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Antibacterial therapy. II. Some considerations of specific treatment of selected bacteremic infections

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IT seems unlikely that it will ever be possible automatically to administer antibacterial therapy safely and effectively without prior deliberation. This deliberation is necessary because of the complexity and variability of patients, pathogens, infections, antibacterial drugs and their interaction. In the companion report (I),[1] some general aspects of the strategy of antibacterial therapy are presented. This report is concerned with specific antibacterial therapy of selected bacteremic infections, including those due to gram-negative bacilli, coagulase-positive staphylococci, streptococci, pneumococci, meningococci, and clostridial organisms.

Bacteremia due to gram-negative bacilli

Bacteremia due to gram-negative bacilli is now a common cause of shock and death in hospitalized patients.[2, 3] Hemodynamic derangements may vary widely among patients whose disorders are diagnosed as bacteremic shock, or at different stages of disease in a specific patient. Underlying diseases and therapies often are of paramount importance in the pathogenesis and eventual outcome of the bacteremia.

The most frequent pathogens are *Escherichia coli,* Klebsiella-Enterobacter, Pseudomonas, Proteus, and Bacteroides. Because of the fulminating nature of the infection, treatment must frequently be started before the results of cultures or in vitro susceptibility tests are available; knowledge of the location of the primary infection and certain clinical clues may often lead to suspicion of the pathogen. The susceptibility pattern of gram-negative bacilli is somewhat unpredictable and may vary in different geographic locations. Antibiotics that are most likely to be effective often are those that have the greatest potential for toxicity.

Commercially available antibiotics having possible application in gram-negative bacteremia and some of the potentially most disabling adverse effects are listed in *Table 1.* At this time unfortunately there is no single agent that is effective against all gram-negative bacilli (*Table 1*). For example, kanamycin is active against a majority of strains of *E. coli,* Klebs-

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Table 1.—Bacteremia due to gram-negative bacilli: some potentially useful antibacterial drugs and possible adverse effects

Some pathogens likely to be susceptible*	Antibacterial drugs†	Some disabling adverse effects‡
Escherichia coli; Proteus mirabilis	Ampicillin	Hypersensitivity
E. coli; Klebsiella; *Proteus mirabilis*	Cephaloridine§	Nephrotoxicity; hypersensitivity
E. coli; Klebsiella; *Proteus mirabilis*	Cephalothin	Hypersensitivity
E. coli; Klebsiella; *Proteus mirabilis;* Bacteroides	Chloramphenicol	Hematotoxicity; cardiovascular collapse in newborn infants
E. coli; Klebsiella-Enterobacter; Pseudomonas	Colistin§	Nephrotoxicity; apnea
E. coli; Klebsiella-Enterobacter; Serratia; *Proteus mirabilis;* indol-positive Proteus;‖ Pseudomonas	Gentamicin§	Labyrinthine toxicity; nephrotoxicity
E. coli; Klebsiella-Enterobacter; Serratia; *Proteus mirabilis;* indol-positive Proteus‖	Kanamycin§	Ototoxicity; nephrotoxicity; apnea
E. coli; Klebsiella-Enterobacter; Pseudomonas	Polymyxin B§	Nephrotoxicity; apnea
E. coli; Bacteroides	Tetracycline§	Hepatotoxicity

* In vitro susceptibility patterns of some gram-negative bacilli may vary in different geographic locations.

† Commercially available. Streptomycin is not included because many gram-negative bacilli are now resistant to it.

‡ Superinfections may develop after therapy with any of the agents listed in column 1.

§ Must be given in reduced dosage to patients with renal functional impairment.

‖ *Proteus morganii, rettgeri,* and *vulgaris.*

iella-Enterobacter, Proteus, and Serratia, but is ineffective against most strains of Pseudomonas. Conversely, the polymyxin drugs (colistin and polymyxin B) are effective against the majority of strains of Pseudomonas. The polymyxins are also effective against the majority of strains of *E. coli* and Klebsiella-Enterobacter, but ineffective against most strains of Proteus and Serratia. Gentamicin currently is effective against the majority of strains of *E. coli,* Klebsiella-Enterobacter, Serratia, Proteus, and Pseudomonas, but is ineffective against Bacteroides. Likewise, neither kanamycin nor the polymyxins are effective against Bacteroides; the tetracyclines or chloramphenicol are the drugs of choice for infections due to these anaerobic organisms.[4, 5]

Early treatment of bacillary infections in susceptible patients may reduce the incidence of lethal bacteremic shock.[6] The antibiotics currently preferred for initial presumptive therapy of gram-negative bacteremia are listed in *Table 2.* Alterations in the initial antibiotic regimen must be made on the basis of the patient's clinical course and of the results of in vitro sus-

Table 2.—Bacteremia due to gram-negative bacilli: currently preferred antibacterial drugs for initial presumptive therapy*

Suspected or proved causal organism	Choice of drugs	
	First	Second
Escherichia coli	Gentamicin	Kanamycin
Klebsiella-Enterobacter	Gentamicin	Kanamycin
Serratia	Gentamicin	Kanamycin
Proteus	Gentamicin	Kanamycin
Pseudomonas	Gentamicin	A polymyxin
Bacteroides	Chloramphenicol†	A tetracycline

* Definitive antibacterial therapy is determined subsequently from the results of in vitro susceptibility tests and the patient's response to treatment.
† Chloramphenicol in preference to a tetracycline on the basis of data from the study of Saksena and associates.[5]

ceptibility tests. Considerations of efficacy and safety are of utmost importance in the clinician's decisions in regard to altering the therapy.

Other measures that may lead to successful therapy of gram-negative bacteremia include drainage of abscesses, relief of obstruction of viscera, correction of hemodynamic aberrations, and control of underlying predisposing diseases.

Bacteremia due to *Staphylococcus aureus*

Drainage of abscesses and prolonged antibacterial therapy are important considerations in the management of serious staphylococcal infections. Endocarditis frequently develops in patients with bacteremia due to *Staphylococcus aureus* and the diagnosis is often missed during life.[7] Accordingly, prolonged therapy with large doses of appropriate bactericidal antibiotics is indicated in patients with staphylococcal bacteremia even when the usual clinical manifestations of bacterial endocarditis are absent.

The unpredictable susceptibility pattern of *Staphylococcus aureus* makes in vitro susceptibility testing mandatory. Penicillin G is the preferred drug for treatment of bacteremia due to nonpenicillinase-producing staphylococci in patients who are not allergic to this drug (*Table 3*). Virtually all staphylococci that are not inhibited by 1 μg (1.6 units) of penicillin G per milliliter are penicillinase producers and are resistant to the drug.[8] One of the semisynthetic penicillinase-resistant penicillins, such as methicillin, oxacillin, or nafcillin, may be administered parenterally for treatment of bacteremia due to penicillinase-producing staphylococci, provided that the organisms are susceptible to these agents. For patients with known penicillin allergy, cephalothin or vancomycin are suitable alternative drugs. Cephalothin has been well tolerated by a majority of patients with hypersensitivity to the penicillins; however, it should be given cautiously to those

Table 3.—Bacteremia due to *Staphylococcus aureus:* currently preferred antibacterial drugs

Characteristic of strain of *Staphylocous aureus*	Choice of drugs*	
	First	Second
Nonpenicillinase-producing	Penicillin G	Cephalothin; vancomycin†
Penicillinase-producing	A penicillinase-resistant penicillin	Cephalothin; vancomycin†
Resistant to the penicillinase-resistant penicillins	Vancomycin†	—
In vitro susceptibility tests still pending	Vancomycin†	Cephalothin; a penicillinase-resistant penicillin

* Bactericidal agents preferred because of the frequency of bacterial endocarditis in patients with staphylococcal bacteremia.
† Must be given in reduced dosage to patients with impaired renal function.

patients because serious allergic reactions have occurred. In patients with bacteremia due to staphylococci that are resistant to the penicillinase-resistant penicillins and cephalothin, vancomycin is the drug of choice.[9, 10]

Because of its efficacy against virtually all staphylococci, vancomycin also is currently preferred for the initial therapy of staphylococcal bacteremia before the results of in vitro susceptibility tests are available. Vancomycin must be given intravenously and may cause local thrombophlebitis. It is potentially nephrotoxic and ototoxic and dosages must be reduced for patients with renal insufficiency. Gentamicin is bactericidal against most strains of staphylococci, but clinical experience is not sufficient at present to justify its use in infections due to these organisms.[11] Erythromycin and lincomycin are bacteriostatic agents[12] and ordinarily would not be used for therapy of staphylococcal bacteremia unless endocarditis seems to be absent. Furthermore, lincomycin has been reported[13] to have caused cardiopulmonary arrest when administered intravenously in large doses.

Streptococcal bacteremia and endocarditis (*Table 4*)

Although streptococci of Lancefield groups A and D are the most frequent cause of human infections, it is now evident that other serologic groups are also significant human pathogens.[14] For example, Lancefield group B streptococci were the most common single cause of neonatal sepsis at the Boston City Hospital in recent years.[15]

Pencillin G is preferred for treatment of bacteremia due to streptococci of Lancefield groups A, B, C, and G. For patients who are allergic to penicillin, a cephalosporin (cephalothin or cephaloridine) may be administered cautiously. The total daily dosage of cephaloridine should not exceed 4 g in adults with normal renal function because of the danger of nephrotoxicity.[16] In patients with bacteremia due to Lancefield group A streptococci,

Table 4.—Streptococcal bacteremia or endocarditis: antibacterial drugs

Streptococcus	Choice of drugs	
	First	Alternative
Lancefield groups A, B, C, and G	Penicillin G	A cephalosporin
*Streptococcus viridans**	Penicillin G with or without streptomycin	A cephalosporin; vancomycin
Enterococcus (Lancefield group D)	Penicillin G, or ampicillin with streptomycin	Erythromycin with streptomycin; vancomycin
Microaerophilic or anaerobic Streptococcus*	Penicillin with or without streptomycin	A cephalosporin

* Strains resistant to 0.2 unit or more of penicillin G per milliliter should be considered in a therapeutic category similar to that for enterococci.

without endocarditis, bacteriostatic agents such as erythromycin, lincomycin, and the tetracyclines, might be considered as alternatives for penicillin G and the cephalosporins. However, from 10 to 30 percent of Lancefield group A streptococci now seem to be resistant to the tetracyclines,[17] and strains resistant to erythromycin and lincomycin have appeared.[18]

For patients with endocarditis due to sensitive viridans streptococci, penicillin G with or without streptomycin is considered to be an acceptable form of therapy. Treatment with penicillin and streptomycin is usually given for from two to four weeks, and penicillin alone for at least four weeks. Quinn and Colville[19] have achieved a satisfactory cure rate of *Streptococcus viridans* endocarditis with large doses of penicillin V administered orally and streptomycin intramuscularly. For patients known to be allergic to penicillin, cephalothin[20] or vancomycin[21] may be suitable drugs for treatment of endocarditis due to these organisms. *Streptococcus viridans* or other species of streptococci that are resistant to 0.2 unit or more of penicillin G per milliliter probably should be considered in a therapeutic category similar to that of enterococci.[22]

For patients with enterococcal (Lancefield group D streptococcal) endocarditis, penicillin G is administered conjointly with streptomycin. Considerably larger daily doses of penicillin G are required for therapy of enterococcal endocarditis than for endocarditis due to sensitive *Streptococcus viridans*. Treatment is usually continued for six weeks. Some investigators[23] have reported that patients with enterococcal endocarditis have been cured with ampicillin alone; however, experience with this form of therapy is limited and it is not generally recommended at this time. For patients allergic to the penicillins, vancomycin[21] or erythromycin and streptomycin are possible alternative drugs for treatment of enterococcal endocarditis. Cephalothin is inadequate for treatment of enterococcal endocarditis.[20]

Pneumococcal bacteremia

Pneumococci are uniformly susceptible to the penicillins and cephalosporins, but strains resistant to the tetracyclines,[17] erythromycin, and lincomycin[24] have been reported. Penicillin G is the drug of choice for treatment of bacteremia due to *Diplococcus pneumoniae*. The dosage, route of administration, and duration of therapy are determined by the nature of the underlying lesion predisposing to bacteremia, that is, pneumonia, endocarditis, or meningitis. For patients who are allergic to penicillin, a cephalosporin may be a suitable agent. However, experience with the cephalosporins in the treatment of pneumococcal meningitis is not sufficient to make recommendations in regard to their use in this condition at the present time. Some physicians[25] prefer chloramphenicol for therapy of uncomplicated pneumococcal meningitis in patients who are allergic to penicillin.

Meningococcemia

Penicillin G or ampicillin are the preferred drugs for treatment of patients with bacteremia or meningitis due to *Neisseria meningitidis*. The sulfonamides are no longer indicated in the initial therapy of serious meningococcal infections because many strains of *Neisseria meningitidis* are now resistant to these agents. There are disturbing reports[26] of suboptimal responses of patients with meningococcal meningitis to therapy with cephalothin. Chloramphenicol appears to be suitable for treatment of meningococcal meningitis in patients known to be allergic to penicillin.[26]

Clostridial bacteremia

In recent years, there has been an increase in the incidence of bacteremia due to clostridial organisms in hospitalized patients.[27] Surgical procedures often are of primary importance in the successful therapy of clostridial infections.[28] Penicillin G, the cephalosporins, or the tetracyclines are considered to be appropriate drugs for treatment of clostridial bacteremia.

Summary and conclusion

Specific antibacterial therapy has been briefly considered in regard to selected bacteremic infections due to gram-negative bacilli, coagulase-positive staphylococci, streptococci, pneumococci, meningococci, and clostridial organisms. By its very nature, antibacterial therapy of these conditions is a complex procedure. However, knowledge and the utilization of currently available data may help to simplify the procedure and result in safer, more effective treatment.

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