Endocarditis Complicating Open-Heart Surgery

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Bacterial endocarditis following intracardiac surgery for congenital defects with use of extracorporeal circulation is a new entity, as old only as open intracardiac surgery. The reported experience is therefore meager. Suggestions regarding its pathogenesis, recognition, behavior, management, and prevention are few.

Heins and Linde reported five cases of bacterial endocarditis in a series of 205 heart defects repaired with extracorporeal circulation. They stress the facts that the classical signs usually associated with bacterial endocarditis are absent and that the bacterial flora encountered is unusual and frequently antibiotic resistant. Two of their patients acquired their infection with achromobacter from a contaminated heart-lung machine when ethylene oxide sterilization rather than autoclaving was employed. One of their five cases died. Of additional interest, fever occurring shortly after surgery was the only clue that ultimately led to diagnosis.

Mandel et al. first reported a case of bacterial endocarditis following repair of an interventricular septal defect. The operation was performed under hypothermia and coronary perfusion. The infecting organism was Staphylococcus aureus, and the patient died. Their review of the literature revealed 30 cases of endocarditis following operations for repair of congenital and acquired cardiac lesions but none of these was done with extracorporeal circulation.

Teitel and Florman reported an unusual case of Pseudomonas aeruginosa infection on a silk suture used in the repair of an atrial septal defect with extracorporeal circulation. The infection resisted medical therapy until the infected suture was removed at a second operation 1 year later.

Two proved and one suspected case in a series of 20 operative procedures performed by our group for congenital cardiac defects performed with extracorporeal circulation prompted this report. It is thought that certain suggestions regarding its management might be deduced from the cases reported. Questionnaires sent to several groups performing this type of surgery are the basis for a summary of additional experience.

Case Reports

Case 1

A. M., an 11-year-old girl was admitted to the hospital for surgical repair of an interventricular septal defect. On physical examination a grade-IV pansystolic murmur was audible over the entire precordium with maximal intensity in the pulmonic area. A grade-II middiastolic murmur was also heard at the left sternal border and at the apex. Staphylococcus aureus hemolyticus, coagulase positive, was found in culture of the nose and throat. This organism was sensitive to nine antibiotics including penicillin, chloramphenicol, and erythromycin.

On November 12, 1958, repair of the ventricular septal defect during extracorporeal circulation was undertaken. A Mark-Cooley oxygenator and Sigmamotor pumps were employed. An interventricular septal defect measuring 15 mm. in diameter was found high in the membranous septum and was repaired with a 10-mm. compressed Ivalon patch sutured in place with 3-0 braided silk continuous and interrupted sutures. The high location of the defect made suture of its upper margin difficult. Perfusion lasted 30 minutes, and the entire operation required 2 hours and 45 minutes. The patient withstood the procedure well and was returned to the recovery room in good condition.

Two and a half hours after surgery, the temperature had risen to 102.4 F, and through the sixth postoperative day the daily temperature peak was 102.8 or higher.

Procaine penicillin 400,000 units and streptomycin 0.5 Gm. intramuscularly twice daily had
been administered for 2 days prior to surgery and were continued the first 2 days postoperatively (fig. 1). Intravenous aqueous penicillin (1,000,000 units per day) was begun on the day of surgery. On the third postoperative day, the penicillin and streptomycin were discontinued because of urticaria and intravenous chloramphenicol (500 mg. twice daily) was begun. On the fifth postoperative day, this dosage was changed to 250 mg. intravenously every 6 hours.

Blood cultures drawn on the second, third, and fourth postoperative days grew Staphylococcus aureus hemolyticus, coagulase positive. In vitro sensitivity tests revealed the organism to be sensitive to chloramphenicol and novobiocin and resistant to penicillin. Subsequently on the fifth postoperative day, novobiocin (100 mg. every 6 hours intramuscularly), and aqueous penicillin (2,000,000 units per day intravenously) were instituted. Chloramphenicol was continued as chloramphenicol palmitate (250 mg. every 8 hours by mouth). On the sixth postoperative day, the daily dose of penicillin was increased to 20,000,000 units and probeneid (0.25 Gm. three times a day) was started. The patient improved clinically.

At this time, a new, prominent harsh systolic murmur was heard along the left sternal border. Reoperation was considered but was deferred in view of the patient's good clinical response to antibiotic therapy, and the mortality risk of a second surgical procedure. A careful examination of the literature yielded relatively little information useful in guiding us in the management of this problem.

The fever gradually subsided, six blood cultures drawn between the sixth and fifteen postoperative days were negative, and the previously mentioned murmur diminished in intensity. On the fifteenth postoperative day, penicillin, probeneid, and novobiocin were discontinued. Chloramphenicol was continued. On the nineteenth postoperative day, the temperature spiked to 101.6 F.; serial blood cultures drawn on the following 3 days grew Staphylococcus aureus, coagulase positive. The in vitro sensitivity tests were unchanged, and the temperature was not elevated at this time.

On the twenty-eighth day, because of the positive blood cultures, novobiocin and penicillin were restarted. The temperature dropped to within normal limits and the patient appeared to be doing well. Serial blood cultures were sterile.

On the forty-eighth postoperative day, 20 days after its readministration, penicillin was discontinued. The patient's clinical condition continued to be good, and on the sixty-sixth postoperative day, all antistaphyloccocal medications were terminated.

Two days thereafter the temperature spiked to 104.8 F., the patient became toxic, and petechiae and splinter hemorrhages were noted. Serial blood cultures were positive for Staphylococcus aureus, coagulase positive. Despite vigorous antimicrobial therapy with a variety of anti-staphyloccocal agents, the patient's clinical condition rapidly deteriorated. She died seventy-four days after surgery. Intra-cardiac postmortem blood cultures demonstrated Staphylococcus aureus.

Postmortem examination revealed the Ivalon sponge to be partially detached at the postero-superior rim. A pulmonary thromboembolus was found in the left lower lobe.

Microscopic examination of sections of the Ivalon sponge and an overlying fibrinous deposit demonstrated dense infiltration of the fibrinous mass by hematoxylin-stained masses of cocci. A microscopic embolus containing clumps of cocci in a small arterial branch in the left lower lobe was also noted. No further site of infection could be found on the heart valves, in the region of the septal defect, or on the silk sutures.

Case 2

N. S. was a 12-year-old obese boy in whom the diagnosis of infundibular pulmonary stenosis with interventricular septal defect without clinical cyanosis was made on the basis of cardiac catheterization. Significant physical findings consisted of a grade-IV harsh systolic murmur heard best in the second left intercostal space. Nose culture yielded hemolytic staphylococcus albus, coagulase-positive, mannite negative, and sensitive to 10 antibiotics including penicillin, chloramphenicol, streptomycin, and erythromycin. (fig. 2). On September 24, 1959, through a transternal incision with use of a Mark-Cooley oxygenator and Sigmamotor pumps for extracorporeal circulation and intermittent aortic occlusion to produce cardiac arrest, a 10-mm., high interventricular septal defect was repaired through a right ventriculotomy with interrupted 4-0 braided silk sutures. Closure was difficult, and closely placed sutures were necessary. The infundibular stenosis was corrected by removal of markedly fibrotic endocardium. The ventriculotomy was closed with continuous braided 3-0 silk. Total bypass time was 61 minutes, and the heart was open for 56 minutes. The only untoward reaction occurred early when transient superior vena caval obstruction of 10 to 15 minutes' duration was reported by the anesthesiologist.

The patient received no preoperative antibiotics, but postoperatively 300,000 units of procaine penicillin were given intramuscularly every 8 hours and 2 Gm. of chloramphenicol daily by continuous intravenous drip for 7 days. He awoke fairly promptly postoperatively but the next morning he became confused, developed car-

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pal spasm, and fever to 103 F. By the second postoperative day his temperature had reached 105 F., and ear-papped spasms with turning of the head to the right side and coma supervened. The white cell count was 18,000. A diagnosis of cerebral edema secondary to transient superior vena cava obstruction was made. A neurosurgeon advised acetazolamide (Diamox) 250 mg. intramuscularly daily, diphenylhydantoin sodium (Dilantin) 100 mg. intramuscularly every 4 hours, and phenobarbital in 0.060-Gm. doses as necessary to control convulsions. Cooling by use of a water mattress was also employed. The child's condition gradually improved with lightening of coma and subsidence of temperature to between 97.2 and 101 F. By the eighth day his sensorium cleared and blood cultures were negative, so that the chloramphenicol and the Diamox were discontinued.

On the ninth postoperative day he was digitalized because of a persistent tachycardia. Temperature again rose to 105 F., the white cell count was reported as 35,250, and erythromycin, 500 mg. every 6 hours, was administered. Blood cultures taken this day before starting erythromycin were sterile. During the next 48 hours fever to 102.6 F. persisted, and 10 million units daily of sodium and potassium penicillin were given by continuous intravenous drip. The murmur was of considerably diminished intensity. After another week, the general condition of the patient improved so markedly, and the temperature response had been so gratifying that, in the face of blood cultures which were repeatedly negative, intravenous penicillin was discontinued. Cultures taken during the next 2 days revealed hemolytic staphylococcus aureus resistant to all antibiotics except chloramphenicol, albamacin, kanamycin, vancomycin, and ristocetin. Since the sensitivity studies were not reported for some days, erythromycin was continued and 25 million units of penicillin were given daily by continuous intravenous drip as well as 500 mg. of probenecid every 6 hours. A week later because of continued fever, erythromycin was replaced with novobiocin, 500 mg. every 6 hours. Seventeen blood cultures and one bone marrow culture have since been negative. Penicillin and probenecid were discontinued after another week, and chloramphenicol, 2-Gm. daily, was resumed. Fever persisted and ranged between 98.6 F. and 103 F. although the peaks became progressively lower. At no time during his illness did this child show petechiae, hematuria, spleno-
Megaly, or other evidence of embolic phenomena. Chloramphenicol was discontinued on November 9, 1959, and albamyacin on November 23, 1959. Antibiotics were given for a total of 7 weeks.

At the present time except for a suture sinus at the lateral end of the transsternal incision the boy has made a complete recovery from his surgery and presumably from his infection.

**Questionnaire Data**

To learn the magnitude of the problem of infection in open-heart-surgery procedures for congenital cardiac defects, a questionnaire was sent to several groups throughout the country (table 1).

**Discussion**

The factors to be considered in evaluating the pathogenesis of surgical bacterial endocarditis may be classed into three main groups: bacterial factors, local host predisposing factors, systemic predisposing factors.

**Bacterial Factors**

Staphylococcus is the most commonly encountered organism in this disease and unfortunately also the most widespread pathogen in our environment. Pathogenic staphylococci, coagulase-positive strains, have been found in from 25 to 30 per cent of cultures taken from normal adult noses and in 60 to 80 per cent of those from hospital personnel. In a series of 164 nose cultures taken from all personnel coming in contact with our cardiac surgical patients, 53 per cent grew Staphylococcus, 7 per cent of the pathogenic 80-81 phage type. One member of the team, responsible for the assembly of the heart-lung machine, was found to harbor this strain in his nose and might possibly have been the carrier in our first case. Skin and pharyngeal cultures of patients have also been found positive. Cultures of
operating room air almost invariably reveal organisms, sometimes as many as one colony per minute of exposure.5 Air-borne staphylococci can be found in as many as 10 per cent of operative procedures.6

The mere presence of bacteria, however, is not sufficient to result in clinical infection. In a study of traumatic wounds, Rustigian and Cipriani7 found that 100 per cent of the wounds contained large numbers of pathogenic bacteria covering a wide spectrum, while a relatively small percentage of patients developed clinical infection. An experimental evaluation of the factors that result in the development of clinical septicemia as opposed merely to bacteremia revealed that the virulence, kind, and dosage of organisms were extremely important.8 Experimental animals tolerate intravenously administered bacteria to a certain number with complete clearing from the blood stream by the lungs and parenchymatous reticuloendothelial organs (liver, spleen, lymph nodes). Beyond that number clinical infection supervenes. The lethal dosage varies from a single anthrax bacillus to many billions of nonpathogenic bacteria. Dosage therefore is critical in the outcome of the introduction of any particular bacterial organism into the circulation.

Because of the ubiquity of the Staphylococcus no single measure can assure absolute sterility in the operating field.6 Elaborate measures have been taken by some to control air-borne infection. These have included special masking devices in helmet form with an impermeable substance covering the nose and mouth and suction tubes to carry away exhalations. Careful attention to footwear and to traffic patterns, with introduction of decontamination zones prior to entry into the "sterile" operating area, are practicable measures.8 Virtual elimination of conversation during surgery is indeed advisable. The use of ultraviolet light in the range of 2500 A ± 200 (Ehrissmann and Noethling) to be used in the operating theater at all times is of proved value in greatly reducing the number of air-borne bacteria but has not found wide acceptance.10,11 Recently the incorporation of ultraviolet radiation into the air-conditioning system of the operating room has been reported to be of great benefit.12

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Table 1

<table>
<thead>
<tr>
<th>Total cases</th>
<th>Mortality</th>
<th>Proved cases of endocarditis</th>
<th>Deaths from endocarditis</th>
<th>Incidence of staphylococcus endocarditis</th>
<th>Other organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,585</td>
<td>19%</td>
<td>18</td>
<td>10</td>
<td>9</td>
<td>9+</td>
</tr>
</tbody>
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*Data from 12 groups reported by Dr. Henry T. Bahnson, Johns Hopkins Hospital, Baltimore, Md., Dr. George H. A. Clowes, Jr., Western Reserve University, Cleveland, Ohio, Dr. Denton A. Cooley, Baylor University, Houston, Texas, Dr. Frank Gerbode, Stanford University, San Francisco, Calif., Dr. Robert E. Gross, Children's Hospital, Boston, Mass., Dr. George Holswade, New York Hospital-Cornell Medical Center, New York, N. Y., Dr. George H. Humphreys II, Columbia Presbyterian Medical Center, New York, N. Y., Dr. Elliot S. Hurrwit and Dr. George E. Robinson, Montefiore Hospital, New York, N. Y., Dr. C. Walton Lillehei, University of Minnesota, Minneapolis, Minn., Dr. Leonard M. Linde, University of California at Los Angeles, Westwood, Calif., Dr. Jere Lord (authors' cases), and Dr. Andrew G. Morrow, National Heart Institute, Bethesda, Md. The authors gratefully acknowledge their assistance and cooperation.

†Other organisms were: 1, Streptococcus fecalis; 2, Achromobacter; 1, Pseudomonas; 2, Candida guillermondii; 3, not specified.
The recent publications of Adams and Fahlman have shown quite impressively that any area in an operating suite can be rendered nearly sterile by sufficient mechanical cleansing and by the application of detergent-disinfectant solutions to all articles entering or present within the suite. Proper isolation and protection technics then help to maintain this sterility.

Periodic culture studies of operating-room personnel and other contacts have revealed the presence of staphylococci at different times that have been difficult to eradicate permanently by either topical or systemic antibiotic therapy. Banning key personnel from the operating theater because of culture studies could have disastrous consequences on the performance of a medical unit. It would seem, therefore, that the other measures cited should be used to keep down the amount of air-borne contamination. In instances of personnel having infected skin lesions, however, it would seem imperative to ban these individuals from the operating theater.

Instrument and Pump Sterilization

Instrument and pump-borne contamination should be nonexistent with the availability of equipment that can be thoroughly cleaned of debris, autoclaved, and assembled under sterile conditions prior to use. In the data presented from other centers two infections were ascribed to pump contamination when ethylene oxide sterilization of the heart-lung machine was used. Kirklin is quoted by Teitel and Florman as having experienced Pseudomonas infections during the time when the mechanical pump oxygenator was sterilized by filling with benzalkonium chloride (Zephiran). In January 1957, autoclave sterilization of all parts of the oxygenator except lucite reservoirs was introduced. The reservoirs were sterilized with formaldehyde, and infection was controlled. Keown reported five cases of fatal Pseudomonas septicemia when their extracorporeal circulation apparatus was cold sterilized with Zephiran. When their mode of sterilization was changed, infection ceased to occur. All parts of the heart-lung machine coming in contact with blood are sterilized by autoclave in our hospital.

At two sites in the usual open-heart technic direct contact is made between sterile and nonsterile or nonautoclaved fomites—one at the coupling for pressure recordings, the other at the coupling of the oxygen tank to the oxygenator. Since Staphylococcus remains viable for weeks or even months when dried in pus or fomites, the possibility of massive contamination exists. Attempts have been made to pass the oxygen stream through various baffles but it would appear that infection would occur more often were this a portal of entry. Pressure gages are sterilized by immersion in Zephiran solution. Autoclaving would seem preferable but in view of the large numbers of right-sided heart catheterizations with pressure recordings that are performed daily without endocarditis, it would seem unlikely that this alone contributes significantly to contamination.

Dosage of Contaminating Organisms

It has long been recognized that repeated injections of small doses of organisms into the circulation are poorly tolerated. When septicemia was a more common problem than at present, it was known that septic thrombophlebitis was a relatively common cause of initiation and persistence of septicemia. Indeed we know of two cases, and a third is reported in the summary of reported cases, in which a septic thrombophlebitis, sometimes difficult to recognize as such, was responsible for septicemia and death of the patient. Accordingly, the formerly casual attitude towards venous cut-down has been changed so that it is now performed in the operating theater under the same conditions as the major portions of the operation. Polyethylene catheters are removed from veins as soon as possible. Although one of our patients repeatedly developed thrombophlebitis, septic thrombophlebitis could not be demonstrated. In one of the cases reported by Cooley (personal communication), septic thrombophlebitis was the focus for development of septicemia.
The unfortunate introduction of organisms via contaminated blood has frequently resulted in death because of the massive contamination involved. One of the cases reported by Cooley was thought to be due to contaminated blood but the patient survived. It is a credit to blood-banking activities that this accident does not occur more often, since the opportunity for contamination during skin puncture is ever present. Although normal serum will inhibit the growth of many bacteria, it will not inhibit the growth of pathogenic coagulase-producing bacteria.¹⁴

The possibility of infection being introduced by means of a plastic prosthesis in spite of the fact that it can be autoclaved is ever present. Autoclaving is subject to pitfalls, since adequate sterilization with steam requires contact with every portion of the surfaces to be sterilized. Failure to eliminate air pockets from prepared packs is known to result in incomplete sterilization because of failure of penetration of the steam. Cultures from the surfaces of a prosthesis would not reveal contamination within its interstices. Much the same can be said for braided or woven suture material and would perhaps suggest that monofilament suture material be used. In the reported cases a clear-cut correlation between the use of plastic intracardiac prostheses, Ivalon sponge, and infection cannot be drawn because of insufficient detail.

Local Predisposing Factors

Local factors that predispose to endocarditis following transient bacteremia have long been known. Damaged heart valves, arteriovenous shunts, and coarctation predispose to endocarditis. Rodbard¹⁵ stated that vascular injury is not a prerequisite. High velocity flow through narrow orifices producing diminished lateral pressure locally determines the localization of the endocardial bacterial lesion. Endocarditis does not occur at large openings such as at interatrial septal defects or at the widely patent ductus arteriosus. If so, then absolutely complete closure of intracardiac defects with elimination of the very thin high-speed jets, which can occur between interrupted sutures or at needle holes, must be achieved to protect against bacterial endocarditis. It is difficult in the clinical case of infection at the site of closure of a defect to know whether the breakdown of a repair preceded or followed infection. In both of our cases there was difficulty in securing complete closure of the shunts, in the one because of the very high location of the interventricular septal defect with difficulty in finding adequate tissue to which to sew the upper border of the prosthesis, in the other because of persistence of a very small narrow jet between sutures.

The placing of foreign material within the heart, either a prosthesis or silk sutures, undoubtedly predisposes to infection. Elek and Coven¹⁶ showed experimentally that the subcutaneous inoculum of pathogenic staphylococci required to produce local infection in human volunteers could be reduced by a factor of 10,000 by the introduction of a single silk suture into the area. Bahnson et al.¹⁷ Jawetz,¹⁸ and others have reported the persistence of infection around intravascular suture material. There seems little doubt that when infection persists or recurs in the presence of an intracardiac prosthesis, the prosthesis must be removed to eradicate the infection. In case 1, removal of the prosthesis immediately after infection occurred might have resulted in its elimination and possibly in survival of the patient. Whether the use of absorbable suture material is indicated is unsettled. It would appear at the present time that the use of nonabsorbable material is a necessary and unavoidable hazard in the repair of intracardiac defects.

Systemic Factors

Systemic factors of importance in the development of infection may exist but if they were important, infection should occur more frequently. Transient metabolic acidosis, transient thrombocytopenia, transient disorders of liver, adrenal, and kidney function occur so universally that it would be difficult to incriminate them in this process among the survivors. For those who die during the
early postoperative period, however, frequently with marked alteration of physiologic processes, conceivably defensive mechanisms could be so unalterably changed that an unrecognized failure to defend against infection also exists. In experimental animals endocarditis can be produced on normal heart valves by the intravenous injection of staphylococci in the presence of arteriovenous fistulas. Presumably this occurs because of the increased work load imposed on the heart by the fistula. Dietary deficiency, shock injection of polysaccharides, bacterial extracts, cortisone, dinitrophenol, thyroxine, and organic acids, each is said to increase susceptibility to endocarditis.

**Therapy**

Antibiotic therapy is of inestimable value in the treatment of the proved case of endocarditis. As prophylaxis, especially in the dosages usually employed, its value is debatable. Both of our patients received prophylactic antibiotics postoperatively; case 1 receiving it for 48 hours preoperatively as well. One developed infection with a chloramphenicol-sensitive strain after having received 2 Gm. of chloramphenicol intravenously for 6 days postoperatively. Does this signify endogenous infection, a newly acquired exogenous infection, or merely re-exacerbation of previously existing but inadequately treated infection? Does this imply the emergence of antibiotic-resistant strains not recognized by our present bacteriologic methods? Does this indicate the need for more prolonged antibiotic therapy perhaps with a bactericidal rather than a bacteriostatic agent? In the absence of a large control series managed without prophylactic antibiotics, one can again only speculate. The study now being carried out by Kittle in which no prophylactic antibiotics are used in open-heart procedures should prove to be of great interest. Conceivably prophylactic antibiotics as now employed have helped to maintain the infection rate at its present overall low level.

The use of massive doses of penicillin as an adjunct in the treatment of "penicillin-resistant" staphylococcal infections is controversial. Resistant strains of this organism are found to produce penicillinase, which converts penicillin to penicilloic acid thus inactivating it. Penicillinase inhibitors (trypsin, chymotrypsin, quinine, and others) prevent this process. It is reasoned by some that perhaps penicillin itself in sufficient concentration will exhaust penicillinase activity. The crux of the controversy seems to hinge upon whether intrabacterial penicillinase can be so inhibited. Neither the need nor the ability of penicillin to accomplish this seems definitely settled. Clinical experience indicates that except when definitely penicillin-sensitive strains are encountered, even massive doses of penicillin used as the sole antibiotic cannot be relied upon to bring about clinical cure.

The occurrence of 39 per cent of all the cases of endocarditis recorded here in the 12 per cent of patients in whom prophylactic preoperative antibiotics were used is striking. Whether unproved cases were cured by antibiotics or prevented by certain aspects of technic cannot be said at the present time. If the experience in the reported series is significant, it would appear that the preoperative prophylactic use of antibiotics is associated with a higher incidence of postoperative endocarditis. All groups here reported used prophylactic antibiotics postoperatively.

**Recognition of Endocarditis**

The detection and management of endocarditis poses special problems. Heins and Linde stated that fever soon after surgery was often the sole clue. In our case 1 high fever 36 hours postoperatively associated with signs of pulmonary atelectasis was not suspected of being a sign of endocarditis, since this is a classical picture produced by these pulmonary changes during the early postoperative period. Blood cultures drawn 12 hours later revealed Staphylococcus. One wonders whether elimination of prophylactic antibiotics and repeated blood cultures during the first 3 days with antibiotic sensitivity
studies might not result in earlier diagnosis and more adequate and specific treatment with the very large doses of antibiotics required for eradication of this type of infection.

**Conclusions**

In conclusion, it would appear that the incidence of postoperative surgical endocarditis in patients who have had extracorporeal circulation for repair of congenital cardiac defects represents an unusual complication sustained not because of the usual low-grade contamination that occurs in every well-managed operating theater but rather because of massive contamination such as from contaminated blood, contaminated heart-lung machines, septic thrombophlebitis, or complete breakdown of aseptic technic. Early detection, as early as 24 to 48 hours postoperatively, depends entirely upon drawing frequent blood cultures, since it is during this period that fever, the major and frequently the only sign of postoperative endocarditis, occurs so often from relatively minor causes (atelectasis, blood in serous cavities, etc). Treatment for the proved case should probably be prolonged, specifically based upon studies of antibiotic bacterial sensitivity and probably include the use of bactericidal as well as bacteriostatic agents. Failure to respond to therapy or relapse after apparent response should lead to serious consideration of reoperation to remove infected foreign material from within the heart.

**References**

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