, clinical pharmacologists, microbiologists and nurses). For each particular antimicrobial, the clinical indication (therapeutic, prophylactic or empirical) and the dosage (for adults, children and, if appropriate, patients with hepatic or renal impairment) must be mentioned. Objective information should be distributed by the committee, based on data from the manufacturer and independent drug information. The committee should conduct periodic evaluations of the functioning of the formulary.

Choice of antimicrobial and options for treatment

In this book, the recommendations for initial empirical treatment of infection are based on current knowledge of the prevalence of antimicrobial resistance. Most infections are treated initially on the basis of clinical evidence, without full knowledge of the causative organism or its susceptibility. As the prevalence of resistance varies considerably from one community to another, the recommendations are presented as a series of options. The local choice of an option for treatment will be influenced by the prevalence of resistance (where known), the availability and tolerability of the antimicrobial, and the cost of a full course of treatment. The range of antimicrobials listed in this book conforms, in the main, to the WHO Model

List of Essential Drugs[1] and to other recent publications by WHO.[2–5]

Rational use of the many different classes of antimicrobials depends on the points discussed above. Because of the inconsistent availability of drugs and the variation in the needs of patients — in turn a result of differences in age, hypersensitivity and factors influencing metabolic fate in the body — options are given rather than a single "best choice". The range of antimicrobials is wide but most conditions can be managed using well-established drugs rather than the newest ones.

Some institutions restrict certain antimicrobials as "reserve" agents. A reserve antimicrobial is one that is useful for a wide range of infections but, because of the need to reduce the risk of development of resistance and because of its relatively high cost, it would be inappropriate to recommend its unrestricted use. The drug should be included in the drug formulary of the institution with the clinical indications clearly defined and be made available without delay when needed. It should have restricted availability and be prescribed only under the supervision of a senior medical officer. Within this context the β-lactam drugs, the fluoroquinolones and vancomycin are particularly important.

β-Lactam antimicrobials

Resistance to β-lactam antimicrobials is generally due to the production of β-lactamases in staphylococci, enterobacteria, *Haemophilus* spp., gonococci and *Pseudomonas* spp. In several of

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[1] *The use of essential drugs. Ninth report of the WHO Expert Committee (including the revised Model List of Essential Drugs).* Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 895).

[2] *WHO model prescribing information: drugs used in sexually transmitted diseases and HIV infection.* Geneva, World Health Organization, 1995.

[3] *WHO Expert Committee on Malaria. Twentieth report.* Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 892).

[4] Gilles HM. *Management of severe malaria: a practical handbook*, 2nd ed. Geneva, World Health Organization, 2000.

[5] *The use of artemisinin and its derivatives as antimalarial drugs: report of a Joint CTD/DMP/TDR Informal Consultation, Geneva, 10–12 June 1998.* Geneva, World Health Organization, 1998 (unpublished document WHO/MAL/98.1086; available from Communicable Disease Research and Development, World Health Organization, 1211 Geneva 27, Switzerland).

these species and in others such as *Streptococcus pneumoniae* and enterococci, non-enzymatic mechanisms also occur. Many new β-lactam antimicrobials are included in the WHO Model List of Essential Drugs as reserve antimicrobials. In order to preserve the activity of these antimicrobials it is recommended that these agents are used only where rates of resistance to all normally appropriate essential drugs are high or for specific indications, as listed below.

The β-lactamase inhibitor amoxicillin + clavulanic acid is resistant to degradation by many of the enzymes produced by enterobacteria and *Bacteroides* spp. A specific indication for its use is in polymicrobial infections related to surgical conditions of the intestinal tract and female genital tract. Amoxicillin remains active against many common bacteria such as β-haemolytic streptococci and a high proportion of strains of *Haemophilus influenzae* in many countries. The emergence of strains of *Streptococcus pneumoniae* with reduced susceptibility to penicillins does not at this time justify replacement of this group of antimicrobials for the treatment of respiratory tract infections.

Many parenteral cefalosporins active against Gram-negative and Gram-positive bacteria are now widely used for the treatment of infection. WHO's Model List of Essential Drugs includes ceftriaxone as a reserve agent for the treatment of meningitis due to *Streptococcus pneumoniae* in areas where the incidence of resistance to penicillins is high. It has been listed as an example of a therapeutic group because the results of clinical trials indicate that cefotaxime is equally effective and may be preferred in some hospitals or treatment centres. Ceftriaxone is specifically recommended for the treatment of gonorrhoea and chancroid where resistance to other antimicrobials is common. At its eighth meeting in 1997,[1] the WHO Expert Committee on the Use of Essential Drugs noted that several other cefalosporins such as cefuroxime are widely used for chemoprophylaxis in surgery and for the treatment of respiratory infections. These cefalosporins are not as effective as ceftriaxone or cefotaxime in the treatment of meningitis due to

[1] *The use of essential drugs. Eighth report of the WHO Expert Committee.* Geneva, World Health Organization, 1998 (WHO Technical Report Series, No. 882).