SPECIAL ARTICLE

The "Tough Case" of Bacterial Endocarditis

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Many cases of bacterial endocarditis can now be cured rapidly and easily. However, there remains a group of patients in whom the eradication of the cardiac infection presents great problems. Some principles of treating these "tough cases" of endocarditis are outlined by means of illustrative patients. Stress is placed on early diagnosis, isolation of the etiologic microorganism, determination of bactericidal antibiotics or combinations, and use of the serum bactericidal test to establish an adequate dosage regimen.

The treatment of bacterial endocarditis consists of 2 parts: the eradication of the bacterial infection, and the management of the cardiac disability and other organ dysfunctions developing in the course of the disease. Only the first of these aspects, the treatment of the bacterial infection is considered here. Excellent and exhaustive reviews of the general antimicrobial therapy of bacterial endocarditis have been published recently. It would be futile therefore to recapitulate the entire subject. Instead, a few points of importance in the management of the difficult case are illustrated.

The advent of penicillin transformed bacterial endocarditis from an interesting, but uniformly fatal entity into an infection that was often cured without much difficulty. The eradication of Streptococcus viridans, the commonest etiologic agent, has become a simple matter in most cases. There remains, however, a group of patients in whom, for one reason or another, the eradication of the infection presents the physician with unusual problems. A few such illustrative cases are presented here.

The key to the successful treatment of any case of bacterial endocarditis is early recognition and accurate etiologic diagnosis. The physician must maintain an exceedingly high index of suspicion to include bacterial endocarditis in the differential diagnosis of vague or puzzling complaints. After all, bacterial endocarditis does not always present the full range of typical signs and symptoms. The patient might show nothing more than tiredness or anemia with a mild elevation of temperature, or, conversely, he might present the picture of an overwhelming sepsis without signs pointing to cardiac involvement. The earlier the physician thinks of bacterial endocarditis, the more promptly he can undertake the isolation of the etiologic agent and begin treatment.

In bacterial endocarditis, perhaps more than in any other infection, cure depends on the identification of the infecting microorganism and its availability for laboratory study. Thus a determined effort must be made in every case to culture the blood (and occasionally the bone marrow) promptly and repeatedly. Even in extremely severe, fulminating cases it is well to defer the administration of antimicrobial agents for at least a few hours in order to obtain several blood cultures. When the patient is not acutely ill, it is fully justified to obtain 1 or 2 cultures on each of 3 to 5 days before beginning treatment. The recovery of the etiologic bacteria permits a
much sounder guess as to the best drugs to be used than if the etiology is uncertain, and, above all, provides direct laboratory support for devising a satisfactory treatment regimen. As soon as the requisite number of cultures has been obtained, treatment may be started on the basis of the "best guess," to be modified when laboratory findings become available. In about 10 per cent of cases of bacterial endocarditis, an organism cannot be cultured even with exhaustive and competent efforts. In those few instances the choice and dosage of antibiotics must continue to be based on guesswork and past experience. In virtually all other cases, it should be founded upon the results of laboratory examinations.

When requested to determine the antibiotic sensitivity of a microorganism, most hospital laboratories report results based on the "disk test." In many diseases, the antimicrobial activity of a drug estimated by the "disk test" gives a valuable prediction of the probable effect of that drug in the patient. In bacterial endocarditis, however, the results of the disk test are not only without value, but, on the contrary, may be entirely misleading. The conventional disk test only estimates the ability of a drug to inhibit the growth of microorganisms. Such inhibitory action is of great therapeutic value in many diseases—but not in endocarditis. The antibacterial defenses of the host, which are effective in many other illnesses, are unable to eradicate the microorganisms from their protected location within vegetation. Drugs which are predominantly bacteriostatic (e.g., sulfonamides, tetracyclines, chloramphenicol, erythromycin, novobiocin) generally do not cure bacterial endocarditis if employed alone.2, 3, 6 Cure requires drugs that are rapidly bactericidal for the etiologic microorganism. Laboratory tests suitable to guide therapy in bacterial endocarditis must evaluate the bactericidal action of single or combined drugs. Conventional "disk tests" cannot do that, but several techniques for the estimation of bactericidal action are available.7-10 In "simple" cases of bacterial endocarditis caused by Strep. viridans, which is generally very sensitive to penicillin, this deficiency of the disk test may not be apparent. If penicillin is selected as the drug of choice on the basis of experience as well as the marked inhibition reported in the disk test, it may be forgotten that penicillin is also a very effective bactericidal agent. But in cases of endocarditis caused by penicillin-resistant bacteria, the reliance on the "disk test" may lead to the selection of entirely improper antibiotics. An example is shown in figure 1.

This 64-year-old man with endocarditis had many positive blood cultures for hemolytic Staphylococcus aureus. Repeated "disk tests" were employed for the selection of drugs. They revealed that the organism was not inhibited by penicillin, but was markedly inhibited by tetracycline, erythromycin, novobiocin, oleandomycin, and streptomycin. The patient was treated with each of these drugs in succession. Each time he showed some temporary clinical improvement, but either during therapy or shortly after its cessation he relapsed clinically and bacteriologically. Permanent cure was obtained only when bactericidal drug combinations (tetracycline + streptomycin + bacitracin) in appropriate concentrations were employed.

The first rule, then, is the selection of bactericidal drugs for treatment. Admittedly certain drugs are rapidly bactericidal in vitro yet fail to eradicate the apparently susceptible bacteria in the patient. To be effective in bacterial endocarditis the bactericidal drugs must diffuse well into the vegetation and must not be bound by tissue or components of the thrombotic lesion. The inability to reach the infecting organisms may account for the frequent failure of polymyxin B in endocarditis caused by Pseudomonas.11

As a general rule, however, diffusible antibiotics, which are rapidly bactericidal in vitro for a given organism, tend to cure endocarditis caused by that organism, if administered in adequate dose for a sufficient period. The dosage can be roughly estimated from the amount of drug required to kill the organism
Fig. 1 Top. Staphylococcal endocarditis in a 64-year-old man. The misleading results of "disk tests" in guiding antibiotic therapy. (Reproduced, by permission, from Arch. Int. Med. Jawyetz, E., 102: 289, 1959.)

Fig. 2 Middle. Streptococcus viridans endocarditis in a 39-year-old man. The serum bactericidal test indicates adequate antibiotic therapy in spite of a stormy clinical course. (Reported by permission of Dr. W. Atchley.)

Fig. 3 Bottom. Staphylococcal endocarditis in a 39-year-old man, with slow initial response to therapy. Serum bactericidal test used in adjusting drug dosage to "secure" levels. (Reported by permission of Dr. M. Sokolow.)
in vitro under standardized conditions. But what if the patient's response leaves much to be desired? The physician's anxiety over a patient's stormy course may tempt him to add or withdraw drugs at frequent intervals and thus interfere with effective chemotherapy. Once a definitive regimen of antibacterial therapy has been decided upon, the physician should not alter it without compelling reasons. Reassurance concerning adequacy of antibiotic dosage may be derived—in addition to sterile blood cultures—from an evaluation of the bactericidal power in vitro of the patient's serum under therapy against his own infecting organism. This point is illustrated in figure 2.

This 39-year-old man had a 'simple' bacterial endocarditis on a rheumatic mitral valve. The Strep. viridans isolated from his blood stream was rapidly killed in vitro by penicillin 0.2 unit per ml. Accordingly a treatment regimen was outlined consisting of penicillin, 5 million units daily intramuscularly for 20 days, and streptomycin, 1 Gm. daily intramuscularly for the first 10 days. The patient's initial response was satisfactory and his blood cultures promptly became sterile. However, he exhibited repeated febrile episodes with severe pains pointing to embolic events in lungs and kidney. Was he receiving adequate amounts of antibiotics? The physician's concern was allayed by finding that the patient's serum, diluted 1:20, killed his own organism rapidly in the test tube. In spite of a stormy course, treatment was continued and terminated as planned. The patient required anticoagulant therapy but his bacterial infection was eradicated and he recovered completely. Embolic phenomena occur before, during, and even after successful antibiotic therapy. Their occurrence is disquieting and, at times, leads to tragic results. Yet by themselves they should not induce the physician to abandon a well-conceived treatment plan. Similarly the frequent occurrence of drug fever must not be permitted to interfere with an established treatment regime.

The patient shown in figure 3 also had an unsatisfactory initial response to treatment. He was a 39-year-old man who had recovered from 2 previous attacks of bacterial endocarditis due to Strep. viridans during the past 9 years. His present attack was due to a hemolytic Staph. aureus implanted on an insufficient aortic valve, and had failed to respond to 1 month's intensive treatment at another hospital. Laboratory examination indicated that his organism could be killed in vitro by several combinations. After treatment with laboratory-selected drug combinations was begun (fig. 3), blood cultures became sterile but defervescence was slow and the patient did not feel well. His serum killed his staphylococcus in a dilution of 1:5, but not 1:10. This was considered an inadequate safety margin and consequently the dose of penicillin was increased from 20 to 50 million units daily. There was immediate, marked, subjective improvement as the serum became bactericidal in a 1:80 dilution. After 3½ weeks of therapy at that level bacteriologic cure was established.

Different laboratories, using slightly different technics for the assay of the bactericidal activity of serum of the patient under treatment, have slightly different standards of what serum dilution reflects drug levels adequate for cure of endocarditis. However, within the framework of its own experience with the serum bactericidal test each laboratory can give valuable guidance to the antibiotic treatment of 'tough cases' of endocarditis. While reliable data are available indicating what average blood levels may be expected from different time-dose schedules of antibiotics in the usual dose range, the combined antibacterial effect of several drugs at very high dose levels is difficult to predict and must be assayed directly in the patient's serum.

One of the difficult problems in bacterial endocarditis concerns the treatment of the hyperacute, destructive lesion, often associated with staphylococci. It is particularly important to treat such patients with the utmost speed and vigor, with use of bactericidal combinations of usually not less than 3 drugs in very large doses. An example is given in
figure 4. This 55-year-old man was entirely well until 8 days before entry, when he developed a mild "flu-like" illness with fever and diarrhea. His physician treated him for 4 days with chloramphenicol but there was only slight improvement. He then noted the presence of a heart murmur and the development of petechiae on the lower extremities. He suspected bacterial endocarditis and referred the patient to the University hospital because there was a history of an allergic reaction to benzathine penicillin 1 year earlier. On admission to the hospital the patient was acutely ill, lethargic, with occasional shaking chills and a fever of 39 C. He had not received antibiotics for 2 days. His lower extremities were covered with petechial hemorrhages, and there were petechiae also on his eyelids, conjunctivae, and palate. He had splinter hemorrhages under several nails. A harsh grade-III systolic murmur was heard over the entire precordium. The white blood cell count was 16,000 with 85 per cent polymorphonuclear leukocytes, the corrected erythrocyte sedimentation rate was 34 mm. per hr., and 2 blood cultures taken within 2 hours of admission yielded (the next day) more than 300 colonies per ml. of hemolytic, coagulase-positive \textit{Staph. aureus}.

The clinical diagnosis upon admission was acute bacterial endocarditis, probably caused by staphylococci. If the patient's life was to be saved, it was essential to start effective treatment immediately. It was reasoned that (a) the staphylococcus might be penicillin-sensitive because the patient and his family had not had contact with a hospital environment; (b) the earlier slight response to chloramphenicol suggested that the organism might be sensitive to that drug; (c) streptomycin at times enhances the bactericidal effect of penicillin against certain cocci. Because of these considerations the patient was started on combined therapy with chloramphenicol, penicillin, and streptomycin as soon as blood cultures had been taken. In view of the history of a penicillin reaction in the past, this drug was administered with several precautions. At first a skin test with 100 units penicillin O was performed, which gave no immediate reaction. Then 1,000 units of penicillin O were given intramuscularly, again without local or systemic response. An hour later an intravenous infusion of penicillin O was begun, together with intravenous benadryl 100 mg., and cortisone injection was held in readiness. Penicillin was tolerated then and subsequently without any difficulty. Laboratory examinations for antibiotic sensitivity (fig. 4) supported the empiric choice of drugs. After a few days of continued lethargy and high fever, the patient defervesced and improved gradually. His serum was bactericidal for his staphylococcus in dilutions of 1:40 or more. After 5 weeks of antimicrobial treatment all antibiotics were stopped and follow-up examinations for 4 months indicated bacteriologic cure. The patient suffered a brief episode of congestive heart failure 2 months after the end of antimicrobial therapy. This was attributed to violent exercise, a high salt intake, and discontinuing digitalis intake against medical advice. There was prompt response to conventional therapy and to date no evidence of significant valve destruction has appeared. The course of this patient illustrates the need for immediate treatment with very large amount of bactericidal antibiotics chosen initially on the basis of reasoning, and later by laboratory test. It also shows that if penicillin is the drug of greatest life-saving potential, it can often be administered in spite of a history of past allergic reactions. Finally, it suggests that treatment might be extended for more than 4 weeks in staphylococcal endocarditis, although the optimal period of antibiotic therapy in such cases is not known.

Among the "tough cases" of endocarditis it is necessary at the present time to include patients who acquired their microorganism from a hospital environment. Such bacteria are notoriously resistant to the more widely used antibiotics and their eradication is extraordinarily difficult. While the principles of selecting bactericidal drugs in appropriate doses, and assaying the bactericidal potency of serum during treatment, are the same as
Fig. 4 Top. Acute endocarditis due to hemolytic *Staphylococcus aureus* in 55-year-old man. Immediate massive antibiotic therapy based on 'best guess.' Drug selection confirmed by laboratory result. (Reported by permission of Drs. H. D. Brainard and D. Mitchell.)

Fig. 5 Bottom. Acute endocarditis, pericarditis, and chorioretinitis due to hemolytic *Staphylococcus aureus* introduced during mitral valvulotomy in a 44-year-old man. (Reproduced, by permission, from Arch. Int. Med., Jaretz, E., 103: 289, 1959.)

outlined above, markedly toxic antimicrobial substances often must be employed. In the use of full systemic doses of such drugs as bacitracin, neomycin, kanamycin, vancomycin, or ristocetin the risk of serious toxic side effects must be weighed against the risk of treatment failure in a disease that is uniformly fatal unless the infection can be eradicated. An example is given in figure 5.

This 44-year-old man had a very tight mitral stenosis that seriously embarrassed cardiac function. After thorough study a mitral valvulotomy was performed. In the course of surgery a "hospital staphylococcus" was apparently introduced which resulted in sepsis with endocarditis, pericarditis, and multiple abscesses at other sites. In vitro the staphylococcus appeared highly resistant to commonly used antibiotics but could be killed by combinations of bacitracin with erythromycin or chloramphenicol. The patient was treated with these drugs as shown in figure 5 (with
the addition of penicillin on the basis of hope rather than factual evidence). The nephrotoxic effects of bacitracin were carefully evaluated at frequent intervals. The patient responded after an initial stormy course but became psychotic, so that treatment had to be stopped prematurely. After some weeks of remission his mental status improved but the infection relapsed. When re-treated for 4 full weeks with the same combination of drugs (but with the omission of penicillin for part of the time), the patient was cured to enjoy the benefits resulting from the surgical procedure. With experience in the use of toxic antibiotics, it is often possible to minimize their toxic effects and employ them for the protracted periods necessary to eradicate both cardiac and metastatic infection. Laboratory guidance is essential to select optimal drugs and doses and to keep careful check on the toxic side effects. Obviously every effort must be made to drain collections of pus.

The above description may give the impression that rational selection and use of drugs invariably succeeds in curing patients with "difficult" forms of endocarditis. Unfortunately this is not true. While we firmly believe that in every patient the rational sequence outlined above should be followed, occasional failures occur. Most commonly they are associated either with the presence of metastatic infection (e.g., lung abscesses), which cannot be drained adequately, or with damage to valves or myocardium, which leads to cardiac failure.

It would likewise be misleading to claim that only the rational selection of drugs can ever lead to the cure of endocarditis. In an occasional patient, infected with a particularly resistant organism we have observed repeated failure with laboratory-guided rational therapy, yet unexplained success when additional drugs—of doubtful activity against the particular organism—were employed. Such multiple antibiotic "shotgun" therapy must be accepted for the desperately ill patient with acute endocarditis awaiting laboratory studies, and for the rare case where carefully selected bactericidal antibiotic combinations have failed to eradicate the infection. However, these exceptional situations should not detract from the validity of the rational approach.

**Summary**

The advent of penicillin has converted bacterial endocarditis from a uniformly fatal to a readily curable disease in most instances. However, the treatment of some cases still presents great difficulties. Efforts must be made to obtain the etiologic organism in every patient.

The frequently employed laboratory tests for bacterial sensitivity to antibiotics ("disk test") are meaningless and misleading in endocarditis. They measure bacteriostatic drug effects, whereas in endocarditis bactericidal, antibiotics must be employed. By the use of suitable examinations, the laboratory can suggest the single or combined drugs and doses necessary to kill the organisms. The adequacy of the antibiotic dosage regimen may be evaluated (in addition to sterile blood cultures) by the bactericidal action of the patient’s serum against the organism previously isolated from his blood stream.

When the endocarditis is caused by drug-resistant bacteria, bactericidal antibiotic combinations may have to include toxic drugs for prolonged treatment periods. The risk of employing the drug has to be weighed in each case against the risk of possible treatment failure due to its omission. Using these principles we have been fortunate in curing a high proportion of "tough cases" of bacterial endocarditis.

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**Summario in Interlingua**

Depost le advento de penicillina, endocarditis bacterial ha cessate esser un condition uniformemente mortal e es hodie un morbo prestemente curabile in le majoritate del casos.
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Tamen, in certe casos le tractamento remane difficilissime. On debe efforitar se a obtener le organismo etiologic in omne patiente individual.

Le frequentemente emplote tests laboratorial pro determinar le sensibilitate bacterial a antibioticos ("test a discos") ha nulle valor e es mesmo illudent in le caso de endocarditis. Illos mesure efectos bacteriostatic del droga, sed in endocarditis antibioticos de forta bactericida debe esser emplote. Super le base de appropriate examine, le laboratorio pote proponer le droga o combination de drogas e le dosage necessari pro occidar le organismos. Le adequatia del dosage de antibiotic pote esser evaluate—a parte le obtention de sterile culturas de sanguine—per observar le action bactericida del sero del patiente contra le organismo previemente isolate ab su circulacion de sanguine.

Quando le endocarditis es causate per bacterios pharmacoresistente, il pote devenir necessari includer in le combination de antibiuticos bactericida un supplemento de drogas toxic e administrar los durante prolongate periodos de tempore. Le risco representate per le uso del drogas toxic pote esser ponderate in omne caso individual contra le risco de un possibile fallimento del tractamento si illos es omittite. Per le uso de iste principios nos ha habite le bon fortuna de curar un alte percentage de "casos recalcitrante" de endocarditis bacterial.

REFERENCES


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