Infective endocarditis: Perioperative management and surgical principles

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Despite advances in microbial prevention and elimination, the frequency of endocardial infection is still increasing and it remains to be a serious condition. The strategies and aggressiveness of medical and surgical algorithms for managing these patients are evolving and having a significant effect on morbidity and mortality. This review addresses the current understanding of the processes by which the most common and most threatening complications occur, and the current management strategies that cardiologists and cardiac surgeons should be aware of when treating these seriously ill patients. (J Thorac Cardiovasc Surg 2014;147:1133-41)

Despite major advances in diagnostic modalities and antimicrobial therapies, infective endocarditis (IE) remains an extremely ominous infection, with a 1-year mortality rate of up to 40%. Management of these critically ill patients requires an understanding of the disease process in its various microbial, hemodynamic, embolic, and immunologic forms. At the time of diagnosis, patients have often progressed to complications through 1 aspect of the disease. An appreciation of the spectrum of the disease processes is crucial for providing a timely and effective intervention. In this article, the processes by which the most common and most threatening complications occur, as well as what every physician ought to know when treating these seriously ill patients are discussed.

OVERVIEW OF COMPLICATIONS

After bacteria seed the endocardium, erosions into various cardiac structures take place through an interplay of direct bacterial invasion, enhanced inflammatory response, and liquifactive enzyme release within cardiac tissues. This is particularly pronounced in IE caused by Staphylococcus aureus, especially in the aortic valve position. This is probably due to the less annular fibrous tissue support in the aortic position compared with the mitral position. Unfortunately, IE tends to occur more frequently in the aortic valve than any other valve, and the frequency of S aureus as the cause of IE has increased dramatically over the past 2 decades, from 2% in 1990 to 25% in 2009.

Congestive heart failure (CHF) through a sudden volume overload on the ventricles, whether caused by a sudden regurgitant lesion or shunt creation, can complicate IE. Sudden regurgitation usually occurs as a result of chordal rupture in native valve endocarditis (NVE), a valve leaflet perforation in NVE or in bioprosthetic valve IE, or valve dehiscence in prosthetic valve endocarditis (PVE). In NVE and PVE, CHF is the complication with the greatest independent impact on prognosis whether medically or surgically treated. Early studies comparing antimicrobial therapy with surgery in patients with IE complicated by CHF demonstrated a clear superiority with surgery (23% vs 71% mortality rates). Much less commonly, heart failure can be obstructive in nature when large vegetation obstructs a heart chamber outflow.

A similar pathophysiology also leads to paraannular extension (PAE) of the infection. Given the similar pathophysiology, PAE is also more common with necrotizing organisms, and in the aortic position. In addition, PAE is one of the most frequent complications of IE, occurring in up to 100% of infected prosthetic valves and 40% of infected native valves. The infectious process around the valve weakens the annulus, and eventually leads to tissue destruction, valve dehiscence, abscess formation, and sometimes fistulization. This is associated with an increased occurrence of CHF and a higher mortality rate. A PAE-related fistula has been shown to lead to up to 40% mortality.

In addition to the local destruction that complicates IE, systemic embolization is the most common complication. Emboli usually consist of vegetations or friable necrotic and often infected tissues. Unlike local effects, this is more common in the mitral valve position. Although the embolic risk is high (embolic events occur in up to 50% of patients), this risk declines dramatically with initiation of antibiotic treatment, and even more after 2 weeks of effective continuation. The rate of systemic embolization is significantly higher in patients who have had a previous embolic event, those in the first 2 weeks of antibiotic therapy, those with left-sided IE especially in the mitral position, those with mobile vegetation that is large (10-15 mm) or increasing in size despite antibiotic therapy, and those patients infected with certain pathogens...
Criteria have been proposed including those by Pelletier for antimicrobials that are unnecessary. Several defining patients leads to exposure to high doses of potentially toxic likely leads to a poor outcome or death, and overdiagnosing making the diagnosis is not always straightforward, given that 25% to 30% of patients in this era present with no previously known cardiac structural abnormality. This is in part due to the more acute rather than subacute disease process taking place with the increased prevalence of *S. aureus* as a causative agent. An accurate diagnosis has been made even more difficult by increasing rates of culture-negative IE. In the United States, 79% of cases with culture-negative IE were found to be due to early administration of antimicrobials or faulty culturing technique, emphasizing their relative importance and how seemingly trivial details may alter or complicate the diagnosis.

Echocardiography should be done as soon as IE is suspected. The role of echocardiography goes beyond the diagnosis, and repeat echocardiography is recommended on clinical deterioration or when complications are suspected. Echocardiography guides the decision on whether to operate and when, as discussed later. However, the role of transesophageal echocardiography (TEE) in the assessment of left-sided IE is controversial, because of its significantly lower negative predictive values compared to transesophageal echocardiography (TEE). Although TEE has a near 100% negative predictive value with NVE, it is operator dependent and is far less sensitive for PVE and abscesses of the mitral valve associated with posterior annular calcification. In these situations, repeat TEE as well as a combination of TTE and TEE might mitigate the limitations caused by acoustic shadowing. Unfortunately, 15% of patients with proven IE were reported to have no echocardiographic findings.

### STARTING MANAGEMENT

Managing a patient with IE aims at 2 goals: eradication of infection and restoration of cardiac structures. Eradicating infection, whether medically or surgically, should abort the disease process, and thus prevent further local, hemodynamic, immunologic, or embolic complications. Structural restoration is primarily surgical and is aimed at repairing the damaged tissue in which healing would not be sufficient, and would otherwise have short-term or long-term hemodynamic implications.

Once the diagnosis of IE is suspected, at least 3 sets of blood culture samples should be drawn from different sites and at 30-minute intervals. This should be followed immediately by initiation of intravenous empirical antibiotic therapy as shown in Table 2. With no justification for delay, this empirical therapy should be qualitatively bactericidal and quantitatively in high doses for up to 6 weeks. Selecting the best antibiotic for a particular patient should be guided by the presence or absence of previous antibiotic use, whether this is a suspected case of NVE,
TABLE 1. Major and minor revised Duke criteria

<table>
<thead>
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<th>Major</th>
<th>Minor</th>
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<tr>
<td>Persistent positive blood culture with typical infective endocarditis microorganism</td>
<td>Predisposing factor: known cardiac lesion, recreational drug injection</td>
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<tr>
<td>Evidence of endocardial involvement with echocardiogram</td>
<td>Fever &gt;38°C</td>
</tr>
<tr>
<td>Evidence of embolism</td>
<td>Immunologic problems</td>
</tr>
<tr>
<td>Positive blood culture (that does not meet a major criterion)</td>
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In general, the nature and pathogenesis of early PVE is different from other forms of IE. NVE and late PVE usually occur with distant blood stream pathogen access, which eventually leads to pathogen adherence at a point in the heart that has been previously predisposed, whether by disease causing a jet and Venturi effect on the low-pressure side or by an implanted prosthesis. On the other hand, early PVE is mostly caused by microbes that can adhere to the annulus-ring interface and to the perivalvular suture pathways when they are coated with fibronectin and fibrinogen before endothelialization takes place. Inoculation typically takes place within the first 60 days after surgery and is usually nosocomial. After this period, and up to 12 months, there is a transition in pathogenesis and causative organisms that ends with complete endothelialization. The mechanism, the microbiology, and the incidence of PVE beyond 12 months are similar to NVE.

Both the American Heart Association (AHA)/American College of Cardiology (ACC) and the European Society of Cardiology (ESC) guidelines regard gentamicin as an optional addition to initial combination therapy, because of its presumed synergistic effect with cell-wall inhibitors. The ESC guidelines, however, recommend it for PVE.

A valid argument against gentamicin has been proposed, given its proven renal toxicity against the background of doubtful benefit.31,32 These studies recommended the use of daptomycin as a noninferior option for proven staphylococcal infection rather than standard therapy including gentamicin. However, the impact of gentamicin on creatinine clearance did not seem to lead to dialysis or otherwise adversely affect the patients’ course in these studies.

With the exception of staphylococcal infections, fever should resolve within a few days after starting therapy, and all patients should have surveillance blood cultures after 3 to 4 days of intravenous drug therapy. In a significant number of patients, cultures are negative, and this should never rule out IE. As mentioned earlier, previous antibiotic use is a common reason why cultures are not positive. Also slow-growing or atypical organisms (Q-fever and Bartonella) and fungal infection might be present.30,33

TABLE 2. Empirical antimicrobial therapy with early PVE, late PVE, and NVE

<table>
<thead>
<tr>
<th>Early PVE (&lt;12 months after surgery)</th>
<th>NVE and late PVE (≥12 months after surgery)</th>
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<tbody>
<tr>
<td>Vancomycin plus rifampin (± gentamicin)</td>
<td>Combination penicillins (ampicillin-sulbactam and amoxicillin-clavulanate) (± gentamicin)</td>
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<tr>
<td></td>
<td>If intolerant to penicillins: vancomycin plus ciprofloxacin (± gentamicin)</td>
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MODIFYING THERAPY

In most true cases of IE, blood cultures are positive and therapy should be modified accordingly. Lists of different drug regimens, doses, combinations, and durations of therapy for cultured organisms have been published previously.3,30 Medical regimens should not be modified based only on qualitative microbial sensitivity. Minimum inhibitory concentrations (MIC) of specific drugs for specific pathogens should be followed. For example, S. aureus exists in strains that are vancomycin intolerant and stop growing in the presence of the drug rather than die. These strains resurge after the treatment stops. Moreover, the high trough levels of vancomycin that are necessary for this growth inhibition are also enough to cripple the patient’s renal function. In this situation, the MIC should guide the substitution of vancomycin with less nephrotoxic alternatives such as daptomycin or teicoplanin.12,34

Generally, antimicrobial combinations are preferred over monotherapy. This increases efficacy, reduces required drug doses and thus adverse effects, reduces the emergence of resistant strains, and shortens the duration of therapy. Aminoglycosides synergize with β-lactams and glycopeptides, and slow-growing or dormant pathogens residing within vegetation or biofilms justify the need for rifampicin for prolonged duration.3

CLOSE MONITORING

While antibiotic therapy is continued, close monitoring for treatment effectiveness and disease progression is key to the success of treatment. Fever and various indicators of ongoing inflammation have to be followed attentively, renal function and other side effects of the drugs should be anticipated, and complications of disease progression should be vigorously dealt with. The importance of close monitoring should be emphasized to allow for effective modifications of therapy and timely surgical intervention.
As previously described, CHF is the most common and the most ominous complication of IE, and must treated aggressively. It is an AHA/ACC and ESC class I indication for surgery in patients with IE.\(^2\) The status of the infection should be completely disregarded when there is any evidence of hemodynamic instability or pulmonary edema, and surgical delay beyond 24 hours in not acceptable. In hemodynamically stable patients, urgent surgery should be performed when there are echocardiographic features of poor hemodynamic tolerance.\(^7\) With mitral valve IE, evidence of severe mitral regurgitation, including a rapidly decelerating late systolic transmural signal (V-wave cutoff Doppler sign) as a result of markedly increased left atrial pressure or a finding of moderate to severe pulmonary hypertension, are signs of impending CHF. With aortic valve IE, premature closure of the mitral valve is an early sign of an overfilling left ventricle. These features should be specifically looked for, and emphasize the importance of repeat echocardiography when monitoring patients with known IE. In patients with mild CHF who are responding favorably to medical therapy, afterload reduction may be adopted with strict clinical and echocardiographic monitoring, while having the patient and the facility ready for urgent surgery.

A ruptured sinus of Valsalva into a heart chamber or into the pericardium is a complication that should be treated with similar urgency with a delay in surgery of no more than 24 hours. Otherwise, the indications for surgery are less clear and the decision and timing of surgical intervention is a difficult balance between the need to optimize the patient’s medical condition and the fact that these patients are often extremely unwell and can deteriorate irreversibly at any moment. Generally, fungal, staphylococcal, or gram-negative endocarditis is almost always a surgical disease. PVE and device-related (pacemaker or implantable cardioverter defibrillator) endocarditis, a steeply increasing type of IE, should have a much lower threshold for surgery compared with NVE. On the other hand, right-sided endocarditis should have a higher threshold for surgery, and should primarily be considered a medical disease with some exceptions. In any case, consultation between the cardiologist and the cardiac surgeon should take place, and the patient with PVE should be taken off coumadin and aspirin, with heparin infusion replacement.

When fever and inflammatory mediators are persistently high despite adequate doses of appropriate antibiotic treatment, PAE has to be suspected. With any degree of unexplained heart block noted, abscess formation is likely. In both situations, TEE should be ordered immediately. An annular or aortic abscess, a new heart block, or valve dehiscence are considered class I indications for surgery.\(^11,28\) However, some investigators argue that nonresolving fever and increased inflammatory mediators despite 1 week of antibiotic therapy, together with positive surveillance blood cultures, should suffice for making the decision on surgery.\(^35\) In the case of shunt caused by IE and its high mortality rate, surgical intervention should be always performed, even in the absence of any evidence of heart failure.\(^11\) In a few selected cases, medical therapy alone would be accepted in the context of confirmation of PAE. This can be the case when the isolated organism is sensitive, there is no evidence of valve destruction or heart block, and when abscesses are less than 1 cm in size. Otherwise, surgery should not be delayed.\(^35\)

Because of the relatively high rate of embolism in the first 2 weeks after diagnosis, patients at high risk of embolization should be identified, given that early surgery would potentially be more beneficial in these patients. As described earlier, with left-sided and especially mitral valve IE (anterior leaflet in particular), timely surgery might save patients who have had previous embolism and infections caused by certain organisms from disabling embolic events. The decision of surgery based on vegetation criteria alone is still controversial. The 2006 ACC/AHA guidelines recommend surgery as a class IIa indication only for those with recurrent emboli and persistent vegetation after antibiotic therapy.\(^33\) The 2009 ESC guidelines recommend urgent surgery as a class IIb indication for vegetation greater than 15 mm in diameter.\(^7\) A recent randomized controlled study has clarified this gray zone regarding the impact of early surgery on embolic events. Kang and colleagues\(^36\) randomized patients with left-sided IE and vegetation greater than 10 mm to either conventional early antibiotic treatment or surgery within 48 hours of randomization. Early surgery showed a significantly reduced composite end point of death from any cause and embolic events by effectively decreasing the risk of systemic embolism.

For patients who have already had a neurologic event, surgery is not contraindicated after transient ischemic attacks or ischemic (nonhemorrhagic) strokes. Although some controversy exists around the exact time frame for surgery after the event, in consensus, surgery should not be delayed after a nonhemorrhagic stroke in the presence of heart failure, PAE, ongoing sepsis, or persistent high embolic risk.\(^37\) A computed tomography (CT) scan should be done on the brain before surgery to exclude the possibility of a hemorrhagic stroke. In the extremely unfortunate situation with an emergency indication of surgery in the setting of a hemorrhagic stroke, limited data are available and poor outcomes are expected with either conservative or operative management. In this situation, a wise decision should be made weighing the benefits and risks depending on the extent of hemorrhage, duration since onset, and association with neurologic deficit on the one hand, and the degree of hemodynamic compromise, the response to antimicrobial therapy, the anticipated complexity of surgery, and thus the anticipated cardiopulmonary bypass time on the other hand. On the contrary, recurrent pulmonary embolization in right-sided IE is not considered an
indication for surgery in the absence of pulmonary abscesses.38

Splenic infarctions are common (44%) and usually improve with medical therapy alone, but splenic abscesses, which are not easily differentiated from infarcts are not expected to improve with medical therapy. Abdominal CT scan and magnetic resonance imaging (MRI) should be correlated with a high index of suspicion with poor clinical response to ongoing antibiotic therapy, and once a splenic abscess is diagnosed, a splenectomy is warranted as soon as the patient’s clinical status permits.13 The management is highly individualized, however, it is crucial to remove the spleen, whether by open or laparoscopic surgery, because it is a source of ongoing sepsis, before operating on the heart; otherwise, prosthetic valves, patches, or grafts will likely get infected.39 If the patient’s clinical status necessitates urgent or emergency cardiac restoration surgery, concomitant splenectomy should be done if the patient is expected to tolerate such a procedure, otherwise immediate percutaneous aspiration of splenic abscesses is reasonable, followed by immediate cardiac surgery.13

The situation with poor clinical and inflammatory improvement with adequate and appropriate antibiotic therapy can be less straightforward. When abdominal CT or MRI scans are negative for abscesses, an alternative focus should be searched for. This can be difficult, and entails a detailed history for implants, orthopedic or any other hardware, as well as a thorough physical examination including a dental examination. When no septic focus is found, we believe that a positron emission tomography/CT scan is a reasonable modality to accurately identify a hypermetabolic infected site.40-42 As with splenic abscesses, the septic focus should be dealt with before or at the same time as implanting any prosthetic valves, patches, or grafts in the heart (Table 3).

### OPERATING

Approximately half of patients with IE require surgery. Surgery for IE revolves around eradicating infection and debriding all necrotic tissue, with subsequent reconstruction of the cardiac chambers and valves. The reconstructive material should ideally provide durability and a low reinfection rate. Achieving these goals can be technically challenging at times. Repairs generally tend to be more complex and technically difficult when the infection spreads beyond the annulus. To a great extent, this is proportional to the virulence of the organism. Every effort should be made to avoid implanting a prosthesis. In some cases, implanting a prosthetic becomes inevitable because of extensive tissue destruction, and bioprostheses are always preferred over mechanical valves, and homografts and stentless valves may provide valvular support when the perivalvular tissue is extensively destroyed.43,44 The use of antibiotic-impregnated fibrin glue has been proposed to seal prosthetic valve sewing cuffs as well as abscess cavities.45,46 This is

### TABLE 3. Potential complications of infective endocarditis and the recommended approaches for management

<table>
<thead>
<tr>
<th>Complication</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (clinical or echocardiographic)</td>
<td>Surgery within 24 h, regardless of the status of the infection</td>
</tr>
<tr>
<td>Paraannular extension</td>
<td>Surgery within 24 h, regardless of the status of the infection</td>
</tr>
<tr>
<td>Ruptured sinus of Valsalva</td>
<td>In the absence of congestive heart failure, stabilizing the patient and controlling the infectious process medically should be attempted first. Surgery will be required eventually for structural restoration</td>
</tr>
<tr>
<td>Abscess</td>
<td>Hemorrhagic stroke should be excluded first. Ischemic stroke does not preclude emergency or urgent surgery for hemodynamic and infectious complications of infective endocarditis</td>
</tr>
<tr>
<td>Conduction block</td>
<td>Result from a recent randomized controlled trial show superior outcomes with surgery within 48 h for left-sided infective endocarditis with vegetation &gt;10 mm</td>
</tr>
<tr>
<td>Prosthetic valve dehiscence</td>
<td>Splenic Differentiation between infarcts and abscesses is crucial. Infarcts should be conservatively managed whereas abscesses will fail conservative trials and warrant splenectomy after stabilizing the patient. The splenic abscess should be addressed before any prosthetic valves, patches, or grafts are placed in the heart</td>
</tr>
<tr>
<td>Cerebral</td>
<td>Renal Multifaceted medical management should be initiated to address renal ischemia, immune glomerulonephritis, as well as modification of antimicrobial therapy type or dose</td>
</tr>
<tr>
<td>Splenic</td>
<td>Right-sided (pulmonary) In the abscess of lung abscess, conservative management is recommended</td>
</tr>
</tbody>
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largely based on in vitro studies showing a decreased infection rate using antibiotic-impregnated fibrin glue compared with antibiotic alone, fibrin glue alone, or saline.\textsuperscript{47} However, comparative studies in humans are lacking.

Especially with mitral valve IE, every attempt should be made to repair. Reparability ranges between 34\% and 80\% in different reports.\textsuperscript{48-51} The feasibility of repair seems be highest with either early active disease or with healed disease as an elective procedure. The former emphasizes the importance of prompt surgery with the earliest echocardiographic signs of decompensation with regurgitant lesions. Even with more advanced active IE with extensive leaflet destruction, repair should be attempted first.

Annuloplasty, as with all mitral regurgitation repairs, is recommended. With IE, the outcomes after autologous glutaraldehyde-fixed pericardial (GFP) annuloplasty are effective and durable.\textsuperscript{52} Leaflet repair is always preferred over valve replacement, and excellent results have been reported. Zegdi and colleagues\textsuperscript{53} reported a 10-year freedom from mitral reoperation of 91\% using the Carpentier techniques in mitral valve endocarditis repair. Preservation

of the left ventricular structure as well as the subvalvular apparatus might partly explain why repair can be better tolerated than replacement in the setting of CHF. Other studies have also reported favorable results and lower rates of reinfection with repair.48,50,54,55 With extensive bileaflet destruction, a GFP fashioned leaflet can be attempted.
however, success rates and variations in durability are significant for different institutions and surgeons with mitral valve expertise. Total mitral valve homografts should be the last resort, given their technical difficulty as well as their less than optimal durability and high rates of reoperation.

In contrast to the mitral position, aortic valve IE that requires surgery usually requires valve replacement. Homografts seem to be the best option, given the increased tendency of aortic valve infections to extend beyond the annulus. This is also the case with PVE, for which significant tissue debridement is necessary. Infections extending into the left fibrous trigone or aorto-mitral curtain can pose a challenge. Less extensive lesions can be repaired primarily or using a GFP patch, however more extensive lesions require extensive debridement and total en-bloc replacement using an aorto-mitral homograft (Figures 1 and 2). The Ross procedure is an option, although not many surgeons would achieve acceptable results.

Right-sided IE less commonly requires surgery. Tricuspid valve excision has been advocated in intravenous drug users with a high incidence of recurrence of tricuspid valve infection, but this was followed by an unacceptable severe right-sided heart failure, and thus, this approach is no longer recommended. Bioprostheses seem to offer better results at the cost of higher chances of reinfection, especially with continued drug abuse.

The duration of therapy should be based on the first day of effective antibiotic therapy, not on the day of surgery, if surgery took place. A new full antimicrobial course is only started after surgery if valve cultures are positive, and in this case, the choice of antibiotic should be modified accordingly. With PVE and device-related IE, prolonged antibiotic therapy is recommended for at least 6 weeks, and a new device should not be implanted except when complete microbiological eradication is achieved.

References


