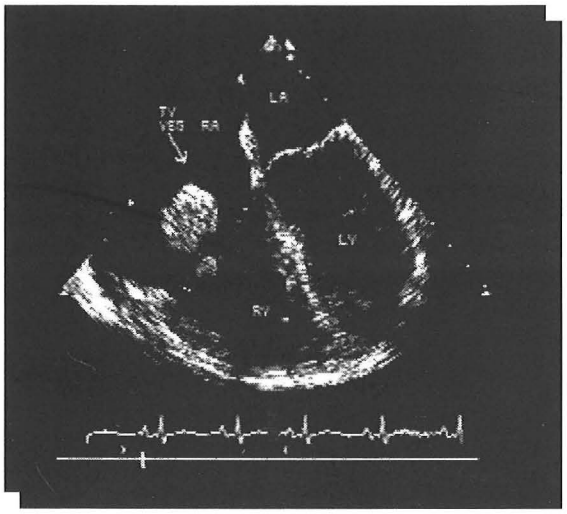
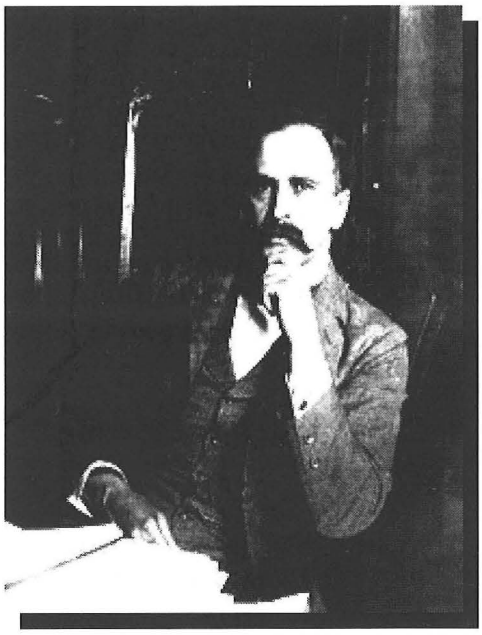
Infective Endocarditis

A Modern Approach to a Historical Disease





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This is to acknowledge that Gail Peterson has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Peterson will be discussing "off-label" uses in her presentation.

Introduction

"It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future"

It is with these words that William Osler began his famous Gulstonian lectures on malignant endocarditis in 1885.[1] In Osler's time, there was no therapy for infective endocarditis (IE) and the disease was universally fatal. Advances in diagnosis were made in the early 1900s when blood culture techniques developed, becoming the primary laboratory test for endocarditis as it remains today. The greatest therapeutic advance occurred with the introduction of penicillin in 1943. Although initial treatment results were disappointing because of inadequate dosing and duration of therapy, within 5 years antibiotic therapy reduced endocarditis mortality from 100% to about 30%.[2]

The introduction of cardiac surgery in the 1950s resulted in further advances in the treatment of IE, reducing long-term morbidity and mortality from heart failure and offering additional therapeutic options in patients with difficult to treat organisms. Paradoxically, the introduction of valve surgery placed patients at risk for a new and more malignant form of infection occurring on prosthetic heart valves.

Advances in the diagnosis of endocarditis include the development of echocardiography, formalized diagnostic criteria, refinement of histologic evaluation of tissue, and new and improved methods of detecting difficult-to-culture pathogens. Despite these advances, endocarditis continues to portend a poor prognosis, with an in-hospital mortality ranging from 15-30%[3-8] and significant long-term complications for hospital survivors.

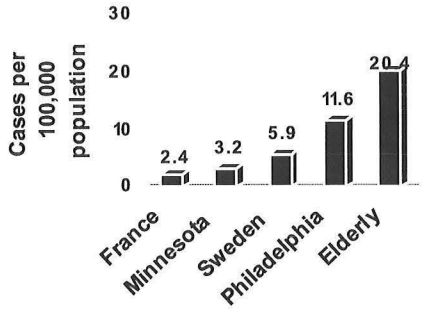
In Osler's time, the understanding of endocarditis was based on clinical observations, autopsy findings, and small published case series. Even today, our knowledge of this disease is primarily based on traditional case series with relatively small numbers of patients. Few randomized trials have been performed to test strategies for treatment and prophylaxis of endocarditis. As a result, clinical practice guidelines [9-11] are based largely on expert opinion and practice experience rather than on adequately sized randomized trials. The study of endocarditis is hampered further because it is a relatively rare disease involving variable underlying risk factors, a heterogeneous patient population and a wide array of infecting microorganisms. With changes in patient populations at risk and advances in medical technology, it is an appropriate time to take stock of our current understanding of endocarditis, to use this knowledge to look toward the future, to consider innovative approaches to clinical research, and to identify effective treatment strategies and incorporate them into clinical practice.

Epidemiology

Endocarditis is an uncommon disease, with an incidence ranging from 2.4 to 6.0 per 100,000 person-years.[12, 13] (Figure 1) The incidence of IE appears to be higher in urban

populations compared with rural groups, which may reflect intravenous drug use or other socioeconomic factors.[14]

Figure 1. Reported Incidence of Infective Endocarditis



Historically endocarditis has been a disease associated with underlying valvular abnormalities, particularly rheumatic heart disease, and with community-acquired bacteremia. Approximately two-thirds (53-70%) of patients with endocarditis have pre-existing cardiac disease.[12, 15, 16] There are few studies available that quantify the actual risk for the development of IE based on predisposing cardiac risk factors. Therefore, organizations such as the American Heart Association (AHA) base their recommendations for prophylaxis not only on the risk for the development of IE, but also on the risk for an adverse outcome if IE was to occur (Table 1). In a recent population-based case-control study the associations between certain predisposing risk factors and community acquired IE in non-intravenous drug users were quantified; the 3 most important independent risk factors were prior heart valve surgery, previous IE, and a self-reported history of mitral valve prolapse (MVP) (Table 2).[17]

Table 1. Patients at risk for adverse outcomes in setting of IE

High risk	Moderate risk
Prosthetic valves	Most other congenital heart disease
Prior IE	(excluding secundum ASD)
Cyanotic congenital heart disease	Acquired valvular heart disease
Surgically constructed systemic to pulmonary shunts	Hypertrophic obstructive cardiomyopathy
	MVP with thickened leaflets or regurgitation

Although structural heart disease independently contributes to risk for IE, the strongest risk factor remains intravenous drug use. Only 10-30% of patients with IE from IVDU have underlying cardiac disease.[18, 19] The incidence of IE among the projected 1.2 million IV drug users in the United States is estimated to be between 1 and 5% per year, and is highest among cocaine users.[20] The high prevalence of right-sided involvement (approximately 70% of cases)[18, 19, 21, 22] in patients using injection drugs results in a less

Table 2. Common Underlying Abnormalities Associated with Infective Endocarditis

Risk Factor	Case Patients (n=273)
Mitral valve prolapse	52 (19)
Congenital heart disease	26 (9.5)
Rheumatic fever	32 (11.7)
Cardiac valvular surgery	37 (13.6)
Prior episode of IE	17 (6.2)
Other valvular heart disease	12 (4.4)
Heart murmur	37 (13.6)
Any cardiac valvular abnormality	104 (38.1)

Reference[17]

aggressive infection with excellent short-term prognosis.[23] The reason for the predominance of tricuspid valve involvement in this patient population is not known; several mechanisms have been proposed. Repetitive injection of particulate material may damage right-sided valves, creating a nidus for infection. In addition, the drugs themselves may cause physiologic changes such as pulmonary hypertension or vasospasm, which may promote right-sided valve damage. The type of bacteria involved may also contribute to the predilection for right-sided lesions. While there are data to support each of these hypotheses, no single explanation is fully adequate and it is likely that these and other factors work in a complex fashion to result in the predominance of right-sided IE found in these patients.[24]

The reported prevalence of HIV infection among injection drug users (IDU) with IE ranges from 40-90%[25-29]. The full consequences of HIV infection in IE are not fully known as few studies have been published on this topic. Advanced HIV is associated with an increased risk of developing IE in IDU (OR 2.10 (0.95-4.25) for patients with CD4 $\geq$ 200 cells/microL vs. OR 3.61 (1.52-8.59) for patients with CD4 < 200).[30] However, the risk of IE in patients with HIV who do not inject drugs does not appear to be increased.[31]

Paradoxically, medical progress has also contributed to the evolution of the spectrum of IE. With advancements in medical technology, endocarditis is shifting from a subacute to an acute, aggressive disease, increasingly involving the elderly, patients receiving hemodialysis, and those with prosthetic cardiac devices. The US population is aging, and elderly patients constitute a particularly vulnerable group due to the co-morbidities associated with medical illness at an advanced age. The incidence of endocarditis in the elderly is 4-9 times greater than the general population, and has increased over the last decade.[3, 32, 33] The incidence of IE in patients receiving hemodialysis has also increased over the last decade and hemodialysis has emerged as an independent risk factor for *S. aureus* IE.[34]

Over the last few decades there has been a shift in the spectrum of microorganisms causing IE (Table 3). This shift has been attributed to the changing prevalence of predisposing cardiac conditions, the aging population, intravenous drug use and intensive and invasive medical care (including long-term intravenous catheters, hemodialysis, hyperalimentation, and prosthetic cardiac devices). Over time, viridans group streptococcal IE has decreased while IE due to *S. aureus* and to non-viridans streptococci has increased. During the same period with the development of better microbiologic techniques, the proportion of blood cultures that fail to identify an etiologic organism in the setting of IE has decreased by 72%.

Table 3. Microorganisms Causing Infective Endocarditis

	Viridans group	Other Strep	*S. aureus*	CNS	GNR	Other	NG
Before 1970	43%	12.5%	14%	4%	5.5%	3%	18%
1970's	42.5%	16%	13%	3%	5%	10%	10%
1980's	29%	19%	24%	9%	4%	7.5%	5%
1990's	28%	23%	28%	7%	4%	5%	5%

Legend: CNS, coagulase-negative staphylococci; GNR, gram-negative rods; NG, no growth.
Reference[35]

The common infecting microorganisms of prosthetic valve endocarditis (PVE) depend on the interval between surgery and development of infection (Table 4). Epidemiologic and microbiologic studies link PVE caused by *Staphylococcus epidermidis*, the cause of 31% of early PVE (traditionally defined occurring within 60 days after valve surgery), to intra-operative contamination. Most patients with PVE due to coagulase-negative staphylococci develop symptoms within 60 days, but some patients present as late as 13 months post-operatively. This finding illustrates the potential for slow-evolution from early infection to symptomatic PVE. The microorganisms causing PVE presenting 12 months or more after implantation resemble the causes of native valve IE with the exception of an increased number of cases caused by coagulase-negative staphylococci.

Table 4. Microorganisms causing prosthetic valve IE

Organism	Time of Onset after Cardiac Surgery		
	2 mos (N = 161)	*> 2- 12 mos (N = 31)*	*> 12 mos (N = 194)*
Coagulase-negative staphylococci	51 (32)	11 (35)	22 (11)
S. aureus	36 (22)	4 (13)	34 (18)
Gram-negative bacilli	19 (11)	1 (3)	11 (6)
Streptococci	5 (3)	3 (10)	61 (31)
Enterococci	13 (8)	4 (13)	22 (11)
Diphtheroids	9 (5)	0	5 (3)
Fastidious gram-negative coccobacilli	0	0	11 (6)
Fungi	12 (7)	2 (6)	3 (2)
Culture negative	7 (4)	4 (13)	16 (8)
Miscellaneous	12 (7)	2 (6)	9 (5)

Reference[36]

Pathogenesis

The two most common organisms causing IE, *S. aureus* and streptococcal species, often present with very different disease syndromes. Understanding the basics of the pathogenesis of infection caused by each organism lends some insight into the reasons for these differences.

Most patients with IE have predisposing valvular disease. While the normal valvular endothelium is resistant to bacterial invasion, aberrant and turbulent blood flow associated with valvular abnormalities may result in mechanical trauma to the endothelium. Damage to the endothelium leads to exposure of the underlying extracellular matrix (ECM) proteins, production of tissue factor and deposition of platelets and fibrin as a part of the normal healing process. This resulting platelet-fibrin aggregate may become a nidus for bacterial colonization. (Figure 2) Once a nidus is formed, the next step in IE development is bacterial adherence. The likelihood a given microorganism will cause IE is related to its ability to bind to the platelet-fibrin matrix. Bacterial adherence is mediated by a family of bacterial adhesion proteins termed microbial surface components recognizing adhesive matrix molecules (MRSCAMMs), which have only partially been characterized[37-41] (Table 5).

Figure 2. Formation of a sterile vegetation.

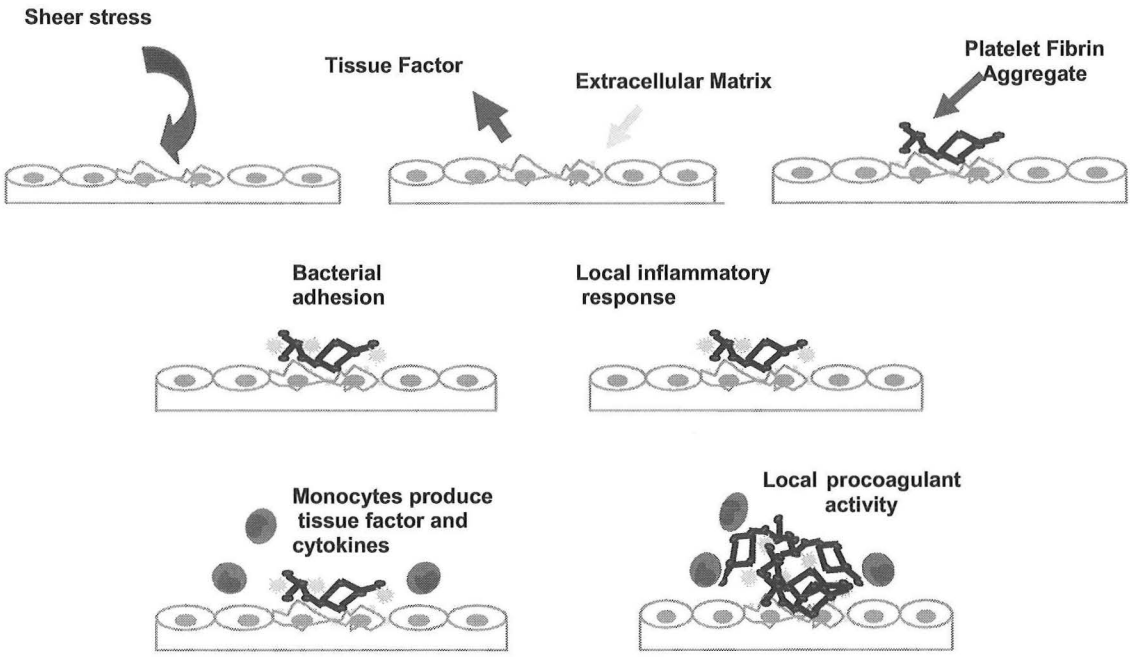


Table 5. Bacterial surface molecules implicated in pathogenesis of IE

MSCRAMM	Gene	Adherence substrate	Implicated in IE pathogenesis
Streptococci			
Surface glucans	gtf Ftf	Fibrin-platelet aggregate	yes
ECM adhesion molecules	fibronectin binding proteins	fibronectin	yes
	Fim A	salivary pellicle and possibly ECM	yes
Platelet binding and aggregating factors	phase I & II antigens	platelets	yes
Staphylococcus aureus			
Clumping factor A	ClfA	fibrinogen/fibrin	yes
Fibronectin-binding proteins	FnBPA FnBPB	Fibronectin	yes

Adapted from[42]

After valve colonization the microorganism must elude host immune defenses to grow and proliferate. Platelet aggregation and the local inflammatory response play major roles in this process. Fibrin-adherent bacteria attract monocytes and induce them to produce tissue factor and cytokines. Once tissue factor is activated, it not only triggers platelets, but also drives local procoagulant activity resulting in fibrin formation. As the vegetation matures, the organism becomes fully enveloped in a platelet and fibrin mesh, thus protecting it from cellular and soluble host defense mechanisms.

While a platelet-fibrin aggregate may be the nidus for IE in patients with valvular abnormalities, IE may occur without preceding abnormalities. This is particularly true for *S. aureus* IE. *S. aureus* is coated with fibronectin-binding proteins that bind avidly to immobilized fibronectin on the endothelial surface itself. Fibronectin bridging triggers endothelial internalization of bacteria. When invaded, endothelial cells produce tissue factor activity and cytokines that trigger the same cascade of events that lead to vegetation formation on abnormal valves. Internalized *S. aureus* eventually lyse the endothelial cells by secreting membrane-active proteins such as alpha hemolysin. *S. aureus* differs from streptococcal species in that it induces tissue factor expression not only from fibrin-adherent monocytes but also from physically intact endothelial cells, promoting vegetation formation on normal, undamaged valves.

The final step in vegetation growth, local tissue damage and extension to adjacent structures, has not been well described. Tissue invasion, a primary feature of *S. aureus* infection, appears related to the coordinated expression of surface adhesion molecules and secreted factors that are tightly controlled by global regulators, agr and sar.

While platelets are essential for vegetation formation, they actually play a dual role in IE. Platelets harbor alpha granules that contain a group of antimicrobial peptides, collectively called Platelet Microbicidal Proteins (PMPs) (rabbits) or thrombocidins (humans). PMPs are secreted by platelets under conditions present at sites of damaged or infected endothelium. Unfortunately, some strains of organisms have developed PMP/thrombocidin resistance. tPMP-1 resistant organisms exhibit a survival advantage for propagation of endovascular infections in experimental endocarditis. For example, PMP-resistant *S. aureus* strains produce more severe experimental IE in rabbits than their PMP-susceptible parent and are more difficult to eradicate by antimicrobial therapy.[43, 44] Patients infected with tPMP-1 resistant isolates of *S. aureus* are significantly more likely to have endocarditis as a consequence of an infected intravascular device, and less likely to be injection drug users, than are patients infected with tPMP-1 susceptible *S. aureus*.[45, 46] PMP may play a role in future therapy of *S. aureus* bacteremia, as it has been shown to act synergistically with several antibiotics both in vitro and in vivo.

Diagnosis

Our ability to diagnose IE has advanced over the last century with the evolution of standardized diagnostic criteria. In 1994 David Durack and colleagues from Duke

University described new diagnostic criteria that incorporated echocardiographic findings and a history of intravenous drug use for the first time (Table 6).[47]

Table 6a. Duke Clinical Criteria Definitions

Major critieria

Positive blood culture for IE

- Typical microorganism consistent with IE from 2 separate blood cultures as noted below:
  - Viridans streptococci (includes nutritionally variant strains), *Streptococcus bovis*, or HACEK group, *or*
  - Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, *or*
- Microorganisms consistent with IE from persistently positive blood cultures defined as
  - 2 positive cultures of blood samples drawn > 12 hours apart *or*
  - all of 3 or a majority of ≥ 4 separate cultures of blood (with the first and last sample drawn ≥ 1 hour apart

Evidence of endocardial involvement

- Positive echocardiogram for IE defined as
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation, *or*
  - Abscess, *or*
  - New partial dehiscence of a prosthetic valve, *or*
- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria

- Predisposition: predisposing heart condition or intravenous drug use
- Fever: temperature ≥ 38 C
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots and rheumatic factor
- Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above, or serological evidence of active infection with organism consistent with IE
- Echocardiographic findings; consistent with IE but do not meet a major criterion as noted above

Table 6b. Duke Criteria for Diagnosis

Definite IE

Pathological criteria

- Microorganisms: demonstrated by culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, *or*
- Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical criteria using specific definitions in table

- 2 major criteria, *or*
- 1 major and 3 minor criteria, *or*
- 5 minor criteria

Possible IE

- Findings consistent with IE that fall short of "definite" but not "rejected"

Rejected

- Firm alternate diagnosis for manifestations of endocarditis, *or*
- Resolution of manifestations of endocarditis with antibiotic therapy for ≤ 4 days, *or*
- No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for ≤ 4 days

The clinical utility, sensitivity and specificity of the Duke criteria have been independently validated and found to have superior performance compared with older criteria not utilizing echocardiography.[48-50] As our understanding of endocarditis has improved, modifications have been proposed. These include expanding the major criteria to include nosocomial *S. aureus* bacteremia and serologic criteria for *Coxiella burnetii*,[51] and adding splenomegaly, elevations in C-reactive protein and erythrocyte sedimentation rate, and the presence of indwelling intravenous catheters to the minor criteria.[52] While these modifications have a sound basis, they have not been formally tested by independent investigators.

Clinical Presentation

The most common clinical manifestation of IE is fever, occurring in as many as 90% of patients.[12, 53] However, fever can be absent in some patients including those with CHF, renal failure, chronic debilitation and in the elderly.[15] Most patients (>85%) have a murmur at some point during the illness.[53] Murmurs may not be evident at the time of initial evaluation but they can appear later in the disease course, underscoring the importance of careful serial examinations. Before microbiologic diagnosis was available, physicians relied on physical exam to detect the presence of classic findings such as Osler's nodes, Roth spots, or subungual hemorrhages (common in long-standing infection). However, these classic findings are nonspecific and are less frequently seen today, presumably because many cases are diagnosed before the disease has been present long enough to give rise to these late signs.[53] Frequent abnormal laboratory tests include anemia (present in 50-80% of patients), elevated erythrocyte sedimentation rate, C-reactive protein, and microscopic hematuria.

Microbiologic diagnosis

Blood cultures remain the primary means of diagnosis of IE today. The presence of multiple positive blood cultures, taken at different times, indicates that the bacteremia is continuous and provides evidence for an endovascular source. While there is no consensus regarding the definition of "continuous bacteremia," the Duke criteria require two positive blood cultures for the same organism drawn more than 12 hours apart, or all of 3 culture sets positive with the first and last set being drawn at least an hour apart. In the setting of presumed acute IE (i.e. hemodynamic instability) the time between the 3 sets of cultures may be shortened to allow for more expedient antibiotic therapy.

The bacteremia in subacute IE is "low-grade" with only 1-10 CFU/mL of venous blood.[54] The greater the volume of blood cultured the greater the chance of organism recovery. To maximize chances of recovery, it is recommended that 20 of mL of blood be obtained for each two-bottle blood culture set in adults.[55]

When collected according to recommendations, blood cultures from patients with IE will be positive for the etiologic agent in as many as 95% of cases.[53, 54] The vast majority of commercially available blood culture systems recover most clinically important pathogens within 5 days. The most common reason for negative blood cultures in the setting of IE is concurrent or recent antimicrobial therapy. If cultures (taken from patients not receiving antibiotics) remain negative at 5 days but IE remains likely on

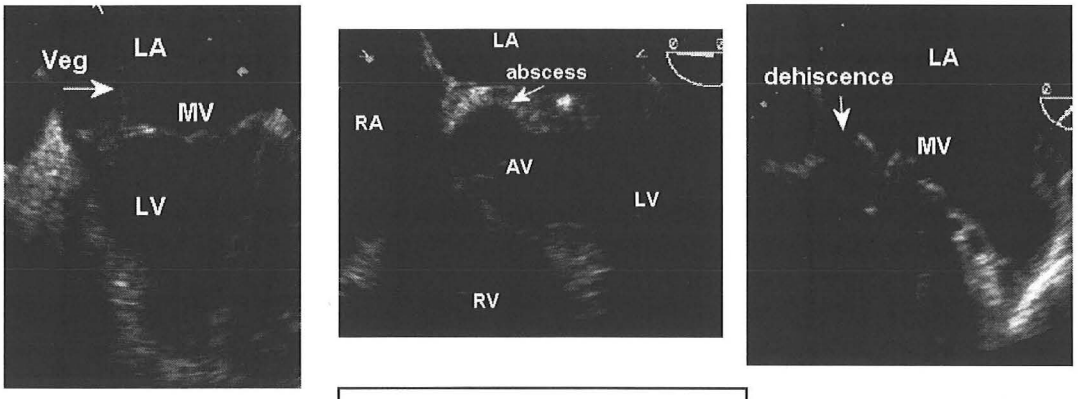
clinical grounds, subculturing bottle contents on chocolate agar plates may be a more effective means for recovery of organisms than is extended bottle incubation.[55]

Most species of Candida grow in standard blood culture media. However, when a high index of suspicion remains for IE despite negative blood cultures, it may be useful obtain a fungal culture. The best system for the recovery of filamentous fungi such as Aspergillus is the Isolator lysis centrifugation tube. Even using this technique, recovery of filamentous fungi remains < 30%. Serologic testing for fungi (cryptococcus and histoplasma) along with other species known to cause IE (*Bartonella* species, *Coxiella* species, *Tropheri whipplei*) can also be helpful in determining an etiologic agent.

Echocardiography

Echocardiography, which provides excellent visualization of cardiac anatomy, has contributed to earlier diagnosis and detection of complications. The hallmark lesion of IE is a vegetation (Figure 3a), evident in 67% - 86% of cases.[12, 56, 57] Vegetations typically occur on the low-pressure side of a high velocity turbulent jet, and are often accompanied by other hemodynamic or anatomic abnormalities. When infection invades contiguous structures, an abscess may result.(Figure 3b) This most commonly involves the aortic root and the anterior mitral annulus, and may extend into the ventricular or atrial septum, right ventricular outflow tract, and anterior mitral valve leaflet. Periannular extension may result in tissue necrosis and ultimately result in communication between or external to chambers. When periannular invasion occurs in the setting of a prosthetic valve, valve dehiscence and perivalvular regurgitation may result (Figure 3c).

Figure 3. Echocardiographic findings meeting Duke "major" diagnostic criteria.



a. Vegetation: irregularly-shaped discrete echogenic mass adherent to but distinct from cardiac surface with the consistency of mid-myocardium.

b. Abscess: thickened area or mass within the myocardium or annular region with a nonhomogenous echogenic or echolucent appearance.

c. Dehiscence: Rocking motion of the prosthetic valve with excursion greater than 15 degrees in at least one direction.

Which form of echocardiography to employ when evaluating the patient with suspected endocarditis depends in part on the prior probability for endocarditis. Advantages to transthoracic echocardiography (TTE) are that is easily performed, noninvasive, and does not require conscious sedation. However, in approximately 15% of adults, interfering tissue and air attenuates sound conduction so that spatial resolution is severely compromised. Advantages to transesophageal echocardiography (TEE) include the enhanced image quality due to the close proximity of the ultrasound probe to the cardiac structures, resulting in improved ability to detect smaller vegetations and complications of endocarditis. Under ideal conditions, TTE can reliably detect structures 3-5 mm in diameter, while TEE can detect structures as small as 1 mm. The sensitivity and specificity for TTE and TEE are shown in Table 7.

Table 7. Sensitivity and Specificity of Echocardiography in the Diagnosis of IE

	TTE		TEE	
	Sn	**Sp**	**Sn**	**Sp**
NVE	50-60%	91-98%	92%	91-98%
PVE	17-36%	100%	82-96%	97%
Abscess	28-36%	99%	76-100%	95%

Legend: NVE, native valve endocarditis; PVE, prothetic valve endocarditis; Sn, sensitivity; Sp, specificity; References from: NVE[58-62]PVE[58, 63-66]abscess[60, 67, 68]

Formal prospective trials comparing the relative costs and benefits of TTE versus TEE in endocarditis have not been performed. Heidenreich and associates sought to answer the question of which form of echocardiography to use with decision tree analysis and Markov modeling, using published data to simulate costs of care and outcomes of patients suspected of having IE.[69] Based on these analyses, TEE was found to be cost-effective for patients with a pre-test probability in the range often found in clinical practice (4-60%), while TTE was better only for those patients with a very-low prior probability of IE.[69] TEE is favored at many institutions for the evaluation of most patients with *S. aureus* bacteremia. There is supporting evidence that this may be the most cost-effective strategy in patients with catheter-associated *S. aureus* infections in determining the duration of antibiotic therapy.[70]

There are certain clinical situations where TEE may be preferable as an initial study over TTE, shown in Table 8. TEE may be particularly effective in patients with cardiac devices such as prosthetic heart valves, internal cardiac defibrillators (ICDs) and pacemakers, patients with persistent bacteremia, new conduction abnormalities, or patients presenting with community-acquired *S. aureus* bacteremia. In prosthetic valve endocarditis (PVE), TTE should be performed in addition to TEE, as it provides complimentary information, particularly for aortic prosthesis. TEE is important not only for diagnosis of IE but is superior in detecting complications and providing important prognostic information.

Echocardiographic images should be interpreted only in conjunction with clinical findings. Examining echocardiographic images in isolation may lead to both false

positive and false negative results. False negative studies may result from vegetations smaller than the limits of imaging resolution, recent loss of vegetation that has embolized, or acoustic shadowing from a heavily calcified or prosthetic valve. False positive studies occur in patients with severe myxomatous valvular disease, ruptured chordae, non-bacterial thrombotic endocarditis, benign cardiac tumors, or Lambl's excrescences (small tags occurring on 70-90% of adult heart valves).

Table 8. Situations when TEE is preferable to TTE

- Prosthetic valves
- Intracardiac devices (pacemaker, ICD)
- Patients at high risk for complications
  S aureus, fungal infection, prior IE, new heart block, cyanotic congenital heart disease, systemic to pulmonary shunts, poor response to antimicrobials
- Intermediate clinical suspicion of IE
  Unexplained bacteremia with gram positive cocci, catheter-associated *S. aureus*, IDU with fever or bacteremia
- Meeting modified criteria for possible IE
- When TTE images are inadequate

Antibiotic therapy

The cornerstone of antibiotic therapy centers on the isolation of the appropriate microorganism. Susceptibility testing helps in the appropriate choice and route of antibiotic therapy. Basic principles of antibiotic therapy include the need for bacteriocidal agents, given for an appropriate duration, and in doses that result in predictable and therapeutic serum levels. The recommended antibiotic therapy for IE is summarized by the AHA guidelines (Table 9).[10, 11] Antibiotic therapy for PVE caused by specific organisms is the same as for native valve endocarditis (NVE), except that patients are treated for a longer duration. PVE caused by *S. aureus* is an exception. The addition of rifampin to two other anti-staphylococcal drugs is recommended in this case, as rifampin has a unique ability to kill staphylococcus adherent to foreign material. In selected patients with uncomplicated right-sided IE due to *S. aureus*, short-course antibiotic therapy (2 weeks) results in low-recurrence and high cure rates.

Surgical therapy

Surgical therapy is required during the early phase of IE in 20-30% of patients.[16, 71-73] Recent published experiences of surgery during active IE show operative mortality rates ranging from 5.2-16%, with actuarial 5 and 10 year survival rates of 75% and 61% respectively.[74-80] By comparison, mortality for the same operative procedures are lower when performed for reasons other than IE.[79, 80] Commonly accepted indications for surgery are shown in Table 10.

Table 9. Recommended Antimicrobial Therapy for Common Microorganisms in IE

Microorganism	Native-Valve	Prosthetic Valve
PCN-susceptible Viridans streptococci & S. bovis, MIC < 0.1 mcg/ml	Penicillin G or ceftriaxone x 4 wks NOTE: 2-wk course of penicillin G or ceftriaxone alternative in uncomplicated cases in patients at low risk for gentamicin toxicity	Penicillin G x 6 wks and gentamicin x 2 wks
Relative PCN-resistant Streptococci MIC > 0.1, < 0.5 mcg/ml	Penicillin G x 4 wks and gentamicin x 2 wks	Penicillin G x 6 wks and gentamicin x 4 wks
Streptococcus species with MIC of penicillin > 0.5 mcg/ml, entero-coccus species or abiotrophia species	Penicillin G (or ampicillin) and gentamicin x 4-6 wks NOTE: 6 wk course recommended for patients with symptoms > 3 months or complicated infection (e.g. abscess)	Penicillin G (or ampicillin) and gentamicin x 6 wks
Methicillin-susceptible staphylococci	Nafcillin or oxacillin x 4-6 wks; may add gentamicin for first 3-5 days of treatment	Nafcillin or oxacillin with rifampin x 6 wks, and gentamicin x 2 wks NOTE: Consider delay of rifampin treatment for first 2 days until therapy with 2 other antistaphylococcal drugs established to avoid development of rifampin resistance
Methicillin-resistant staphylococci	Vancomycin x 4-6 wks; may add gentamicin for first 3-5 days of treatment	Vancomycin with rifampin x 6 wks and gentamicin x 2 wks
Right-sided staphylococcal native valve endocarditis	IN SELECTED PATIENTS: Nafcillin or oxacillin with gentamicin x 2 wks NOTE: Exclusion criteria to 2 wk therapy include: MRSA, antibiotics other than penicillinase-resistant penicillins, any cardiac or extracardiac complications, vegetation size > 2 cm, slow clinical response (> 96 hours), and HIV infection.	
HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella* species)	Ceftriaxone x 4 wks NOTE: Ampicillin and gentamicin x 4 wks Can also be used, but some isolates may Produce beta-lactamase, reducing the efficacy of this combination	Ceftriaxone x 6 wks NOTE: Ampicillin and gentamicin also used for prosthetic valve infection, but the same concerns regarding native valve disease apply.

Adapted from[10, 81]

Table 10. Indications for surgical therapy in native valve IE

Valvular dysfunction with congestive heart failure
Extension of infection into adjacent structures
Fistula formation
Rupture into pericardium
New conduction disturbance
Abscess
Persistant bacteremia or fever despite appropriate antimicrobial therapy
No available effective antibiotic treatment
Difficult to treat organisms
Coxiella burnetti, left-sided *Pseudomonas aeruginosa*, fungal infections

The decision for surgical therapy should not be based on absolute indications but on serial clinical evaluations, microbiologic results (including surveillance blood cultures on appropriate therapy) and echocardiographic findings. Treatment failure should not be assumed unless (1) fever persists for more than 7 days or (2) blood cultures remain positive after 7 days of appropriate antibiotic therapy, and a search for metastatic infection is negative. Patients with persistent fever or bacteremia should also undergo TEE to rule out an intracardiac abscess.

Results of surgery depend on many factors including the preoperative condition of the patient, timing of the surgery, surgical techniques and postoperative management. Predictors of operative mortality include NYHA classification, age and the presence of renal failure preoperatively.[74-78, 82] Aggressive disease of a shorter duration as occurs with *S. aureus* is also associated with increased mortality.[33]

Early surgical intervention in the acute phase, particularly in the presence of uncontrolled infection, may seem risky due to concerns about placing prosthetic material into a highly infected field with the potential for failure and recurrence of IE. Some investigators reported that surgical intervention during the acute phase was associated with increased risk for persistent or early recurrent PVE.[80, 83, 84] In contrast, others did not find this to be true,[4, 7, 71, 85, 86] particularly for mitral valve disease.[79, 83] The final surgical outcome appears to have little relation to the duration and intensity of antibiotic therapy before surgery.[71, 74, 75, 77, 87-89] However, it is important that adequate bactericidal concentrations of antibiotics be present to kill bacteria entering the circulation during surgical debridement. In general, when surgery is indicated, prognosis is improved if surgery is performed early before the general condition of the patient has deteriorated too severely.[71, 72, 90]

Identification and management of complicated IE

Congestive heart failure

Congestive heart failure (CHF) is the most common cause of death in IE. Causes of CHF in the setting of IE are listed in Table 11. In NVE, acute CHF occurs more frequently with aortic valve IE (29%) than with mitral valve IE (20%).[91] Endocarditis complicated

by acute aortic insufficiency (AI) is particularly high risk as acute AI is poorly tolerated and results in rapid progression of CHF in most cases. The risk of CHF is also increased in the presence of virulent pathogens such as *S. aureus*, hemolytic streptococci groups A-C, F and G, and *Streptococcus pneumoniae*.

Table 11. Causes of CHF in IE

Acute aortic insufficiency
Rupture of infected mitral chordae
Perforation of valve leaflets
Vegetation-related valve obstruction
Sudden development of intracardiac shunts
Prosthetic valve dehiscence
Progressive worsening of valve regurgitation and LV dysfunction
Coronary artery embolism with myocardial infarction

Heart failure is the most common and best-validated indication for surgery. It is the primary indication for surgery in 22-71% of cases of surgically treated IE[76, 80]. Heart failure carries a worse prognosis with medical therapy alone, but it also constitutes a surgical risk factor. Operative mortality is 6-11% in the absence of CHF vs. 17-33% with CHF.[11, 92, 93] Four studies from the 1970s and 1980s compared combined medical and surgical therapy with medical therapy alone in the treatment of IE complicated by CHF. In these earlier studies the mortality with surgery ranged from 11-35% while the mortality with medication alone was 56-86%.[91, 94-96] In more recent studies, the mortality for surgically-treated patients with decompensated CHF is 10% vs. 20-27% in patients treated with medical therapy alone.[16, 75] The mortality benefit was apparent when surgery was performed early in the course of disease, with the greatest benefit found when the procedure was performed on a median of day 4 of the hospitalization.[75]

Surgery should be performed before intractable CHF develops. Post-operative mortality is proportional to the severity of hemodynamic impairment at the time of surgery.[77] There is no evidence that delaying surgery to give additional antibiotics improves outcome. The 2-7% potential risk of recurrent IE following surgery in the acute phase is far less then the mortality from uncontrolled CHF.[71, 86, 97]

Abscess

Extension beyond the leaflets occurs in 8-40% of NVE[98-101], most commonly in the aortic annular region, and has been reported in more than half of patients with PVE.[90, 95, 101, 102] Periannular invasion is more common in bioprosthetic valves during the first post-operative year compared with later, while invasive disease occurs in mechanical valves regardless of time from implantation.[103]

Significant predictors of abscess include aortic valve involvement, IV drug use, and new AV or bundle branch block.[104, 105 101] The development of new atrioventricular (AV) or bundle branch block has a 77% positive predictive value but a relatively low sensitivity for abscess formation (42%).[101] The presence of intraventricular block (bundle branch or hemiblock) may have prognostic implications, with a mortality of 31% vs. 15% in patients without intraventricular block.[106]

The mortality of medically treated patients with abscess may be as high as 75%.[107] As a result, surgical therapy is preferred in most cases of abscess formation. Provided surgical procedures are radical, resulting in complete resection of the abscess cavity and restoration of near-normal hemodynamics, abscesses are not an adverse predictor of early surgical mortality or reinfection rate.[78] A small number of patients with abscesses may be treated medically provided they are followed by serial TEE for progression of disease. Contraindications for medical management include heart block, valvular regurgitation and dehiscence. If any of these conditions occur during medical management, prompt surgical intervention should be pursued.[108]

Stroke

The incidence of clinically significant embolic events is 22-50%.[109-113] Stroke represents 50-65% of these cases and is a major contributor of morbidity and mortality associated with IE.[114] The majority of strokes are diagnosed before antibiotic treatment begins.[114, 115] Most "preventable strokes" defined as those occurring after the initiation of treatment, occur early. The frequency of embolism dramatically declines after initiation of antibiotic therapy.[16]

Identifying risk factors associated with embolism may be useful to help select patients who might benefit from early surgical therapy. Both clinical and echocardiographic characteristics identify patients at increased risk for embolism (Table 12).

Table 12. Risk factors for Stroke

Clinical	Microbiology	Echocardiography
Prior embolism	*S. aureus*	MV infection
Short symptom duration	*Candida* species	Perivalvular extension
	Abiotrophia	Increase in size during Rx
Older age	HACEK	Vegetation
PVE		number
Atrial fibrillation		mobility
		size > 10mm

Reference:[16, 109, 111, 115-117]

Vegetation size, morphology and location have been associated with embolic risk In a meta-analysis of 10 studies involving a total of 738 patients, 37% of the 323 patients with vegetations more than 10 mm in diameter experienced embolism, a risk almost 3 times greater than in patients with smaller vegetations.[117] Some investigators found large vegetations independently predicted embolic events only in viridans group streptococcus while infections with *S. aureus* have a high risk of embolism regardless of vegetation size.[109, 111]

There is evidence that vegetations on the mitral valve (particularly the anterior leaflet) are associated with the highest risk for embolism and stroke (21-32% with mitral valve IE vs. 11-15% with aortic valve IE)[12, 115] The degree of vegetation mobility may also predict embolic risk.[111, 116] When silent emboli (as assessed by cerebral and thoracoabdominal CT scans) are included along with clinically apparent emboli the composite rate of

embolic events is particularly high (83%) when vegetations are both very large (> 15 mm) and mobile.[111]

Once risk factors for embolism are identified, the treatment plan remains controversial. While current dogma suggests that surgery be performed after 2 or more embolic events occur on antibiotic therapy, preemptive early surgical intervention to prevent embolism has not been well studied. If the patient has another indication for surgical therapy, such as significant valvular regurgitation or CHF, the decision for surgery is easier as it will achieve a two-fold objective. Likewise, surgery may be considered following a single embolic episode in patients with a persistent vegetation when the risk of repeat embolism is felt to be high based on clinical, microbiologic or echocardiographic parameters. It is unclear if surgery is warranted when a large mobile vegetation is present without evidence of embolism. However, when the goal is to prevent embolic events, surgery is best performed early, since the rate of embolism is greatest during the first one to two weeks of medical treatment.

All patients with neurologic symptoms should undergo CT of the brain to clarify the nature and extent of disease and identify hemorrhage before undergoing surgical therapy for IE. Cerebral angiography is recommended in patients with CT evidence of hemorrhage, as 10-50% of these patients will have a ruptured mycotic aneurysm[118, 119] A ruptured mycotic aneurysm should be resected, clipped or embolized prior to valve surgery.[118]

After a stroke has occurred, the risk of possible further neurologic damage during cardiopulmonary bypass becomes a concern. Some authors assert that valve replacement can be performed 72 hours or greater following an ischemic cerebral infarct with a low risk of perioperative stroke in the absence of hemorrhage.[120] However, in a recent multicenter retrospective study involving 181 patients with cerebral complications undergoing surgery for IE the risk for exacerbation of neurologic events persisted for weeks.[121] This risk decreased with time regardless of the type of stroke; the rates of exacerbation were 10% and 2.3% 15 and 28 days after CVA, respectively. Most investigators recommend allowing a 2-3 week interval between neurologic events and the cardiac operation, based on available data.[118, 122]

Prosthetic valve and cardiac device infections

Prosthetic IE can be devastating. The increased frequency of paravalvular invasion, particularly in early PVE, results in a greater incidence of complications such as heart failure, persistent fever, or new conduction abnormalities when compared with NVE. The reported mortality rates for PVE range from 5-69%, with most studies suggesting a rate of 20-30%.[57, 72, 123-129] Early PVE (traditionally defined as occurring within the first 60 days postoperatively) is associated with a particularly high mortality[57] and is more likely to be associated with paravalvular invasion and hemodynamically significant valvular lesions.

The frequency of PVE is highest during the initial 3 months following implantation, remains high through the 6th month and declines gradually to a relatively constant rate of

0.3-0.8% per year at 12 months and thereafter.[130-132] There appears to be no overall difference in the infection rates following implantation of bioprosthetic and mechanical valves.[132] The infection risk may be higher for mechanical valves during the initial year following implantation, but over time the risk of infection for bioprostheses increases so that there is no overall difference in infection rates between the two valve types 5 years post-operatively.[131, 132] Patients with prosthetic valves who develop nosocomial bacteremia are at high risk for developing PVE, with an incidence of 11%.[133]

The use of anticoagulation therapy is controversial. It is agreed that there is no role for the introduction of anticoagulation in patients not otherwise requiring it. Most experts continue administration of anticoagulation during therapy of mechanical valve IE. This approach has recently been questioned, particularly in patient populations at high risk for embolism (e.g. *S. aureus* infection) for the first 1-2 weeks of therapy.[134]

Certain clinical findings help to identify patients at high risk for complications and death when treated with medical therapy alone. Patients who develop pathologic murmurs or moderate to severe heart failure as a result of valve dysfunction, fever more than 10 days despite appropriate medical therapy, new onset heart block, or echocardiographic evidence of abscess or valve dehiscence are at high-risk and unlikely to respond to medical therapy alone.[135, 136] The addition of surgery to the treatment plan for high-risk patients results in greater survival rates, fewer relapses, and fewer rehospitalizations for valve surgery.[135, 137, 138] *S. aureus* PVE is associated with a particularly grave prognosis, with mortality ranging from 28% to 82% in different series.[4, 83, 135, 136, 139] Surgery appears to improve outcomes in *S. aureus* IE regardless of the presence of cardiac complications.[139] Indications for surgical therapy of PVE (Table 13) are not absolute, and should be implemented with careful attention to the relative risks and benefits in a given patient. Patients with late-onset PVE caused by viridans streptococci, HACEK group or enterococci without evidence of paravalvular invasion or valve dysfunction can be treated with antibiotics alone.

Table 13. Indications for surgery in prosthetic valve IE

- Moderate to severe CHF due to valve dysfunction
- Unstable prosthesis
- Paravalvular extension of infection
- Relapse despite optimal therapy
- Very large, mobile vegetations
- Culture-negative PVE with unexplained fever > 10 days duration
- Uncontrolled infection on optimal medical therapy
- PVE caused by:
  S. aureus, fungi, *Pseudomonas aeruginosa*, multidrug resistant enterococci, *Brucella* species, *Coxiella burnetti*

Cardiac device-related infections are becoming increasingly important, representing a leading cause of death and disability following device implantation. Pacemaker infection rates vary widely in the literature, ranging from 0.13 to 19.9%[140-143] and the risk of pacemaker-associated infection among high-risk populations such as those with *S. aureus*

bacteremia may be as high as 45%.[144] Reported internal cardiac defibrillator (ICD) infection rates, while not studied systematically, appear to be at least 0.8-1.3%.[145-147] The last decade has seen an exponential increase in placement of cardiac devices. In the Medicare population, rates have increased from 3.26 to 4.64 implantations per 1000 Medicare beneficiaries, a relative increase of 42%. At the same time, cardiac device infections have outpaced the increase in implantations in this population, with an increase from 0.94 to 2.11 infections per 1000 Medicare beneficiaries, a 124% relative increase.[148]

With recent data expanding the indications for defibrillators and biventricular pacemakers,[149-152] rates of device infections can be expected to increase even further. The importance of device-related infections is further underscored when one considers that the cost of standard therapy includes removal of the entire device, intravenous antibiotics and in most instances reimplantation of the device.[153]

Long-term outcomes

Patients surviving the initial hospitalization are subject to long-term complications related to the predisposing factors that led to the initial infection, new valvular damage, or the prosthetic heart valve placed during the initial hospitalization. Relapse, defined as resumption of IE within 6 months of treatment with the same microorganism, occurs in approximately 3% of patients.[4, 7, 154] Recurrence, infection with a different organism or infection more than 6 months after the initial episode, occurs in 2.5-12.3% of hospital survivors.[2, 4, 57, 154, 155] The probability of recurrence-free survival is lower in men and in the elderly. Mitral valve repair and the use of homografts in the aortic position even in the presence of active infection may reduce the incidence of infective recurrence.[76, 102, 156, 157]

Between 19.7-47% of patients with IE treated medically will eventually require valve replacement, most in the first 2 years of follow-up.[4, 7, 154, 158] Patients receiving valve replacements during the acute episode of IE or during the follow-up period are at risk for all the complications associated with prosthetic heart valves including valve degeneration, thromboembolic events, bleeding and recurrent infection.[159]

In published series, long-term mortality in hospital survivors varies greatly. Most report a 10-year survival rate from 48-80%.[5, 7, 79, 80, 160] Age and recurrent endocarditis are significant predictors of mortality in the follow-up period.[154]

Future directions

A shift in approach is necessary to further our understanding of IE. If we want to develop the high quality evidence needed to help clinicians at the bedside make therapeutic decisions that improve the outcomes of our patients, then we must take advantage of the advances in technology and information systems that have occurred over the last 20 years. International collaboration in this area will lead to opportunities to share data and conduct large scale prospective cohort studies. The information gained from these efforts will be used to design and conduct randomized controlled trials of treatment strategies that may then provide the definitive evidence that is needed to assist in therapeutic decision making.

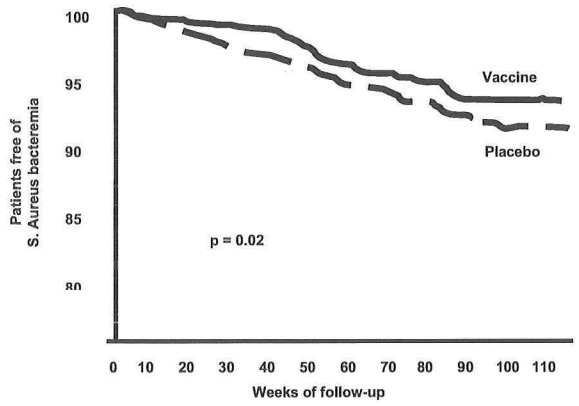
The creation of the International Collaboration of Endocarditis (ICE) investigation provides opportunities to expand our knowledge of IE. From its formation in 1999, three phases of the collaborative effort were launched. The first phase was to merge all existing databases into a single analysis database from which retrospective, descriptive studies could be performed. The second phase involves the development of a large global database of IE patients whose clinical, echocardiographic and microbiologic findings have been characterized with standardized, predefined methods. The third goal of the ICE investigators is the formation of a network of centers with the capability to conduct clinical trials. Although registries can play important roles in recording the epidemiology and practice patterns, randomized trials will be needed to determine the efficacy of innovative and novel therapies.

Since the inception of the prospective database in June 2000, 1024 patients meeting Duke criteria for definite IE have been enrolled from 36 sites in 15 countries. The multinational aspect provides a global view of IE in contrast to the relatively small case series largely from single centers. Identifying patients at high risk for complications and targeting this population for preventative therapy is one of many potential benefits. The knowledge gained from this large database will lead to testing of therapeutic strategies to minimize the morbidity and mortality associated with this disease.

Future directions include treatment with novel therapeutic agents. As mentioned earlier, bacterial adherence is central to initiation of infection and metastatic spread, and the MSCRAMM family of bacterial surface adhesion proteins has been a target for the development of new immunotherapies. *S. aureus* Human Immune Globulin (SA-IGIV, Inhibitex, Inc.), a purified IgG derived from pooled human plasma selected for high antibody titers to MSCRAMMs, interferes with *S. aureus* adherence to extracellular matrix proteins in vitro, and may also enhance opsonophagocytosis of *S. aureus* by PMNs.[161] In an animal model of *S. aureus* IE, combination therapy with SA-IGIV and vancomycin significantly increased clearance of bacteremia when compared with vancomycin alone.[162] An open-label multicenter Phase 1/Phase 2 Pharmacokinetic Study of SA-IGIV in patients with MRSA IE is currently underway.

The development and testing of vaccines targeting high risk groups may reduce adverse outcomes and costs associated with this disease. Immunizations with fibronectin binding proteins or FimA proteins protect against experimental IE (with *S. aureus* and Streptococcal species respectively) in animal models.[163-165] StaphVax (Nabi, Inc.) is a vaccine with *S. aureus* type 5 and type 8 capsular polysaccharides, the strains accounting for more than 80% of *S. aureus* infections. In a double-blind placebo controlled trial StaphVax resulted in a significant, 57% relative reduction in *S. aureus* bacteremia at 40 weeks in hemodialysis patients (Figure 4).[166] Such vaccines could have important clinical applications among patients with indwelling intravascular catheters or prostheses at high risk for *S. aureus* infections.

Figure 4. Staphvax (NABI) in Patients Receiving Hemodialysis



Reference[166]

Conclusion

Despite improved understanding of the pathogenesis and better diagnostic and therapeutic methods, the overall death rate for IE has changed little over the past 40 years. The use of global databases such as ICE can improve knowledge about this heterogeneous disease, identify populations at risk for IE and its complications, and create collaborations between investigators that will lead to new treatment and preventative strategies.

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