CLEVELAND CLINIC QUARTERLY
Volume 37, January 1970

Printed in U.S.A.

Antibacterial therapy. I. Some general considerations in regard to strategy

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THE rational and effective use of antibacterial drugs involves many considerations.[1] All too often the drugs are administered indiscriminately or injudiciously, routinely rather than rationally, invariably rather than selectively, or hastily rather than with appropriate deliberation. Conversely, in patients with potentially curable infections, failures in therapy result all too frequently from incorrect choice of drugs, delay in initiation or from inadequate duration of therapy, improper dosage or route of administration, adverse reactions, and failure to correct underlying abnormalities that predispose to or complicate infection. This report concerns some general considerations in regard to selection and use of antibacterial drugs. The companion paper (II) discusses specific therapy of selected bacterial infections.

Objectives of therapy

A major objective of antibacterial therapy is the elimination of viable pathogens from diseased tissues in the shortest possible time with a minimum of adverse effects and inconvenience to the patient. Another purpose is prophylaxis—the prevention of implantation of specific bacteria in tissues. In order to achieve these objectives and to select antibacterial drugs rationally, the physician must have an understanding of their antibacterial spectrum, mechanisms of action, clinical pharmacology, therapeutic efficacy, and potential hazards. He must first of all have a knowledge of the location, etiology, severity, and natural history of the patient's infection, and of special circumstances that might influence the choice of antibacterial drugs and their method of administration.

Antibacterial spectrum

Knowledge of the antibacterial spectrum of chemotherapeutic agents, the organisms responsible for infection and their in vitro susceptibility is essential for selection of appropriate therapy. In some instances, the proved identity of the pathogen will be a sufficient basis for choice of suitable drugs. For example, pneumococci and group A streptococci are invariably

Presented at the Seminar on Antimicrobial Susceptibility Testing, at the College of American Pathologists and American Society of Clinical Pathologists 1969 Joint Annual Meeting, September 14–20, Chicago, Illinois.

susceptible to penicillin G and it is the preferred drug for treating infections due to those organisms in nonallergic patients. In some instances, the identity of the pathogen will exclude use of specific drugs. For example, infections caused by strains of Proteus and Serratia which appear to be uniformly resistant to the polymyxins could not be treated with those drugs. When the susceptibility pattern of a pathogen is unpredictable, therapy should be based upon the results of in vitro sensitivity tests. Serial tests of in vitro susceptibility may be required when infections are treated with streptomycin, erythromycin, novobiocin, or naladixic acid, because pathogens may become resistant during therapy.

Understanding of disparities between results of in vitro susceptibility tests and the efficacy of antimicrobial agents in patients will be helpful in the management of some infections. Many viridans streptococci are highly susceptible to the tetracyclines and chloramphenicol in vitro, but therapy with these bacteriostatic agents fails in a majority of cases of bacterial endocarditis.[2-4] Group D streptococci are usually resistant to penicillin G and to streptomycin in vitro, but combined therapy with those agents has been beneficial in a majority of cases of enterococcal endocarditis.[5]

Mechanisms of action

In recent years, much has been learned about the molecular mechanisms of action of antibacterial drugs; the reviews of Carter and McCarty[6] and of Sanders and Cluff[7] refer to the pertinent studies. Certain agents act primarily by interfering with synthesis of cell walls of bacteria; in this category are penicillins, cephalosporins, bacitracin, ristocetin, cycloserine, and vancomycin. Agents that affect the function of bacterial cell membranes include the polymyxins (polymyxin B and colistin), amphotericin B, and nystatin. Chloramphenicol, the tetracyclines, lincomycin, erythromycin, and the aminoglycoside antibiotics interfere with protein synthesis of the bacterial cell. The aminoglycoside antibiotics (kanamycin, streptomycin, neomycin, and gentamicin) cause specific misreadings of the genetic code at the level of the ribosome; this leads to the formation of defective bacterial protein. Chloramphenicol interferes with the attachment of messenger ribonucleic acid (RNA) to the ribosomes. The tetracyclines, erythromycin, and lincomycin prevent the attachment of amino acid-activated transfer RNA to ribosomes. Agents that interfere with synthesis of desoxyribonucleic acid (DNA) of the bacterial chromosome are naladixic acid and griseofulvin. The sulfonamides hinder intermediary metabolism of bacteria.

The action of antibacterial drugs against susceptible bacteria may be bacteriostatic or bactericidal. Bacteriostatic drugs (*Table 1*) merely inhibit bacterial growth; bactericidal agents (*Table 2*) cause an irreversible, killing effect. Bactericidal drugs are considerably more effective than bacteriostatic ones in treatment of bacterial endocarditis.[3, 4]

The polymyxins are bactericidal for bacteria both in growth and in rest-

Table 1.—Some common bacteriostatic antibiotics

Chloramphenicol
Erythromycin
Novobiocin
Tetracyclines

Table 2.—Some common bactericidal antibiotics

Ampicillin	Kanamycin
Bacitracin	Methicillin
Cephaloridine	Nafcillin
Cephalothin	Oxacillin
Cloxacillin	Penicillin
Colistin	Polymyxin B
Dicloxacillin	Streptomycin
Gentamicin	Vancomycin

ing phases. Most other agents are bactericidal only for bacteria that are actively multiplying. Bacteriostatic agents, such as the tetracyclines or chloramphenicol, inhibit the bactericidal effect of penicillin in vitro, and this antagonistic effect may be clinically significant. Lepper and Dowling[8] reported a mortality rate of 30 percent among patients with pneumococcal meningitis treated with penicillin alone; whereas the mortality rate was 79 percent among comparable patients receiving chlortetracycline in addition to the same penicillin regimen. Similar results have been reported by others.[9] Recently, investigators have provided evidence suggestive of antagonism between chloramphenicol and the penicillins in bacterial meningitis.[10, 11]

Clinical pharmacology

Eradication of infection depends in large part upon the exposure of bacteria in diseased tissues to adequate concentrations of active drug for sufficient time to inhibit their growth or to kill them. This in turn depends in part upon properties related to absorption, distribution, biotransformation, and excretion of the drugs. Some drugs are absorbed poorly from certain sites of administration (e.g., the oral route). Others are well absorbed, but diffuse poorly into certain tissues or sites of infection. For example, after parenteral administration, kanamycin[12] and gentamicin[13] do not usually achieve high concentrations in bile. Some antibacterial drugs are largely inactivated in the body, and this property may decrease the necessary concentration of active drug in a specific site of infection. For example, chloramphenicol is conjugated to an inactive form in the normal liver, and only from 5 to 15 percent of the active drug is excreted in the urine of patients with normal renal function.[14] Isoniazid may be rapidly inactivated in the body of certain genetically predetermined patients and this may cause therapeutic failures.[15]

Many antibacterial drugs are bound in various degrees to protein in serum and other body fluids and tissues. The significance of this phenomenon has been a matter of controversy and confusion.[16, 17] It is now the consensus that the portion of antibacterial drug bound to serum protein is

without antibacterial activity. Although the binding of antibacterial drugs to serum protein is a reversible process, dosage schedules of highly bound antibiotics, like oxacillin, cloxacillin, and dicloxacillin, should be adjusted to achieve concentrations in serum of *free drug* well in excess of those required to inhibit or kill bacteria in vitro.[17]

Knowledge of the rate and mode of elimination of antibacterial drugs from the body is necessary to determine the size and frequency of the dose required to produce therapeutic levels and to avoid excessive concentrations of potentially toxic ones.[18] Optimally effective, safe dosage under normal circumstances is known with reasonable certainty for most commercially available antibacterial drugs. However, unmodified dosages of some potentially toxic antibacterial agents that depend upon the kidneys for excretion can produce dangerous concentrations in the serum of patients with renal failure. Effective and safe dosage schedules for such antibiotics in patients with renal failure have been devised.[18] Allowances have also been made for dosages of some drugs in patients undergoing peritoneal dialysis or hemodialysis.[19]

Therapeutic efficacy

Whenever possible, physicians select antibacterial drugs known from past experience to be capable of eliminating susceptible bacteria from lesions and of aiding in restoration of health of patients with the type of infection under consideration. This experience is often derived from the results of clinical trials; guidelines for the proof of efficacy of antibiotics have been summarized by Waisbren.[20] When several effective antibacterial drugs are available for treatment of an infection, the choice may be governed by the nature of potential adverse effects, ease of administration, and cost.

Potential hazards

Among the major categories of untoward reactions to antibacterial drugs are hypersensitivity, toxicity, idiosyncrasy, and superinfection. Some antimicrobial drugs have the unfortunate capacity to produce anaphylactic shock, cardiorespiratory arrest, bone marrow aplasia, renal or hepatic failure, deafness, blindness, exfoliative dermatitis, fetal malformations or other devastating effects. Consequently, the physician must be aware of these possibilities[2] and administer such drugs only when the potential benefits to be derived clearly outweigh the risks.

The infection

The clinical spectrum of bacterial infection ranges from the asymptomatic carrier state to rapidly lethal disease. For some bacterial infections, antibacterial therapy may be required for cure, for control, for palliation, or for prophylaxis. In others, it may be optional, and in still others, it may

be unnecessary and potentially hazardous. Depending upon the circumstances, the physician must decide whether antibacterial therapy should be initiated, withheld, continued, modified, changed, or discontinued. Decisions must be based on an understanding of all relevant data and careful consideration of the alternatives.

In otherwise healthy patients with relatively mild infections of multipotential cause, it may be prudent to await the results of microbiologic studies before initiating or changing therapy. Similarly, in some patients with more serious disorders, such as subacute bacterial endocarditis, the risks of waiting a few days to be certain that positive blood cultures are obtained are usually outweighed by the benefits of precise bacteriologic diagnosis.[21]

However, in patients with fulminating infections, or in those with underlying diseases known to permit rapid progression of mild infections, prompt and decisive action may be necessary to prevent serious permanent disability or death.[1, 22] It may be necessary to initiate antibacterial therapy on the basis of a presumptive etiologic diagnosis *after* appropriate bacteriologic cultures have been started, but *before* the pathogens have been definitively identified or their in vitro susceptibility has been determined. Consideration of the age of the patient, the anatomic site of the infection, the place of its acquisition, and the circumstances involved in its development will assist in the formulation of a presumptive etiologic diagnosis. The gram-stained smear of exudates, abscesses, infected body tissues or fluids, may provide valuable immediate information before the results of cultures become available.[23] Knowledge of the antimicrobials that are likely to be effective against the suspected pathogens will provide a rational basis for selection of therapy until the results of cultures and of in vitro susceptibility tests become available.

The location, cause, and severity of an infection may influence the type of drug selected, its dosage, its route of administration, and the duration of treatment. Only a few examples are here cited. In patients with life-threatening infections, such as bacteremic shock, use of potentially toxic agents may be warranted when they are known to be significantly more effective than alternative ones against the suspected pathogens.[24] In patients with bacterial endocarditis, bactericidal antibiotics appear to be necessary for optimal therapy.[2-4] In adults with uncomplicated pneumococcal pneumonia, penicillin G, from 600,000 to 1,200,000 units, intramuscularly daily is all that is usually required for cure;[25] larger doses may be associated with an increased incidence of superinfection.[26] For adults with pneumococcal meningitis, considerably larger daily doses of penicillin are necessary.[27] For patients with meningitis due to Pseudomonas, polymyxin B may be indicated, but it must be administered intrathecally because it does not reach the central nervous system or cerebrospinal fluid through the parenteral route.[28] For patients with group A streptococcal pharyngitis, therapeutic

concentrations of penicillin for at least 10 days are required for bacteriologic cure.[29] For patients with staphylococcal endocarditis, administration of large amounts of appropriate bactericidal antibiotics for at least six weeks is considered essential for cure.[30]

The patient

Circumstances of the patient may influence the choice of antibacterial drugs and their method of administration.[15] Hypersensitivity to a drug may contraindicate its use. Likewise, it may be prudent to avoid certain drugs in treating pregnant women. For example, the tetracyclines are potentially hepatotoxic when given to pregnant women; they may also cause dental abnormalities in the infants. Parenteral therapy may be necessary in patients who are vomiting or have intestinal malabsorption, or in those with life-threatening infections. Intravenous therapy may be preferable to intramuscular administration for patients in shock, with meningitis, hemorrhagic disorders, third-degree burns, or with emaciation and severe muscular wasting. It may be necessary to curtail the dosages of certain potentially toxic drugs for patients with impaired mechanisms of excretion. For example, the dosage of chloramphenicol must be reduced in the newborn because of the inability of the infant liver to conjugate the drug adequately; failure to take the necessary precautions may lead to excessive concentrations of active drug and the development of fatal cardiovascular collapse (gray syndrome).[31] For some patients, a larger than the usual recommended dosage of a drug may be necessary to prevent therapeutic failure; for example, patients known to be rapid inactivators of isoniazid may require increased dosages of the drug.

Miscellaneous considerations

The outcome of antibacterial therapy of infection in some patients may ultimately depend upon appropriately timed surgical drainage of abscesses, or correction of anatomic defects predisposing to and perpetuating infection. The treatment of shock may be important in cases of fulminating infection. Likewise, a favorable outcome of the infection may require concomitant treatment of such diverse conditions as renal, hepatic, respiratory, or cardiac failure, blood dyscrasias, coagulation disorders, or even untoward reactions to antibiotics or adjunctive therapeutic agents.

Summary and conclusion

Some general principles in regard to selection and use of antibacterial drugs have been briefly presented. The approach to the treatment of bacterial infections in patients no longer has to be entirely empiric. In recent years, studies of pathogens, patients, infections, and antibacterial drugs have led to an improved, albeit incomplete, understanding of their interaction. Knowledge of this interaction and an appreciation of the values, limita-

tions, and dangers of antibacterial drugs is essential for their rational use. An orderly diagnostic approach, thoughtful interpretation of the results of microbiologic studies, timely intervention in appropriate situations, careful discrimination in selection of antibacteral drugs, meticulous attention to dosages, routes of administration, and adequate duration of therapy, correction of predisposing or complicating factors, and close supervision of patients are necessary to achieve maximal therapeutic benefits with a minimum of adverse effects. Those steps constitute the essence of the strategy of antibacterial therapy.

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