Diagnosis and management of bacterial endocarditis in 2003

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The diagnosis of infective endocarditis has been notoriously difficult. Over the last decade, the modified Duke criteria have assumed an increasingly important role in the early detection of this often occult disease. Echocardiography has assumed increasing importance. Transesophageal echocardiography is recognized as more sensitive and specific than transthoracic echocardiography at detecting vegetations less than 10 mm in diameter. Vegetations greater than 10 mm in diameter are thought to be at increased risk of embolizing. Combined medical and surgical medical management result in the lowest mortality for those patients with hemodynamic compromise. Curr Opin Cardiol 2003, 18:106–110

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Background

Bacterial endocarditis has long been a challenge for both physician and surgeon. The principal difficulty for the physician is accurate clinical diagnosis. A principal difficulty for the surgeon is completely eradicating infection in the heart, where extensive resections often result in fatality.

In 1646, Lazar Rivière (as described by Major) wrote about perhaps the earliest autopsy findings of endocarditis: "in the left ventricle of the heart, round caruncles were found with an appearance like that of a substance of the lungs, the largest of which resembled a cluster of hazel nuts filling the opening of the aorta" [1]. In 1885, Osler described endocarditis in a series of autopsies published in the *British Medical Journal* [1]. Today, definitive diagnosis of bacterial endocarditis continues to be problematic. The diagnosis is currently established by pathologic criteria characterizing histologic intracardiac or embolic vegetations or demonstration of intracardiac abscess during operation or postmortem examination. Before the operation or postmortem, the diagnosis of bacterial valvular endocarditis is most commonly made on clinical grounds. Current clinical criteria are based on bacteremia and echocardiographic demonstration of valvular vegetations or intracardiac abscesses. Secondary clinical criteria include systemic, immunologic, and vascular consequences of the disease. In 1994, Durack *et al.* [2•] proposed a set of criteria for the diagnosis of bacterial endocarditis now known as the *Duke criteria*. The collective sensitivity of the Duke criteria in numerous studies has been found to be in excess of 80%, with a high specificity and negative predictive value. Despite this accuracy, the Duke criteria have various shortcomings. To increase the sensitivity and specificity of the Duke criteria, the relative risk of infective endocarditis in cases of *Staphylococcus aureus* bacteremia and the increasingly important role of transesophageal echocardiography in the diagnosis of endocarditis have been incorporated in a set of criteria referred to as the *modified Duke criteria* [3•].

This article reviews recent advances in the clinical diagnosis of infective endocarditis and recently proposed surgical techniques for endocarditis.

Pathophysiology

Formation of a sterile fibrin-platelet thrombus at the site of endothelial injury is the initiating event for endocarditis. Bacteremia, endothelial injury, altered hemodynamics, and subsequent valvular injury can all be the

inciting event. The resulting thrombus is susceptible to seeding of bacteria from normally occurring transient episodes of bacteremia. Subsequent cycles of bacterial infections and repetitive thrombus formation lead to the development of valvular *vegetations*. Thus, a vegetation is an aggregate of bacterium, white blood cells, fibrin, and platelets on the endothelial surface of the heart that is often visualized as an echogenic mass.

Infected valvular vegetations result in local tissue destruction, embolic events, and immune complexes. Local tissue destruction may result in valvular regurgitation, paravalvular abscess, pericarditis, aneurysm, or fistula formation. Embolic events can lead to cerebral, systemic, or pulmonary emboli. Immune complexes from bacterial endocarditis may result in polyarthritis and glomerulonephritis.

Any microorganism may cause endocarditis. The most common causative organisms have two very similar attributes: frequent bacteremia and the ability to adhere to cardiac valves or thrombotic surfaces. Streptococci are the most common group of organisms causing endocarditis. The coagulase-positive and coagulase-negative staphylococci are an increasingly frequent cause of endocarditis. *S. aureus* endocarditis may lead to extensive tissue destruction and a high incidence of local and distal complications when the left heart is involved.

Although 20 to 30% of patients with infective endocarditis have no predisposing risk factor, 70% have a history of underlying cardiac valvular disease, congenital heart disease, a prosthetic cardiac valve, or a history of intravenous drug abuse [4]. A bicuspid aortic valve is a particularly high-risk lesion; one third of all cases of aortic valve endocarditis occur on bicuspid valves. Congenital heart disease in particularly patent ductus arteriosis and ventricular septal defects is associated with a high risk of endocarditis (endocarditis is rare with atrial septal defects). Infections of mechanical prosthetic valves usually affect the sewing ring in the paravalvular areas. The use of intravenous drugs often is associated with right-sided cardiac valvular lesions; only 25% of such patients have underlying pre-existing structural heart disease.

Diagnosis

Durack *et al.* [2•] at Duke University proposed standardized criteria for the diagnosis of infective endocarditis in 1994, which have subsequently become widely accepted with some modifications [3•]. These modified Duke criteria are classed into major and minor criteria.

One major criterion is a typical microorganism isolated from two separate blood cultures. Typical microorganisms include *Viridans streptococci*, *Streptococcus bovis*, HACEK organisms (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kinsella kinasae*), *S. aureus*, or a community-acquired enterococci bacteremia without a primary focus. A second major criterion is a microorganism consistent with infective endocarditis isolated from persistently positive blood cultures. A third major criterion is a single positive blood culture for *Coxiella burnetii* or a phase I IgG antibody titer to *C. burnetii* greater than 1:800. A fourth major criterion is evidence of endocardial involvement as documented by new valvular regurgitation murmur. A fifth major criterion is evidence of endocardial involvement by echocardiography (either transesophageal or transthoracic).

One minor criterion is high-risk conditions predisposing to infective endocarditis, including previous infective endocarditis, congenital aortic valve disease, rheumatic heart disease, prosthetic heart valve, coarctation of the aorta, and complex congenital cyanotic heart disease. Moderate risk conditions predisposing to endocarditis include mitral valve prolapse with valvular regurgitation or thickening, isolated mitral stenosis, tricuspid valve disease, pulmonary stenosis, and hypertropic cardiomyopathy. Low or no-risk conditions include secundum atrial septal defect, ischemic heart defect, previous coronary artery bypass grafting, and mitral valve prolapse with thin leaflets in the absence of regurgitation.

Other minor criteria are fever, immunologic phenomena such the presence of rheumatoid factor, glomerulonephritis, Osler nodes or Roth spots, and vascular phenomena (excluding petechiae and splinter hemorrhages).

The last minor criterion is microbiologic findings of positive blood cultures that do not meet the major criteria and serologic evidence of active infections such single isolates of coagulase-negative staphylococci.

Cases are defined as *definite* if they fulfill two major criteria, one major criterion plus three minor criteria, or five minor criteria. Cases are defined as *possible* if they fulfill one major criterion and one minor criterion, or three minor criteria [5].

Echocardiography has assumed a central role in the diagnosis of suspected endocarditis. Because endocarditis is frequently difficult to diagnose and because transthoracic echocardiography is often equivocal, the role of transesophageal echocardiography has become a point of contention. Transesophageal echocardiography is more invasive and expensive than transthoracic echocardiography. Transesophageal echocardiography is reportedly more efficient in detecting smaller lesions, but the impracticality of applying it to all patients with negative transthoracic echocardiograms has limited its usefulness and made its role in routine screening for endocarditis controversial.

Recent studies suggest that transthoracic echocardiography should be used in evaluating patients with suspected native valve endocarditis who are good candidates for imaging. However, for patients with a high probability of infective endocarditis, the initial use of transesophageal echocardiography may be more definitive. Transthoracic echocardiography is 98% sensitive and 60 to 70% specific for the diagnosis of vegetations and regurgitation seen with endocarditis. Transesophageal echocardiography has a slightly lower sensitivity of 75 to 95% but a higher specificity of 85 to 98% [5].

In a study by Erbel *et al.* [6••], the sensitivity and specificity of transesophageal and transthoracic echocardiography were compared. Vegetations greater than 10 mm were visualized in 100% of cases by both techniques. However, those lesions 6 to 10 mm in diameter visualized by transesophageal echocardiography were visualized in only 69% of transthoracic echocardiograms. Vegetations less than 5 mm in diameter visualized by transesophageal echocardiography were seen in only 25% of transthoracic echocardiograms. Transesophageal echocardiography was particularly important in patients with inadequate windows; in patients with native valve abnormalities such as prolapse, calcification, or thickening; and in patients with prosthetic valves. In patients with hemodynamic compromise, transesophageal echocardiography holds its largest advantage over transthoracic echocardiography in evaluating the extent of valve destruction, the extent of abscess formation, and the presence of intracardiac fistulas. Nevertheless, no study to date has documented transesophageal echocardiography to have any significant clinical impact when outcomes such as mortality and morbidity are analyzed.

Does size (and location) matter?

Cerebral, systemic, and peripheral emboli are feared complications of endocarditis. Systemic embolization can occur in 22 to 50% of all cases of endocarditis. Sixty to seventy percent of emboli involve the central nervous system, often with severe and possibly lethal manifestations. Predictions of a person's risk of embolization have become a focus of clinical discussion. The implications of large vegetations in an otherwise asymptomatic patient can be an area of disagreement between physicians and surgeons. Many studies have addressed this problem. Table 1 is a summary of recent studies.

Vilacosta *et al.* [7] examined the risk of embolization after institution of antibiotic therapy in infective endocarditis. They reviewed 217 episodes of left heart endocarditis evaluated between 1996 and 2000. Ninety-one percent had definite infective endocarditis as assessed by the modified Duke criteria. Seventy-two cases occurred on prosthetic valves. Transthoracic echocardiography, transesophageal echocardiography, or both were performed in all patients. Mean follow-up was 151 days. Thirteen percent of the patients suffered embolic events. Sixty-five percent of the events occurred within 2 weeks of initial antibiotic therapy. Fifty-two patients had an operation performed within 2 weeks. The relative risk of subsequent embolus when emboli had occurred previously was 1.73. The risk of an embolic event increased as vegetation size increased (relative risk, 3.77). However, vegetation size had no impact on embolic risk when the lesion was *Streptococcus* or occurred on the aortic valve. Vegetations greater than 10 mm carried an increase risk of emboli if they were *Staphylococcus* and if the mitral valve was involved. Increasing size of vegetation with serial echocardiography also predicted a higher risk of embolization.

Table 1.

Author	EE–size	N	EE	Echo	VEG	EE on tx
Lutas	Negative	77	22	TTE	56	ND
Mugge	Positive	105	31	TTE/TEE	91	19
Jaffee	Negative	70	43	TTE	78	16
Sanfilippo	Positive	204	33	TTE	75	ND
Steckelberg	Negative	207	13	TTE	38	13
Rohmann	Positive	118	26	TEE	42	21
Heinle	Negative	41	49	TTE	73	49
Werner	Positive	106	35	TEE	92	ND
DeCastro	Negative	57	44	TTE/TEE	80	44

A study by De Castro *et al.* [8] from Rome and Boston followed 57 patients with definite endocarditis by Duke criteria. This was a retrospective analysis of patients evaluated between 1993 and 1995. Transthoracic and transesophageal echocardiography was performed the day of diagnosis. Forty-four percent of patients suffered an embolic event. No difference was found between mitral and aortic endocarditis in predicting embolic risk. Transthoracic echocardiography revealed a vegetation in 80% of patients. Whether size was greater or less than 10 mm and whether the vegetation was mobile or fixed did not predict subsequent embolic phenomenon.

The role of transesophageal echocardiography with definitive endocarditis by Duke criteria was examined by Di Salvo *et al.* [9••]. One hundred seventy-eight patients in Marseille, France, were reviewed. Transesophageal echocardiography detected a vegetation in 75%, an abscess in 18%, new regurgitation in 6%, and aneurysm or valve perforation in 8%. To ensure that all emboli were detected, cerebral, thoracic, and abdominal CT scans were performed in 95% of all patients. Thirty-seven percent of their clinical cohort went on to have an embolus. Only 8% were clinically silent, detected only on CT scans. Univariate analysis revealed that the presence of *Staphylococcus*, a right-sided cardiac vegetation, a lesion greater than 10 mm, and increased mobility of the vegetation all were statistically significant predictors of subsequent embolization. In particular, those patients with a vegetation greater than 10 mm went on to develop an

embolus in 60% of cases, compared with only 23% with vegetations less than 10 mm. Emboli occurred in 83% of patients with lesions greater than 15 mm in diameter that were mobile. The presence of vegetations on transesophageal echocardiography was predictive of subsequent embolization for both mitral and aortic valves, particularly if the vegetation was greater than 10 mm in diameter. Patients with vegetations greater than 15 mm in diameter that were mobile were at a particularly high risk for subsequent embolization. A caveat to this study is that the risk of embolization is probably underestimated because early surgery occurred in 61% of patients and because of these 61%, 63% underwent surgery within 10 days of diagnosis.

In 2003, the best consensus is that vegetations of greater than 10 mm in diameter and those vegetations occurring on the anterior leaflet of the mitral valve that are highly mobile are most likely to embolize. However, definitive proof of these conclusions is still lacking and is limited by characteristics of the various studies, including early surgery and the possibility of silent emboli.

Surgical management of endocarditis

Surgical management of endocarditis is indicated when medical therapy has failed, as manifested by congestive heart failure, severe valvular incompetence, or emboli. Surgery is also indicated when the microorganism is unlikely to respond to antibiotic therapy (as with *Staphylococcus* and fungi). Surgery is also indicated, but is associated with a high mortality, in cases of prosthetic valve endocarditis occurring within 3 months of operation.

Indications for an operation on left-sided lesions include severe valvular incompetence with or without congestive heart failure, extravalvular involvements such as paravalvular abscesses, pericarditis, aneurysm, or fistula formation), multiple emboli, or persistent infection. Right-sided lesions on the tricuspid and pulmonic valves are more often treated successfully with antibiotic therapy, and complications are more tolerable (especially from emboli).

Endocarditis resulting from *Streptococcus* is more amenable to medical management with antibiotics, and resolution of sepsis can be anticipated in most cases. On the other hand, infections caused by fungi and *Staphylococcus* are particularly resistant to medical management. Nearly all these cases will require surgical management. Endocarditis secondary to Gram-negative organisms such as *Serratia* and *Pseudomonas* will also require surgery. As soon as an operation is indicated, the only justifiable reason to delay or avoid it is the presence of severe neurologic injury.

Combined medical and surgical management decreases mortality in severely compromised patients, such as those with congestive heart failure, when compared with medical management alone. Medically treated patients with endocarditis and moderate to severe heart failure have a substantially increased mortality when compared with those treated with a combination of medical and surgical therapy (56–86% *vs* 11–35%) [5,10,11]. Clinical hemodynamics are an important predictor of surgical outcome [11,12]. Surgery should be performed before irretrievable deterioration in cardiac performance occurs [13].

The presence of a previous cerebral embolic event can make timing of operative intervention difficult for physicians and surgeons. A multicenter study in Japan of 181 patients addressed this issue [14]. This was a retrospective of study of patients with endocarditis who had a clinically significant neurologic event on presentation. CT scan classified cerebral lesions as nonhemorrhagic or hemorrhagic. In nonhemorrhagic cerebral emboli, cardiac surgery performed less than 7 days after the original event resulted in neurologic deterioration in 44% of patients. If the operation was performed 8 to 14 days after the embolic event, 17% of patients developed neurologic deterioration. If the operation was performed at greater than 4 weeks after the nonhemorrhagic infarct, only 2% of patients suffered neurologic deterioration. Unlike nonhemorrhagic infarcts caused by cerebral emboli, hemorrhagic cerebral events resulted in a significantly increased risk of subsequent neurologic deterioration at up to 4 weeks. Thus, the most recent information indicates that surgery can be performed relatively soon after cerebral emboli but should not be performed on an emergent or urgent basis.

A median sternotomy is used for almost all operations. It permits access to all cardiac chambers and maximum flexibility during the operation to deal with often unexpected findings. Cannulation of both superior and inferior venae cavae offers the best evacuation of blood from cardiac chambers and optimal visualization of cardiac defects. The most difficult areas to expose are the adjacent portions of the aortic and mitral annulae, which constitute the heart's fibrous trigone. Division of the superior vena cava with retraction of the right atrium facilitates exposure of this area. The operative technique depends on the degree of valvular dysfunction and local complications and the age and compliance of the patient. Thorough debridement of all infected tissue is mandatory. As little infected tissue, vegetations, and fibrinous debris should be left as possible. A meticulous inspection for extravalvular extensions and fistulae is mandatory.

After debridement is complete, attention is turned to closing defects between cardiac chambers and reconstructing normal anatomy. Autologous or bovine pericardium can be used. Cloth patches should be avoided because they offer a favorable site for recurrent infection.

Valve reconstruction or replacement begins once integrity of the cardiac chambers and annulus is restored. Repair is the preferred technique for mitral and tricuspid valve lesions. In most cases of successful valve repair, less than 50% of the valve leaflet is affected. Valvuloplasty is particularly rewarding when perforation of a valve leaflet is the dominant pathology. Another important determinant of successful valve repair is the ability of the tissue to hold sutures securely.

Valve excision without replacement can be performed for intravenous drug abusers with tricuspid valve endocarditis. After such operations, as many as 50% of patients will require subsequent tricuspid valve implantation, but the remainder will tolerate valve excision with normal hemodynamics [15].

Conclusions

Endocarditis requires a high index of suspicion for proper diagnosis and management. The modified Duke criteria have assumed an increasingly important role in prompt, accurate diagnosis of this disease. All clinicians should be familiar with these criteria. A consensus is developing that echocardiographically detected highly mobile vegetations greater than 10 mm in diameter are at high risk of embolization; early surgical intervention should be considered in this cohort of patients. Combined medical and surgical management is more effective than medical management alone in treating complicated endocarditis, but surgical mortality increases with increasing severity of the illness. An aggressive stance in both diagnosing and treating infective endocarditis may lead to continued improvements in outcome.

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