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THE TREATMENT AND PROPHYLAXIS OF SUBACUTE BACTERIAL ENDOCARDITIS

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SUBACUTE BACTERIAL ENDOCARDITIS is one of the important bacterial diseases which has been transformed from a uniformly fatal disease to one with a favorable outlook for cure since the era of antibiotic therapy. It is, however, an exceptional and perhaps unique disease in relation to the task that chemotherapy has to perform. Although the prevention of further bacterial growth by antibiotics and the subsequent disposal of surviving organisms by the natural defenses of the body are sufficient to eradicate most bacterial infections, they apparently are not sufficient in subacute bacterial endocarditis. The clinical course of the disease prior to the antibiotic era showed that host factors are incapable of eliminating this type of infection. To prevent relapse, chemotherapy must eliminate the last surviving organisms from the endocardial focus.

Consideration of the pathology in this disease helps us to understand the obstacles that antibiotics must surmount in order to eradicate this infection. The organisms are buried in fibrin and in scarred, avascular, necrotic tissue. To effect a cure, an agent with fibrin-penetrating and bacteria-killing properties must be present in high concentrations over an adequate period of time. It is, therefore, not surprising that bactericidal drugs are indicated in this disease rather than those that are bacteriostatic in their action. Both clinical and laboratory evidence[1] indicate that the presence of bactericidal action is a prerequisite for the cure of subacute bacterial endocarditis.

In the treatment of this condition the failure of sulfonamides was early evidence that bacteriostasis in addition to host factors was incapable of curing this disease. Temporary remission of symptoms and control of bacteremia were observed, but relapse almost invariably occurred after the drugs had been

discontinued. Much the same experience has been noted with the use of the newer bacteriostatic agents, such as chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol, although cures have been accomplished in some patients treated with these drugs. Penicillin and streptomycin, which have bactericidal properties, remain the primary drugs in the treatment of subacute bacterial endocarditis.

It must be kept in mind that the routine sensitivity tests reported from the laboratories measure only the bacteriostatic or inhibitory action of a drug and give no true indications of its bactericidal or actual killing activity. Therefore, though the laboratory report shows that an organism responsible for a case of subacute bacterial endocarditis is highly sensitive to one of the bacteriostatic drugs, clinical experience indicates that these are not the drugs of choice and a bactericidal agent should be used.

The Organisms and the Choice of Drugs

The nonhemolytic streptococci are responsible for about 95 per cent of all cases of subacute bacterial endocarditis. The remaining 5 per cent of the cases are caused by a number of different organisms, many of which are penicillin-resistant gram-negative bacteria, and therapy for these cases has to be individualized (Table 1).

Table 1. — *Organisms causing subacute bacterial endocarditis*

I. Nonhemolytic streptococci	
A. *Streptococcus viridans*	85 to 90% of cases
1. *S. salivarius*	
2. *S. mitis*	
3. *S. s.b.e.*	
B. Enterococci	5 to 10% of cases
1. *S. faecalis*	
2. *S. liquefaciens*	
3. *S. zymogenes*	
II. Multiple other organisms, such as Brucella, diphtheroids, *Hemophilus influenzae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, fungi, yeasts	5% of cases

The nonhemolytic streptococci are of two important groups: (1) *Streptococcus viridans*, and (2) the enterococci. *Streptococcus viridans* continues to be the most common offender in this infection and accounts for up to 90 per cent of all cases due to nonhemolytic streptococci. Fortunately they are usually sensitive to penicillin in the range of 0.1 or less unit per cubic centimeter in vitro, and daily doses of 2 to 2½ million units are sufficient for cure in most cases. The enterococci which make up the remaining 5 to 10 per cent of the cases caused by nonhemolytic streptococci, however, present a more difficult therapeutic

problem. These cases may frequently be therapeutic failures because the enterococci are extremely resistant to penicillin in the range of 1 to 5 or more units per cubic centimeter.

Large doses of penicillin alone—10 to 50 million units daily—have been successful in the treatment of some of the enterococcal infections. However, since the combination of penicillin and streptomycin has been demonstrated to have a synergistic effect on the enterococcus,[2,3] the daily use of large doses (10 to 20 million units) of penicillin with 1 to 2 gm. of streptomycin appears to offer a much better chance for cure. There is evidence that a combination of penicillin and bacitracin also has a synergistic action,[4,5] and it has been used successfully in the treatment of these enterococcal infections.[6] Large doses of penicillin are administered with 60,000 to 100,000 units of bacitracin daily. This combination may be used when there are contraindications to the use of streptomycin, or if a substitution for streptomycin is necessary because of toxic reactions. Bacitracin is a potentially nephrotoxic agent and must be used with care when employed over long periods of time.

The 5 per cent of cases of subacute bacterial endocarditis due to a wide variety of organisms other than nonhemolytic streptococci require individual consideration for the selection of the drug or combination of drugs to be employed. Streptomycin is used in the treatment of many of the gram-negative organisms. A combination of streptomycin and chlortetracycline appears to be the treatment of choice for the Brucella organisms. In rare cases caused by *Pseudomonas aeruginosa*, the use of polymyxin B may be necessary. At times one may have to resort to a trial with the broad-spectrum antibiotics in some infections due to rare organisms that are entirely unresponsive to penicillin or to streptomycin. There is no effective treatment for endocarditis caused by fungi or yeasts.

Methods of Treatment

Although the penicillin-sensitivity studies indicate only the inhibitory action of the drug, they nonetheless are of considerable practical value in estimating the daily dose necessary in the individual case (Table 2). However, this table can be considered to be only a guide, for if the clinical response is not satisfactory the theoretically desirable dose must be increased rapidly and progressively.

Table 2.—*Suggested dosage schedule in relation to the in vitro sensitivity of the organism in units per cubic centimeter of penicillin*

Sensitivity, units per cc.	Penicillin, units per day
0.05 to 0.1	2,000,000
0.1 to 0.2	3,000,000
0.2 to 0.5	4,000,000
0.5 to 1.0	8,000,000
1.0 to 5.0	10,000,000 to 20,000,000
5.0 to 10.0	20,000,000 to 40,000,000

After three or four blood cultures have been taken during a 48 to 72 hour period, a schedule of penicillin treatment may be instituted, such as 2 to 2½ million units of aqueous or procaine penicillin G each 24 hours in divided doses. After the organism has been identified and the sensitivity studies have been completed the dose may be altered as necessary and streptomycin added if an enterococcus is isolated.

In the treatment of highly resistant organisms that require more than 10 to 12 million units of penicillin daily, the intramuscular route of administration may become impractical and the continuous intravenous route may be more satisfactory. Intravenous administration can be conveniently accomplished by using a small polyethylene tube that is anchored in a vein and allows the patient complete freedom of movement in bed with little chance of subcutaneous infiltration. Aqueous penicillin is added to the infusion bottle along with 50 mg. of heparin, and 1000 ml. of this solution is allowed to drip in slowly over each 12-hour period. In this manner, almost unlimited amounts of penicillin can be used.

The use of a drug that inhibits the excretion of penicillin is occasionally desirable when treating an organism that is moderately or highly resistant to penicillin. Probenecid (Benemid, Merck, Sharp & Dohme), in doses of 0.5 gm. every six hours, may double the blood level of penicillin. Fortunately, probenecid does not inhibit the excretion of streptomycin and it can be given without fear of increasing the chances of streptomycin-toxicity reaction.

Sensitivity reactions to penicillin occasionally may complicate the therapy. If they occur during treatment one must resist the temptation immediately to substitute an agent that has only bacteriostatic action, as such a change will compromise the chances of cure. Every effort should be made to continue the use of penicillin. The minor skin reactions frequently can be controlled by the use of antihistaminics. The substitution of penicillin O for penicillin G may readily solve the problem.[7] Occasionally, the employment of corticotropin (ACTH) may permit the continuation of the essentially needed penicillin in the presence of allergic reactions.

When streptomycin is given daily over long periods of time it may have toxic effects. The insidious loss of hearing caused by dihydrostreptomycin would seem to be more serious than the vestibular damage that streptomycin may produce and, therefore, the latter should be used initially. If vestibular symptoms develop, which often are transient, the change may be made to dihydrostreptomycin. This method appears to be safer than using a mixture of the two drugs, in spite of evidence suggesting that the use of the two forms in a 1:1 ratio may reduce toxicity to the eighth cranial nerve.[8]

Duration of Treatment

In the early days of antibiotic therapy for subacute bacterial endocarditis it was believed that six to eight weeks of treatment was indicated. However, about four weeks of treatment has proven to be sufficient in most cases. In recent years

investigation has been directed toward shortening the period of treatment. In 1952, Hamburger and Stein[9] reported that cases caused by penicillin-sensitive *Streptococcus viridans* were successfully treated with doses of 15 million units of penicillin daily for two weeks. Geraci and Martin[10] reported that of 23 patients having subacute bacterial endocarditis due to penicillin-sensitive *Streptococcus viridans*, 18 were cured with moderate doses of penicillin combined with dihydrostreptomycin over a two-week period. It appears likely that the administration of this combination of drugs is satisfactory treatment in selected cases in which the diagnosis has been made early in the course of the disease, and in which the organism has proved to be *Streptococcus viridans* and is highly sensitive to penicillin (0.1 or less unit of penicillin per cubic centimeter). Four weeks of treatment should be used for more penicillin-resistant *Streptococcus viridans*, for all enterococci, and for organisms other than the nonhemolytic streptococci.

Results of Treatment

The results of therapy have been reported many times in recent years, with over-all recovery rates ranging from 65 to 80 per cent. Recovery rates vary according to whether the rate represents only patients who have had bacterial cure, or also includes those patients who, within a few weeks or months after bacterial cure, die from congestive heart failure that was not present prior to the onset of the disease.

It has been demonstrated that healing of the valvular veruccae by fibrosis and endothelialization requires several weeks or months.[11] The additional scarring and retraction of previously diseased valves then may increase the mechanical insufficiency of the heart and result in cardiac decompensation. This complication is particularly apt to be a serious sequela when the aortic valve is involved. To minimize this additional valvular damage, early diagnosis of subacute bacterial endocarditis is important, so that treatment can be instituted before a larger section of the valve becomes involved in the infectious process. Delay in diagnosis and inadequacy of treatment are the primary factors that increase mortality. Factors of lesser influence are the age of the patient, the resistance of the organisms, and the type of predisposing cardiac disease.

Prophylaxis

The ideal form of therapy for most bacterial disease, and certainly for subacute bacterial endocarditis, is prevention. Since bacteremia is essential for the organisms to progress to the endocardium, measures should be taken in all susceptible individuals to prevent bacteremia. There are innumerable sources of bacteremia, with tooth extractions being the most familiar source as related to subacute bacterial endocarditis. However, cases of endocarditis are believed to have been caused by many other operative and diagnostic procedures, particularly those involving the genitourinary system and the oral cavity. Other predisposing factors have been abdominal operation, bronchoscopy, abortion,

and spontaneous delivery. In general it may be said that entrance of organisms into the blood stream may be facilitated by any operation or diagnostic instrumentation that traumatizes a mucosal surface exposed to bacteria.

The routine prophylactic treatment in the past has consisted of the administration of 600,000 to 1,000,000 units of procaine penicillin G a few hours prior to dental or other surgical procedures, and of a similar daily dose for three or four days postoperatively. The simultaneous injection of 600,000 units of aqueous penicillin and 600,000 units of procaine penicillin in oil containing 2 per cent aluminum monostearate 30 minutes before an operative procedure may be adequate for complete protection without need for additional doses. A dependable oral preparation, such as penicillin V, in doses of 200,000 to 400,000 units every six hours, beginning 24 hours prior to surgery and continuing for five days, should provide adequate protection. The bacteriostatic antibiotics also have been shown to be effective in controlling bacteremia[12] and can be used safely as prophylactic agents, even though they are predominantly ineffective after the endocardial infection has become established.

Summary

1. Bactericidal action appears to be essential to the cure of subacute bacterial endocarditis; bacteriostatic agents are largely ineffective.

2. Penicillin is the preferred drug in therapy for the largest group of cases, those that are due to *Streptococcus viridans*. The best treatment for subacute bacterial endocarditis due to the enterococci is the combination of large doses of penicillin with streptomycin.

3. Methods of treatment and prophylaxis are discussed.

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