PROGRESS IN MANAGEMENT OF PATIENTS WITH INFECTIVE ENDOCARDITIS

C. GLENN COBBS and (*by invitation*) WILLIAM E. DISMUKES and ROBERT B. KARP

BIRMINGHAM

The purpose of this communication is to review some observations accumulated by our group at the University of Alabama School of Medicine regarding the management of patients with infective endocarditis. I would like to begin by acknowledging the guidance and assistance of three physicians from my fellowship days at New York Hospital-Cornell Medical Center; Edward W. Hook, Donald Kaye, and the late Anthony S. Werner; and Frank M. Griffin, Thomas N. James and T. Joseph Reeves from the University of Alabama School of Medicine.

Infective endocarditis is an area of special interest among those of us in Infectious Diseases but a number of physicians from all disciplines have contributed to our understanding of this disorder. Some noteworthy milestones in the history of endocarditis are shown in Table 1. Morgagni (1) and later Virchow (2) described the pathologic anatomy of this disorder and Osler (3), in his Gulstonian lecture in 1885, provided one of the first useful clinical descriptions in the English literature. Osler first distinguished between "primary" and "septic" endocarditis. "Primary" subsequently became known as "subacute bacterial endocarditis" and "septic" as "acute endocarditis". Bacterial endocarditis was generally considered a fatal disorder until around 1900 when a few scattered reports described rare "spontaneous" cures particularly in patients with disease caused by the gonococcus. During the 1930's there appeared descriptions of successful use of fever therapy for gonococcal endocarditis (4) and publication of case reports of cures with prontosil (5).

Although initial experience with penicillin in the early 1940's was not very encouraging (7) the dosage employed was quite low (250,000 to 1,700,000 units total dose) and the duration of therapy brief (9–26 days). However soon afterwards, investigators using larger dosages and longer duration of penicillin therapy reported successful outcomes. By 1950 antimicrobial therapy with penicillin was fairly well standardized (9).

Nevertheless, in spite of the life saving effect of penicillin therapy, the

---

From the Department of Medicine, University of Alabama in Birmingham, Birmingham, Alabama

Reprints should be addressed to: C. Glenn Cobbs, M.D., University of Alabama in Birmingham, University Station, Birmingham, AL 35294

TABLE 1.
Some Milestones in (Therapy of) Infective Endocarditis

Date	Event	Investigator(s)
1769	Early pathologic description.	Morgagni JB (1)
1847	Further descriptions of gross and microscopic anatomy.	Virchow R (2)
1885	Description in English literature.	Osler W, Gulstonian Lecture (3)
1937	"Cure" of gonococcal endocarditis with fever therapy.	Williams RH (4)
1938	"Cure" of rare patient with prontosil therapy.	Major RH, Leger LH (5)
1939	Treatment with heparin.	Friedman M, Hamburger WW, Katz LN (6)
1943	Failure of very low dose penicillin therapy.	Committee National Research Council, Keefer CS, Blake FG, Marshall EK, et al (7)
1944	Cure with penicillin plus heparin.	Loewe L, Rosenblatt P, Greene HJ, et al (8)
1950	Appreciation of importance of bactericidal agent(s) in therapy.	Hunter TH (9)
1965	Surgical excision of valve during active infection (Klebsiella endocarditis).	Wallace AG, Young Jr WG, Osterhout S (10)
1972	Additional reports of improved outcome with surgical intervention during active infection.	Griffin FM, Stinson EB, Wilson WR, Boyd AD, Rahimtoola AH and others

outlook for many patients with infective endocarditis was still grim. Cates and Christie, in a classic study (11), demonstrated high mortality, approaching 50 per cent, among patients treated in Great Britain. They also emphasized the striking increase in mortality in patients with moderate or severe heart failure. Indeed heart failure was reported to account for at least 50% of the deaths occurring after otherwise successful therapy of this disease.

During the late 1960's and early 70's, at the University of Alabama School of Medicine, we found ourselves with a superb cardiovascular program and a large number of patients with infective endocarditis. Initially our surgical colleagues were reluctant to replace heart valves early in patients with heart failure and active infection but as we gained experience they began to intervene earlier and earlier during active disease. In 1972, we reviewed our experience both with patients operated upon and not, and analyzed our results, concentrating initially on aortic valve disease (12). Survival in patients with native aortic valve endocarditis and mild or moderate heart failure was significantly improved by early valve replacement. Table 2 which details the outcome in 63 such patients demonstrates these findings. Among 18 patient with moderate heart failure or worse who were not operated upon, all died, whereas only

TABLE 2.
Mortality in Native Valve Endocarditis and Severity of Heart Failure During Active Infection[1]

	Aortic Valve Disease With or Without Mitral Involvement	
	Mild Heart Failure or Less	Moderate Heart Failure or More
Treated medically	2/10	18/18
Treated surgically during active infection (Valve replacement)	0/8	5/27

[1] Modified from Griffin FM, et al, 1972 (12).

TABLE 3.
Duration of Effective Antimicrobial Treatment Before Surgery (42 Patients)[1]

Duration	Number
Less than 7 days	8
8–14 days	4
More than 14 days	30
Relapses	0
Mean duration	16 days

[1] Modified from Griffin FM, et al, 1972 (12).

5 of 27 who were treated both medically and surgically and who had the same degree of heart failure succumbed. In this context moderate heart failure was defined as heart failure which responded completely to digitalis treatment alone—equivalent to New York Heart Association classifications II to III. Table 3 reveals the duration of antimicrobial therapy before surgery in 42 patients operated upon before 1972 who had aortic and mitral valve lesions. Twelve received less than 2 weeks therapy and 8 less than one. In spite of this brief duration of treatment before surgical intervention there were no relapses caused by the original infecting microorganism. Figure 1 shows the complications which occurred in these patients. Among those patients with aortic valve endocarditis with or without mitral involvement the incidence of complications was about equal among those treated medically and those treated both medically and surgically. However in every catagory of complication the mortality was greater in the medically treated group.

In 1977 our group at UAB took another look at the results of surgical intervention in patients with active endocarditis (13). In this study we found that patients with native valve endocarditis (NVE) and heart failure appeared to do better with surgery plus medical therapy than they did with medical therapy alone regardless of the valve involved. The mortality of early prosthetic valve endocarditis (PVE), that is, infection occurring less than 60 days after valve implantation, was not improved by surgical treatment. In addition a positive culture at the time of surgery did not prejudice outcome. Patients with staphylococcal disease appeared

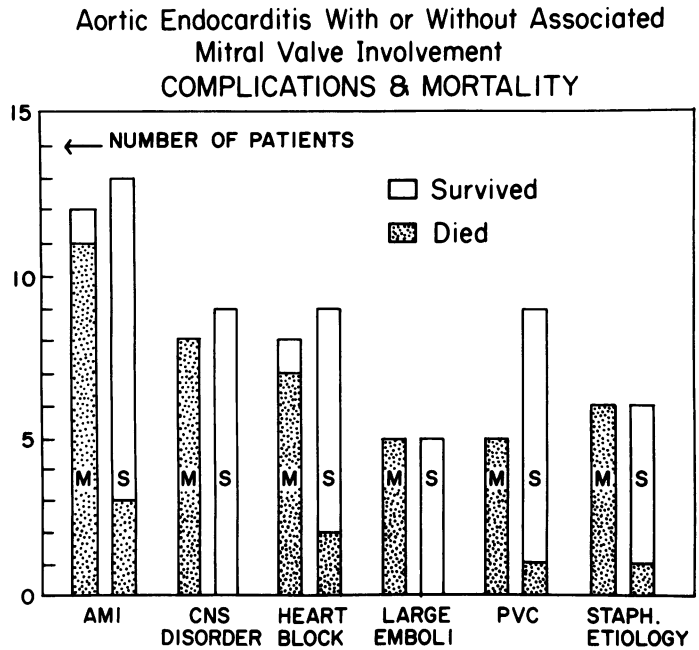

FIG. 1. *Aortic endocarditis with or without associated mitral: valve involvement.* The bars represent the number of patients with a particular disorder AMI (acute myocardial infarction), CNS disorder (mycotic aneurysm, abscess or embolus), PVC (premature ventricular contraction). The bars with an "M" represent patients treated medically, those with an "S" those treated with both medical and surgical therapy.

TABLE 4.
Mortality in Native Valve Endocarditis[1]

	Mild Heart Failure or Less	Moderate Heart Failure of More
Treated medically	3/22	21/32
Treated medically and surgically	3/49	8/32

[1] Modified from Richardson JV, et al, 1978 (13).

to do better with surgery than without. Also sudden onset of low cardiac output syndrome was highly correlated with the presence of emboli to the coronary arteries. Table 4 illustrates these findings in 135 patients with NVE. With medical therapy alone 21 of 32 patients with significant heart failure died; with both medical and surgical therapy only 8 of 32 died.

Table 5 shows our results in patients with prosthetic valve endocarditis. When there was moderate heart failure or worse mortality was 100% unless surgery was carried out. In comparison, the mortality was approximately 40% with combined medical and surgical treatment.

TABLE 5.
Mortality in Prosthetic Valve Endocarditis[1]

	Mild Heart Failure or Less	Moderate Heart Failure or More
Treated medically	1/4	8/8
Treated medically and surgically	4/10	11/25

[1] Modified from Richardson JV, et al, 1978 (13).

TABLE 6.
Current Controversies in Management of Patients with Infective Endocarditis

Problem	Controversy
1. Control of infection.	Best medical regimen, especially for streptococcal and staphylococcal disease.
2. Control of heart failure.	Timing of surgical intervention in moderate to severe heart failure.
3. Management of patient with an embolic event and/or a "positive" echocardiogram.	Indications for surgery.
4. Management of cerebral aneurysm(s).	Coordination and timing of cardiac and neurosurgery.
5. (Early) prosthetic valve endocarditis.	Should all have surgery?

We are presently involved in a multicenter study investigating the treatment of PVE caused by *S. epidermidis*. Preliminary data confirm a high mortality with medical treatment alone and improved survival with combined medical and surgical therapy.

Some current controversies regarding management of patients with infective endocarditis are listed in Table 6. Clearly there are many schemes which appear to be effective for therapy of so-called "sensitive" viridans streptococcal disease, but there is no agreement as to which is best. For patients with staphylococcal infection our second analysis (13) suggested that all patients with staphylococcal endocarditis, except intravenous drug addicts, would probably benefit from valve replacement during active infection. This conclusion was challenged (14, 15) and subsequent experience has led us to modify our recommendations. We no longer advise surgical intervention if a patient with staphylococcal infection is stable and not in heart failure. Investigators are still trying to refine indications and timing for valve replacement in patients who have heart failure. Also, there is still considerable disagreement regarding the precise indications for surgical intervention in patients with systemic emboli. In the past some have recommended valve debridement or replacement for patients with two major embolic events or one major event and an echocardiogram showing definite vegetation on a left-sided valve. Others presently feel these indications are too radical. Two other

important problems are the coordination of neurosurgery and cardiovascular surgery for patients with mycotic aneurysms of the cerebral circulation (16) and the question whether or not all patients with early PVE should have valve replacement once that diagnosis is made.

Table 7 lists some investigations currently underway. As noted our group is presently participating in a collaborative study of the treatment of *S. epidermidis* prosthetic valve endocarditis. We are examining vancomycin and rifampin, with or without gentamicin, for treatment of this disorder. Preliminary results suggest improved survival with all three agents compared to results obtained when a cephalosporin comprised the major portion of the antimicrobial regimen. We have also been involved in discussions regarding the standardization of treatment of "sensitive" viridans streptococcal disease. A number of investigators are examining new antimicrobial agents in the rabbit model of infective endocarditis. One agent which is particularly interesting is thienamycin, the penicillin-like drug which has activity against enterococcus and *S. epidermidis*. Several investigators are evaluating the predictive value of certain *in vitro* procedures such as the Schlichter test (serum bactericidal titer), time-kill curves and examination of bacterial strains for tolerance. Finally in association with our surgical colleagues we are continuing to try to further refine indications for and timing of surgical intervention.

Table 8 lists our present indications for surgical intervention in infective

TABLE 7.
Investigations Currently Underway Which May Improve Care of Patients with Infective Endocarditis

1. Evaluation of vancomycin, rifampin ± gentamicin in S. epidermidis prosthetic valve endocarditis.
2. Standardization of treatment of "sensitive" viridans streptococcal disease.
3. Evaluation of new antimicrobial agents in animal models.
4. Reevaluation of predictive value of *in vitro* tests (i.e., serum bactericidal titer, time-kill curves, "tolerance," etc.) in bacterial endocarditis.
5. Further analysis of indications for and timing of surgical intervention.

TABLE 8.
Indications for Surgery in Active Infective Endocarditis

Indication	Comment
1. Heart failure, NVE or PVE	Emergent valve replacement for severe heart failure. Urgent intervention for progressive disease.
2. "Resistant" microorganism	Especially fungal endocarditis and endocarditis caused by bacteria not susceptible to penicillin-type agents.
3. Systemic emboli	Indication stronger in PVE than NVE. Valve debridement may suffice in NVE.

endocarditis. We advise emergent valve replacement for patients with this disorder and severe heart failure and urgent operation for those with progressive heart failure. The presence of an infecting microorganism which is resistant to available antimicrobial therapy is another indication for surgical intervention. Persistent fever, toxicity and skin manifestations along with bacteremia or fungemia are frequently present in this circumstance.

In patients with evidence for systemic emboli the indication for surgical intervention seems most clear in the case of prosthetic valve infections.

Progress in management of endocarditis has been slow. Success rates leveled off in the 1950's and 60's following the introduction of effective antimicrobial therapy. Further advances in the care of patients with this disorder will necessitate the closest coordination and collaboration between specialists in Infectious Diseases, Surgery and Cardiology. Only with such collaboration will we be able to provide optimal care for patients with this serious disorder.

BIBLIOGRAPHY

1. Morgagni JB: *The seats and causes of diseases.* Translated by Benjamin Alexander. London: Millar & Cadell; 1769:Vol 1, Book 2, Letter 24, Article 18: p 730–731; Letter 26, Article 17: p 803 (Pp. 253 and 277 of original). (Referenced in: Kerr A. *Subacute Bacterial Endocarditis.* Illinois: Charles C Thomas Publisher; 1955:298.)
2. Virchow R: Ueber die akute Entzündung der Arterien. *Arch Pathol Anat* 1847; **1:** 272–378.
3. Osler W: Gulstonian Lectures on malignant endocarditis. *Lancet* 1885; **1:** 415–8, 459–64, 506–8.
4. Williams RH: Gonococcal endocarditis treated with artificial fever (Kettering Hypertherm). *Ann Int Med* 1937; **10:** 1766–74.
5. Major RH, Leger LH: Recovery from subacute infectious endocarditis following protonsil therapy. *JAMA* 1938; **111:** 1919–20.
6. Friedman M, Hamburger WW, Katz LN: Use of heparin in subacute bacterial endocarditis. *JAMA* 1939; **113:** 1702–3.
7. Keefer CS, Blake FG, Marshall EK, Jr, et al: Penicillin in the treatment of infections, a report of 500 cases. *JAMA* 1943; **122:** 1217–24.
8. Loewe L, Rosenblatt P, Greene HJ, et al: Combined penicillin and heparin therapy of subacute bacterial endocarditis, report of seven consecutive successfully treated patients. *JAMA* 1944; **124:** 144–9.
9. Hunter TH: Speculations on the mechanism of cure of bacterial endocarditis. *JAMA* 1950; **144:** 524–7.
10. Wallace AG, Young WG, Osterhout S: Treatment of acute bacterial endocarditis by valve excision and replacement. *Circulation* 1965; **31:** 450–3.
11. Cates JE, Christie RV: Subacute bacterial endocarditis: A review of 442 patients treated in 14 centers appointed by the Penicillin Trials Committee of the Medical Research Council. *Quarterly J Med* 1951; **20:** 93–130.
12. Griffin FM Jr, Jones G, Cobbs CG: Aortic insufficiency in bacterial endocarditis. *Ann Int Med* 1972; **76:** 23–8.
13. Richardson JV, Karp RB, Kirklin JW, et al: Treatment of infective endocarditis: A 10-year comparative analysis. *Circulation* 1978; **58(4):** 589–97.

14. Kaye D: Editorial: Cardiac surgery in infective endocarditis. *Drug Therapy: Clinical Therapeutics in the Hospital* 1979; December: 8–9.
15. Rapaport E: Editorial: The changing role of surgery in the management of infective endocarditis. *Circulation* 1978; **58(4):** 598–9.
16. Jara FM, Lewis JF, Magilligan DJ: Operative experience with infective endocarditis and intracerebral mycotic aneurysm. *J Thorac Cardiovasc Surg* 1980; **80:** 28–30.

DISCUSSION

Allison (New Orleans): Have there been any human or animal studies utilizing fibrinolytic enzymes to modify the management of patients with bacterial endocarditis? In the very early human studies, combinations of penicillin and anticoagulants such as heparin were used together but bleeding problems encountered proved to be a major deterrent to further use. More recently, fibrinolytic therapy in humans with either streptokinase or urokinase has also been complicated by the tendency to bleed. Now that the cardiologists are capable of introducing fibrinolytic enzymes directly into the coronary arteries to lyse occluding platelet-fibrin thrombi to minimize the size of myocardial infarcts, I wonder if the same technique has been applied to the vegetations found in bacterial endocarditis involving either the aortic cusps or the mitral valve. Application of this technique to vegetations on the right side of the heart would be much easier to accomplish. It should be helpful in limiting the size of the vegetations, hasten their resolution, and perhaps, enhance contact of immunoglobulins with bacteria as well as promote entry of phagocytic cells, and even increase penetration of anti-bacterial drugs into the matrix of the vegetation to improve management of this complex problem. I know of no published information in this area and would like to ask if there has been any experience from other institutions.

Barondess (New York): Glenn, that was a beautiful, clear and useful review. In aortic valve endocarditis, the appearance of heart failure usually signals substantial destruction of the valve, with cusp perforation or cusp destruction, and since that's tolerated so much less well than say, mitral valve endocarditis, I wonder what you're presently doing about initiation of antimicrobial therapy in people suspected of having endocarditis on the aortic valve. Do you hold back, waiting for cultures, or do you just draw the cultures and start treatment? How do you attempt to protect the valve against perforation?

Cobbs: In considering the care of patients with endocarditis the two questions are really, how to treat and when to treat, and we've always tried to separate these in our minds. We emphasize to the housestaff that they can look up the recommended therapy for many types of bacterial endocarditis but it is often more difficult to know *when* to initiate therapy. We have established some guidelines which apply to patients suspected of having active bacterial endocarditis. If a patient presents and appears

"clinically" to have infective endocarditis, for example, they've had dental work, they have fever and a murmur, and peripheral cutaneous stigmata, then we would obtain blood cultures and initiate therapy. We would do this no matter what valve we anticipated was involved. If a patient is critically ill, we might intervene surgically as well as medically even before we had blood culture reports available. However, most of the time, one makes some judgement early on as to the clinical liklihood of the disorder, obtains three or four blood cultures and proceeds to treat or not. Certainly when the aortic valve is involved clinical deterioration may proceed very quickly. I might add that in that circumstance one is going to recommend emergent surgery in almost every case. On the other hand, if one can control the infection before heart failure occurs one may avoid valve replacement.

McGuire (Charlottesville): One of the principal models, I believe, in your referring to animal models of endocarditis, involves leaving a catheter across a heart valve, primarily the aortic valve, exposing the animal to bacteremia, and producing endocarditis. The model has interested some of us who were involved with cardiac catheters prior to the development of the model of its relevance to clinical endocarditis. It may be interesting to recall what cardiologists faced 15 years ago when trying to decide which would be the best system for permanently implanted cardiac pacemakers. Some of us were concerned that leaving intravascular hardware in the form of a catheter for a long period of time would create an epidemic of tricuspid endocarditis which never materalized. Can you tell us, in view of that, the clinical relevancy of the model or why our current pacemakers seem to have so few problems with tricuspid endocarditis?

Cobbs: I am unsure of the precise clinical relevance of catheter induced infective endocarditis in animals to the infrequency of rightsided endocarditis in human beings with transvenous pacemakers. I believe the most useful aspect of the animal models of infective endocarditis, especially the rabbit model, has been their help in providing us some understanding about antimicrobial therapy, for example, how long it takes to sterilize a valve using various antimicrobial combinations, etc. It is certainly clear that catheters placed across the tricuspid valve rarely become infected. It is really an unusual complication which few people have seen or at least reported.

Hook (Charlottesville): Glenn, would you comment on the reasons that heart failure seems to exert such a deleterious effect. Is it simply the result of hemo-dynamic consequences of valve injury or is there evidence that maybe microbial multiplication is harder to control in patients with heart failure?

Cobbs: Well let me say—I was hoping when I put your name on the slide acknowledging your assistance it would encourage you to not ask

difficult questions. Actually I don't believe heart failure *per se* has been shown by anyone to interfere with the effectiveness of antimicrobial therapy. I suppose it is possible that the severity of the infection which relates to the virulence of the microorganism and its ability to destroy valve tissue and cause heart failure is in some way associated with microbial inoculum and local anatomy. In other words there may be a correlation between two things, a particularly virulent microorganism and early and severe heart failure. However, I am unfamiliar with any data which correlate failure of antimicrobial therapy and degree in heart failure.

Logue (Atlanta): Powell, et al reported 15 instances of endocarditis secondary to abdominal infections. Four of them were related to Swan-Ganz catheters that had been in place for some period of time.

Cobbs: I wonder if anyone else has noticed a susceptibility of patients with Swan-Ganz catheters to infective endocarditis. I have not seen that myself. It is possible that pulmonary suppuration at the site of the catheter tip might predispose to transient bacteremia but I don't recall reading about endocarditis specifically in patients with Swan-Ganz catheters.