

Antibiotic Guidelines : Pharmacological Parameters to be Considered

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Abstrak

Tujuan pedoman penggunaan antibiotik adalah untuk membimbing penggunaannya secara rasional, sehingga antibiotik digunakan secara efektif dan efisien dengan efek samping sekecil-kecilnya bagi penderita dan masyarakat. Tindakan ini juga berdampak mengurangi biaya tanpa mengorbankan penderita/masyarakat terhadap pemilihan antibiotik yang salah. Pedoman ini harus memenuhi persyaratan tertentu agar dapat diterima oleh pemakainya dan berlaku bagi sebagian besar (kira-kira 90%) kelompok penderita. Antibiotik terpilih yang diusulkan harus efektif tanpa adanya hasil antibiogram. Pedoman ini harus berdasarkan pengetahuan mikrobiologi, farmakologi dan klinik. Parameter farmakologi yang akan dibahas antara lain adalah farmakodinamik, farmakokinetik, efek toksik dan efek samping, hasil uji klinik, percobaan epidemiologi obat serta farmakologi perbandingan antibiotik. Strategi pemilihan terutama berdasarkan penerapan rasio manfaat-risiko serta biaya; manfaat antibiotik yang diperkirakan untuk indikasi tertentu harus lebih besar dari kemungkinan risiko yang dapat ditimbulkannya. Prinsip "Primum non nocere" haruslah merupakan pertimbangan utama. Antibiotik sering menimbulkan efek samping dan karena pemberiannya perlu bertujuan jelas. Menganggap bahwa "bila tidak berefek tentunya tidak berbahaya" tidaklah benar. Pedoman bukanlah suatu aturan yang kaku; pertimbangan ilmiah harus selalu merupakan petunjuk akhir, terutama pada keadaan klinik yang kompleks. Pedoman pemilihan antibiotik perlu diperbaharui terus menerus bilamana ada informasi yang baru. Lazimnya tidak perlu ada sanksi terhadap penyimpangan kecil dari pedoman yang ada, namun penyimpangan jauh dari suatu pedoman memerlukan dasar ilmiah yang jelas.

Abstract

The aim of antibiotic guidelines is to provide guidance on the rational use of antibiotics, so that they serve effectively and efficiently with the least adverse effects on patients and community. The impact of such strategy may also be seen in the containment of cost without jeopardizing the patient to unsuccessful attempts of antibiotic treatment. Guidelines have to satisfy certain requirements in order to be accepted by its users. It should work for the majority (approx. 90%) of patient groups and the antibiotic selections suggested should be effective without or before the results of antibiograms. Antibiotic guidelines must be based on microbiological, pharmacological and clinical knowledge. Among pharmacological parameters of the antibiotic that will be discussed are pharmacodynamics, pharmacokinetics, toxicity and adverse effects, results of clinical trials and drug-epidemiological studies, and the comparative pharmacology of antibiotics. The main strategy for selection is based on benefit-risk-cost assessment; the presumed benefit that the antibiotic could offer for a certain indication should be greater than the possible risks it could give rise to. The principle of treatment: "Primum non nocere" should always be a prior consideration. In this respect the great potential of antibiotics to cause adversity is very often overlooked, causing the erroneous attitude of "if it does not work, it does not harm either". Guidelines are never meant to be rigid rules; scientific judgement should always be the final guide, especially in complicated clinical conditions. Renewal of choices of antibiotics should be instituted whenever recent information is available and updating of an antibiotic guideline is mandatory every year or two. Usually there are no sanctions for violating good advice, but major deviations from guidelines must be scientifically justifiable.

Keywords : Antibiotic use, Antibiotic selection, Rational use

INTRODUCTION

The aim of guidelines for antibiotic-use is to provide guidance on the rational use of antibiotics, so that they serve effectively and efficiently with the least adverse effects on patients and community, and that resistance

of microorganisms could be minimized.^{1,2} The impact of such strategy may also be seen in the containment of cost without jeopardizing the patient to unsuccessful antibiotic treatment.

Antibiotic guidelines set general guidance on how antibiotics should be correctly used. It gives sugges-

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tions on the best antibiotic choice (s) available for the treatment and prophylaxis of bacterial, fungal and parasitic infections.³

Guidelines have to satisfy certain requirements in order to be accepted by its users. It should work for the majority of patient population and the antibiotic selections suggested should be effective without or before the results of sensitivity testings. The majority of infections in fact may be treated without the necessity of doing any culture of an infected biological specimen. Therefore antibiotic guidelines must be based on the integration of microbiological, pharmacological and clinical knowledge; the results of clinical trials and epidemiological studies especially should determine the validity of the selections made. Not to be underestimated is the value of a correct diagnosis before prescribing an antibiotic in order to distinguish the real needs for eradicating or preventing an infection. Furthermore, guidelines should be updated or renewed whenever new knowledge becomes available.

GENERAL CONSIDERATIONS

Among pharmacological parameters that are important to be considered are : pharmacodynamics, pharmacokinetics, toxicity and adverse effects of the antibiotic under scrutiny, site of infection, special effects on high risk patient group in relation to the antibiotic being considered, results of clinical trials, drug-epidemiological studies, and above all, the comparative pharmacology of all antibiotics, especially of those belonging to the same class.

The main strategy for selection of a treatment is based on benefit-risk-cost assessment; the presumed or calculated benefit that an antibiotic could offer for a certain indication should be greater than the possible risks it could give rise to. The principle of treatment : "*Primum non nocere*", which broadly means "do not harm when treating patients", should always be a prior consideration. Cost should only be decided after all scientific judgements have been made and treatment-cost should be put before drug-unit-cost. When two or more antibiotic selections can be made with more or less similar predicted outcome, then cost should be the determining factors.

As for each guideline, it never should be considered as rigid rules; sound scientific judgement and a scientifically based selection for using antibiotics should always be the final guide. But, major deviations from guidelines must be scientifically justifiable, because good guidelines should apply for the majority of subjects for whom the guidelines are developed. Guidelines also should take into consideration the level

of competence of the health service and prescriber for which it is meant; while gentamicin is a good antibiotic to be used in a hospital setting where the close observation of the patient is needed and where monitoring of antibiotic blood levels may be determined, in a primary health setting it may be dangerous.

PHARMACODYNAMIC PARAMETERS

Antibiotics are usually chemicals with no or little pharmacodynamic properties; they do not exert significant actions on the organs of the host. This is a good characteristic of an antibiotic, because they preferably should only have killing properties on the invading microorganisms without doing harm by stimulating or inhibiting other receptors of the host. Some antibiotics however, may have actions on intact human organs or give rise to effects that are adverse in nature, and as such may limit the use or dose of an antibiotic. Examples of such antibiotics are the aminoglycosides that inhibit neuromuscular conductions when administered in high doses. This curariform-like effect is seen with streptomycin, kanamycin, gentamicin, neomycin, and probably other aminoglycosides in high doses. When used with other muscle relaxants this effect will even be enhanced. Circumoral paresthesia is also well-known with drugs like streptomycin; and vestibular dysfunction occurs with relatively high therapeutic doses.

Other reactions may be seen with antibiotics, such as bone-marrow depression with chloramphenicol or cephalosporins, hypoprothrombinaemia with moxalactam, etc. These may not be regarded as pharmacodynamic because they occur seldom and are only seen with very high doses or are a result of idiosyncratic reactions and are therefore unpredictable for any given patient. Phenotyping and genotyping of the way individuals do metabolize certain drugs may in the future determine which patient would be prone to the above mentioned adverse effects.^{4,5}

The pharmacodynamic effects on the microorganisms are reflected in the eradicating properties of the antibiotic itself; they may be bactericidal or bacteriostatic. The degree of eradicating abilities may be expressed by the minimum inhibitory concentrations (MICs) of the antibiotic. While this simple in vitro test is an important parameter, it may not be used as the single determinant to select an antibiotic for therapeutic or prophylactic purposes, because in vivo conditions do not always produce the same results. The clinical evaluation of the patients must always be taken into account.

An important point for consideration is the destructive specificity for each antibiotic class; they

may be divided into groups of microorganisms. Thus there are antibiotics that mainly attack Gram positive bacteria such as benzylpenicillin, phenoxymethylpenicillin, cloxacillin or flucloxacillin, erythromycin, spiramycin, and other macrolides. The fluoroquinolones are more specific against Gram negative bacteria and although it may be active against Gram positive cocci, it is not to be used when the narrow spectrum antibiotics are sensitive to it and therefore fluoroquinolones are not recommended as the first choice for definite Gram positive infections such as streptococcal or staphylococcal. In a group however the antibiotics may have individual specific actions; gentamicin for instance would be more effective against pseudomonas than kanamycin, and the cephalosporins may have different emphasis on antibacterial activity according to the time of development of this class of drugs during the last 20 years.

PHARMACOKINETIC PARAMETERS

First it must be ascertained that the antibiotic chosen is absorbed by the proposed route and is available at the site of infection in the required concentration in its active form. Many antibiotics, although having an adequate MIC may not qualify for some of the other parameters mentioned and therefore may not produce clinically good results.

Orally available antibiotics such as macrolides (erythromycin, spiramycin, etc), lincomycin, certain beta-lactams like ampicillin and phenoxymethylpenicillin are incompletely absorbed. Despite their clinical usefulness it may not produce sufficient enough antibiotic concentrations in certain individuals to rely on in severe infections when given by mouth, especially when taken with food. Injectable dosage forms are most appropriate when high antibiotic levels are required immediately, such as in contaminated surgical prophylaxis.

Tissue levels of an antibiotic is an important parameter for clinical efficacy; some may show relatively high concentrations at the site of infection despite a low bioavailability (spiramycin, azithromycin). Chemical configuration of the antibiotic may determine this property; fat-soluble antibiotics, having higher affinity to tissue, will pass cell-membranes and the blood-brain at greater ease (clindamycin versus lincomycin).

Other important pharmacokinetic parameters are : speed of absorption, peak and trough levels, concentration half-lives, formation of active metabolites, and pathways of excretion.

SPECIAL PRECAUTIONS

There are special precautions that need to be taken when choosing antibiotics in patients with the following characteristics :

- * the premature babies and the geriatric patients
- * child-bearing women and nursing mothers
- * organ deficient patients, especially organs of excretion (liver, gastrointestinal tract, and kidney)
- * specific diseases
- * patients who are on concomitant treatment with drugs that are incompatible with the antibiotic given.

ADVERSE EFFECTS OF ANTIBIOTICS

Although antibiotics may be life-saving when needed, it may produce adverse effects that are not to be disregarded. These side effects rank among the highest in frequency of all drug classes. It may therefore minimize the usefulness of the antibiotics prescribed. Adverse reactions varying from skin rashes, nausea and abdominal discomfort (the most frequent) to blood dyscrasia, hepatitis and fatal anaphylactic reactions are well known. The propensity of one antibiotic giving more frequent adverse reactions than another should be taken into account in the selection process.

An important fact to be considered is the frequency of use of a certain antibiotic; the more frequent it is used the more adverse reactions it will elicit. Assuming the incidence rates of adverse reactions to a certain antibiotic to be constant, the absolute number of cases will therefore increase and become noticeable as the antibiotic is used more frequently. Two examples may highlight this statement. When in earlier years penicillin G procaine injections were so common that almost every other patient got a penicilline shot, anaphylactic reactions were rampant. Although most of these injections were grossly inappropriate and therefore did only contribute falsely to cure, this practice went on for more than 2 decades. Some cases with fatal outcome at last brought a drastic change because of cases of litigation. Although it strangely ended with the verdict "not guilty", the practice of penicillin injections disappeared and now 70% of primary health centres do not even use penicillin any more,⁶ a phenomenon to be deplored. This suggests that if antibiotics were used more appropriately, fewer patients would have been eligible for penicillin injections with a resultant decrease in the number of adverse effects. The opposite happened with flucloxacillin; a total of 179 cases of hepatitis associated with the use of flucloxacillin has been reported to the Australian Drug Adverse Reaction Committee until June 1992.^{7,8} This drug has been

widely promoted in the Australian Antibiotic Guidelines³ as the drug of choice against staphylococcal infections. The resultant steep increase of its use has caused a drastic rise of flucloxacillin associated hepatitis which in turn might not justify the benefit-risk equation for using flucloxacillin routinely any more. The indication for flucloxacillin use has recently been limited to include only *severe* staphylococcal infections, and caution was mandated when prescribing the drug for older people or when the drug is used for more than 14 days.

RESULTS OF CLINICAL TRIALS

The results of clinical trials are the ultimate "proof of the pudding", that the antibiotic is efficacious for a specific indication. However, the accessibility of the results on several clinical trials to make an informed judgement on the profile of an antibiotic is usually scarce. The information is scattered in many journals and contradictory results are difficult to unify, not the least because of the industry's promotional activities in the form of seminars and literature. Evaluated textbooks should give an objective view on the problem. The American Medical Association's Drug Evaluations⁹ is an annual which is an objective guide for selecting drugs including antibiotics; it describes drug classes and individual drugs. Another book entitled *Therapeutic Drugs*¹⁰ is monograph that has been published recently; each monograph deals, among others, with "Major outcome trials" which describes in a nutshell the results of important clinical studies. The generalizability or external validity of such trials, however, are sometimes difficult to assess. Therefore antibiotic guidelines would be very useful in the everyday application of these potent drugs. Studies, involving larger populations, such as in drug epidemiological research are also valid to supplement the smaller scale clinical trials.

LEGAL ASPECTS OF AN ANTIBIOTIC GUIDELINE

The status of a scientific guideline should necessarily deal with scientific issues. Some may have the idea that a guideline of this sort should also be the standard of measure when one is confronted with legal implications when deviations from it become a matter of dispute in a litigation case.

We must emphasize that the legality for such purpose cannot be fully attributed to an antibiotic guideline or any other treatment guidelines. Treatment modalities are a complex subject and adhering simply

to a guideline may sometimes be erroneous when one is confronted by a complex situation or ramification which necessitates one to deviate from a guideline. It may however not be assumed that a guideline can be violated any time for invalid reasons. One may reasonably speculate that a guideline works for the majority (90% or more) of cases, but if one departs substantially from it there must be valid reasons to justify one's choice. In a court case where drugs might have caused injury or death to a patient, there will usually be one or more experts who will testify whether the treatment had caused the injury. But even then it is not easy to establish causality as it was exemplified by the "Bendectin case" recently in an American Courtroom.¹¹ Bendectin is an antihistaminic used against vomiting in early pregnancy that was on the American market from 1956 until 1983, when it was banned because of accusations that it may have caused phocomelia in 2 cases. The Court accepted only peer reviewed journals as "good science" and in 1991 a California appeals court rejected the parent's suit. This was challenged by other scientists and the Supreme Court will reopen the case at the time of this writing. The problem becomes more entangled because of the involvement of the notorious American lawsuit on health related matters and not the least, the statement made that " 'experts' will testify to anything, for a price".¹¹

QUICK REFERENCE FOR ANTIBIOTIC INDICATIONS

It may be useful to design a quick reference in a table-form in which diseases are matched with the appropriate antibiotics. Table 1 depicts such a guidance; a first and subsequent choice is provided to accommodate for situations in which the first one cannot be used. This gives a first impression on what to use routinely before going into the details of the clinical condition. It will serve the reader with a useful antibiotic to start with, which is correct according to the authors' view at the time of this publication. It must be emphasized however that in making the final judgement, many of the above mentioned parameters should be taken into consideration. This guideline should be used in conjunction with other (authoritative) literature so that nuances caused by individual conditions of the patient can be accommodated.

There are certain general principles that are incorporated into this model guideline, some of them are :

- a. When antibiotic treatment has been initiated before an antibiogram is made and clinical improvement has been demonstrated clearly, it would be advisable

Table 1. Antibiotic Choice In Selected Infections*

Infection	Microorganism (s) Involved	First choice	Subsequent choice
Endocarditis, bacterial; acute subacute	Staph., strep, enterococci Striviridans, enterococci	pen.G + clox,+ gentamicin pen.G + gentamisin	vancomycin + gentamicin idem
Cystitis	E.coli, proteus, staphylococci	cotrimoxazole, ampicillin	nitrofurantion, fluoroquinolone
Pyelonephritis	coliform bact.	cotrimoxazole, ampicillin	fluoroquinolone
Gonorrhoea	N.gonorrhoeae	pen.G, ampicillin, ceftriaxone	erythromycin, doxycycline, fluoroquinolone
Urethritis, nonspec.	Chlamydia	tetracycline/doxycycline	erythromycin
Lymphogranuloma ven.	Chlamydia	tetracycline/doxycycline	sulfonamide, erythromycin
Infiltrate/furunculosis	Str.pyogenes, staphylococci	pen.G,erythromycin, (flu) cloxacillin	spiramycin, clindamycin
Erysipelas	Str.pyogenes	pen.G.	erythromycin, clindamycin
Impetigo	Str.progenes, Staph. aureus	pen.G, pen.V.	erythromycin, spiramycin, flucloxacillin
Infection.mouth/teeth	Aerob + anaerobic microorg.	pen V, pen G, erythro, macrolide	+ metronidazol (chronic infection)
Candidiasis, oral	Candida	mycostatin lozenges/suspension	amphotericin lozenges
Tonsillitis, acute	Streptococcuspen.G,	pen.V, erythromycin	spiramycin, clindamycin
Pharyngitis, acute	Virus (> 90%), Str.pyogenes	without antibiotic	pen.V, pen.G, erythromycin
Common cold, flu	Virus	without antibiotic	amoxycillin, erithromycin, doxycycline **
Measles	Virus	without antibiotic	amoxycillin, erithromycin, doxycycline **
Chicken pox	Virus	without antibiotic-bath regularly	amoxycillin, erithromycin, doxycycline **
Parotitis, epidemic	Virus	no antibiotic-chew on chewing gum	is most effective
Pneumonia : adult child	Str.pneumoniae H.influenzae	pen.G, erythromycin amoxycillin	chloramphenicol, clindamycin + aminoglyc chloramphenicol, cotrimoxazole
Otitis media	H.influenzae. streptococci	ampicillin	erithromycin, cotrimoxazole
Septicemia. intra-abdominal	Anything possible Coliform, Bacteroides	cephalosporin G3 (+ aminoglyc.) aminoglyc. + penicillin + metrinid.	clindamycin + aminoglyc clindamycin + cephalosporin G3
Tetanus	Cl.tetani	pen.G	clindamycin, chloramphenicol + metronid
Gas gangrene	Cl.perfringens	pen.G	clindamycin, chloramphenicol
Diphtheria	C.diphtheriae	pen.G	erythromycin
Diarrhea, nonspecific	Virus, food, or bacteria (rare)	without antibiotic - bismust salt	tetracycline (when bacterial [V.cholerael])
Typhoid fever	S.typhi, S.paratyphi	chloramphenicol, ampicillin	cotrimoxazole, fluoroquinolone

* Adapted from Katzung B, ed. Basic and Clinical Pharmacology, 4th ed., 1989:619-21, Gilman AG, Goodman LS, Rall TW, Murad F, ed. The Pharmacological Basis of Therapeutics, 8th ed., 1990, 1024-33, and Antibiotic Guidelines, 6th ed 1990-91, Health Department of Victoria, Australia.

** Only when secondary Infection is evident

- a. not to change the antibiotic initially used for another that was more sensitive according to the antibiogram results. These results may be used later when the first treatment fails.
- b. The local experience based on scientific judgement and the local sensitivity pattern of pathogens tested must be taken into account when making antibiotic selections. When recent sensitivity patterns are lacking, Table 1 may be used as a guide.
- c. Ampicillin may be interchanged with amoxycillin, while cloxacillin with flucloxacillin, without causing significant clinical outcome.
- d. Although penicillin G dan penicillin V have almost the same antibiotic spectrum, penicillin V should never be used for serious infections. Its action is too weak and absorption of the drug is limited, so that a high concentration in the blood cannot be attained.
- e. Different macrolides may be used interchangeably for the indication cited in the table. Although erythromycin is the prototype and is the most studied, it may cause unbearable gastric irritation for some patients. Other macrolides may be more tolerated by the stomach. It should always be given 1/2 an hour before meals to guarantee adequate absorption.
- f. Cotrimoxazole may be substituted by trimetoprim alone, especially in urinary tract infections. The sulfa component in cotrimoxazole gives rise to frequent and sometimes serious adverse reactions, while the efficacy of trimetoprim alone is not different.
- g. When mycostatin lozenges are not available, it may be substituted by drops or syrup or even tablets dissolved in a little water. This may be used as a

mouth-wash; the solution should be kept in the mouth for a few minutes.

- h. The viral infections listed in the table should normally not be treated with an antibiotic, but situations may arise where a patient may be having a complication with a bacterial superinfection each time he/she suffers from flu and in this case an antibiotic is well justified. Lately, epidemic parotitis have been treated with all kinds of antibiotics and isoprinosine. None of these are effective and the only sensible "treatment" is to give chewing gum to chew on, so that the movement of the jaws will open the canal of the parotis gland, thereby draining the contents. Patients with chick-enpox should also take a bath regularly with soap and water so as to keep the skin clean, preventing secondary infections. The use of potassium permanganate in the bath water is redundant.
- i. Fluoroquinolones may not be used in trivial conditions, and where other antibiotics are very effective, fluoroquinolones should be reserved when the first chosen antibiotic has failed to produce satisfactory results.
- j. Finally, guidelines have to be regularly updated.

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