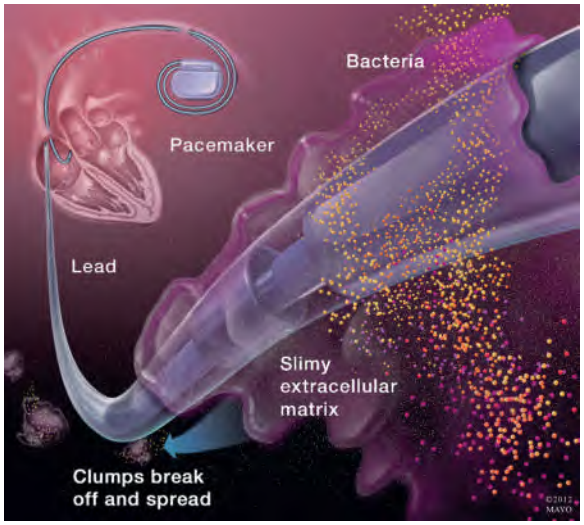

FIG. 82.1 Microbial biofilm formation on pacemaker lead. Biofilm forms on implants when bacteria stick to their surfaces. They multiply into colonies and form a protective slime layer that allows them to move and collect nutrients while staying safe from antimicrobial agents and host immune system. *(Copyright Mayo Clinic.)*

TABLE 82.1 Nonvalvular Cardiovascular Device–Related Infections

TYPE OF DEVICE	RATE OF INFECTION (%)
Intracardiac	
Permanent pacemaker	0.13–19.9
Implantable cardioverter-defibrillator	0.3–3.2
Left ventricular assist devices	13–80
Ventriculoatrial shunts	2.4–9.4
Pledgets (cardiac suture line)	Rare
Patent ductus arteriosus occlusion devices	Rare
Atrial septal defect closure devices	Rare
Conduits	Rare
Patches	Rare
Arterial	
Peripheral vascular stents	0.05–4.0
Vascular grafts, including hemodialysis	1–6
Intraaortic balloon pumps	≤5–27
Angioplasty/angiography-related bacteremias	<1
Vascular closure devices	0.0–5.1
Coronary artery stents	Rare
Patches	1.8
Venous	
Vena caval filters	Rare

TABLE 82.2 Factors Associated With Increased Risk of Cardiovascular Implantable Electronic Device (CIED) Infections

Host Factors
Older age
Comorbid conditions (diabetes mellitus, heart failure, renal failure, malignancy)
Presence of a tunneled central venous catheter (such as hemodialysis catheter)
Chronic anticoagulation
Long-term corticosteroid therapy
Bloodstream infection (especially *Staphylococcus aureus*) from a distant focus
Device-Related Factors
History of multiple device-related procedures
History of CIED infection
Presence of >2 electrode leads
Epicardial leads
Abandoned leads
Recent device manipulation (i.e., generator exchange or lead revision)
Procedure-Related Factors
Fever within 24 hours of implantation
Temporary pacing before permanent device placement
No antibiotic prophylaxis before device implantation
Operator inexperience
Postoperative hematoma or other complications at generator pocket

ability to eliminate infection due to neutrophil dysfunction, poor penetration of antibiotics into the biofilm, and downregulation of metabolic activity in infecting organisms that makes them less susceptible to some antimicrobials, necessitating device removal for the best chance of infection cure (Fig. 82.1). Once a generator or pocket is colonized, bacteria can migrate along the electrode leads and manifest as tunnel infection, bacteremia, or infected vegetations on electrode leads or cardiac valves. However, hematogenous seeding of CIED leads is the predominant mechanism for the majority of late-onset (after 6 months of implantation) device infections, especially when there is no clinical evidence of pocket infection. Up to a third of patients with bloodstream infection (BSI) due to gram-positive cocci, especially *Staphylococcus aureus,* in the setting of CIED may have an underlying device infection.[11,12,13,14] Hematogenous seeding of device leads, however, is exceedingly rare in patients with gram-negative bacteremia that originates from a distant source.[15]

Risk Factors for Cardiovascular Implantable Electronic Device Infections

Several host- and procedure-related factors predispose to an increased risk of CIED infection (Table 82.2).[16–23] These factors predispose to device infection by increasing the risk of generator or lead contamination at the time of implantation and/or delay in wound healing at a generator pocket site or increased risk of BSI from a distant source with hematogenous seeding of device leads.

In a case-control study,[16] presence of a permanent central venous catheter, prolonged corticosteroid use, a history of CIED infection, presence of more than two electrode leads, and a history of multiple device-related procedures were associated with increased risk of pacemaker infection. Other factors associated with higher risk of CIED infection include operator inexperience,[19] use of epicardial leads, postoperative complications at the generator pocket (delayed wound healing, hematoma formation), diabetes mellitus, renal failure, and heart failure.[17,21]

Risk factors associated with CIED infection were evaluated in another multicenter, prospective investigation[18] that included 6319 CIED recipients (5866 PPMs and 453 ICDs). Risk of device infection was significantly higher in patients who had fever within 24 hours of CIED implantation (adjusted odds ratio [aOR], 5.83), presence of a temporary pacing wire before device implantation (aOR, 2.46), and those who underwent an early reintervention (aOR, 15.04) for hematoma evacuation or lead revision. De novo device implantation (aOR, 0.46) and antibiotic prophylaxis (aOR, 0.4) both had protective effects.

Microbiology of Cardiovascular Implantable Electronic Device Infection

Staphylococci are the predominant pathogens in CIED infections.[24,25] In one study from Mayo Clinic,[4] coagulase-negative staphylococci (CoNS) (42%), followed by *S. aureus* (29%), were responsible for more than two-thirds of cases of device infection (Fig. 82.2). Early device infections (within 2 weeks of implantation) are primarily caused by *S. aureus.* Prevalence of methicillin-resistant *S. aureus* (MRSA) is variable depending on the geographic location of reporting institutions. In the previously

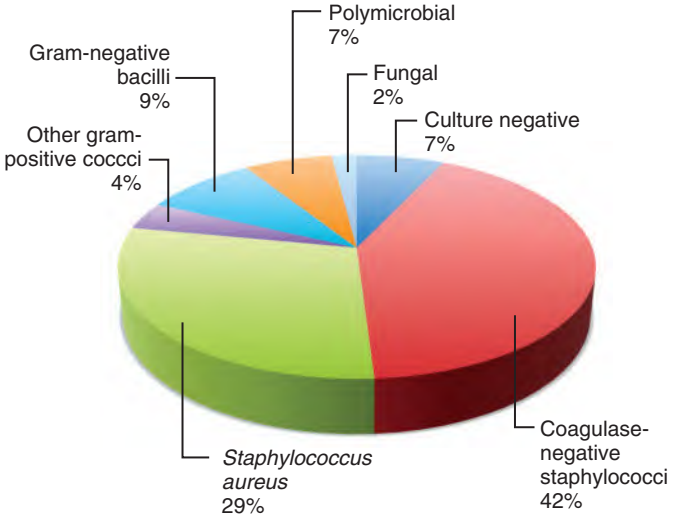

FIG. 82.2 Microbiology of cardiovascular implantable electronic device infections. *(Modified from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections.* J Am Coll Cardiol. *2007;49:1851–1859.)*

referenced study[4] gram-negative bacteria; other gram-positive cocci, including enterococci, streptococci, and micrococci; and fungi (*Candida* spp. and *Aspergillus fumigatus*) were isolated in 9%, 4%, and 2% of cases, respectively. Polymicrobial infection may be present in up to 7% of cases and tends to be more common in patients with diabetes mellitus and those receiving corticosteroids.[26] Pocket site and blood cultures may be negative in patients who have previously received antibiotics or have low-virulence organisms associated with biofilm formation. Sonication techniques to disrupt biofilms can be a useful tool to increase culture yields in specimens suspected of harboring CIED infection.[27] In one study at the Mayo Clinic substantial bacterial growth was observed in 54% of sonicate fluids, significantly greater than the sensitivities of pocket swab (20%), device swab (9%), or tissue (9%) cultures.[28]

Clinical Manifestations of Cardiovascular Implantable Electronic Device Infection

CIED infection typically manifests in three distinct ways.[4] The most common presentation is pocket site infection (>60%). Patients generally present with localized inflammatory changes at the generator pocket site, including erythema, pain, swelling, warmth, drainage, or dehiscence of overlying skin. Systemic signs of sepsis or positive blood cultures are present in less than one-half of these cases. The second presentation is occult bacteremia or fungemia and no local changes at the pocket site. The third presentation is CIED-related endocarditis (lead or valvular vegetations, or both) in 10% to 23% of cases.[29,30] When vegetations are visualized on cardiac structures, the tricuspid valve is the most common site of infection (up to 25% of cases with CIED-related endocarditis).[30] However, vegetations can develop on the pulmonic or left-sided valves, especially in the setting of *S. aureus* bacteremia (SAB). Patients with SAB may have radiographic findings of multiple focal pulmonary infiltrates, abscesses, or cavitations due to septic emboli in as many as 40% of the cases.[31,32] Patients with CIED-related endocarditis have a higher mortality (14%–25%) compared with those without it (<5%), even with percutaneous lead extraction.[30,33] A small proportion (<5%) of the patients can present with erosion of a device lead or generator in the absence of inflammatory signs at the pocket and negative blood cultures.[4] Whether erosion is caused by low-grade infection or purely by mechanical factors may not be entirely clear in all patients.

Diagnosis of Cardiovascular Implantable Electronic Device (CIED) Infection

A diagnosis of CIED infection is easily discernible when pocket site inflammatory changes are present or when device erosion is evident. However, a diagnosis may be difficult to confirm in cases in which positive blood cultures are the sole manifestation of underlying CIED infection. It is critical that blood cultures be obtained in all patients with suspected CIED infection before starting any empirical antibiotics. If drainage is present, swab specimens should be submitted for cultures. Abnormal laboratory findings (leukocytosis, anemia, high erythrocyte sedimentation rate, or C-reactive protein) are present in 50% or less of cases, and the absence of these findings should not dissuade clinicians from considering a possibility of CIED infection in the appropriate setting.

Positive blood cultures, even in the absence of other manifestations of device infection, should prompt a serious consideration for underlying CIED infection. In patients with SAB, concomitant CIED infection is present in 30% to 50% of the patients.[14,34] Risk is especially high within the first year after device implantation. Of note, local signs or symptoms of pocket or tunnel infection may be absent in half of these cases. Patients with BSI due to CoNS or enterococci are also at significant risk of hematogenous seeding of CIED leads.[35] Therefore we recommend thorough evaluation for underlying CIED lead infection in these patients with transesophageal echocardiography (TEE) (Fig. 82.3). Although the presence of clots on CIED leads is considered evidence of lead infection, a major limitation of TEE is that bland (noninfected) clots on leads occur, and TEE is unable to distinguish bland clots from infected lead vegetations. In patients with no evidence of CIED infection (after a thorough evaluation that includes TEE and possibly positron emission tomography [PET]/computed tomography [CT]) at the time of gram-positive bacteremia, and for whom a decision is made to treat conservatively, there should be close follow-up over the next 12 weeks to monitor for relapsing bacteremia. Surveillance blood cultures after completing 2 to 4 weeks of appropriate parenteral antibiotics should be considered. Overall, risk of hematogenous seeding of CIED leads with gram-negative bacilli is low.[36] However, in a recent investigation[37] from Duke University that included patients with CIEDs, prosthetic heart valves, and left ventricular assist devices (LVADs), patients with BSI due to *Pseudomonas aeruginosa* or *Serratia marcescens* had higher risk of hematogenous seeding of cardiac devices compared with bacteremia due to other species of gram-negative bacilli.

Indium-labeled leukocyte or gallium scanning may be helpful in differentiating an infected CIED pocket from a noninfected pocket site. In one study sensitivity of technetium 99–labeled white blood cell (WBC) single-photon emission computed tomography/CT (SPECT-CT) was 94% for both detection and localization of CIED-associated infection. ^{99}Tc-labeled WBC scintigraphy not only enabled the confirmation of CIED infection but was also helpful in defining of the extent of device involvement and detection of associated complications. Moreover, ^{99}Tc-labeled WBC scintigraphy[38] reliably excluded device-associated infection during a febrile episode and sepsis, with 95% negative predictive value.[39]

PET scan combined with CT (PET-CT) is an emerging modality for confirmation of CIED infection in select cases. In one study[40] 32 of 42 patients with suspected CIED infection had a positive PET-CT. Twenty-four of these patients with positive findings on PET-CT underwent extraction with an excellent correlation with CIED infection. Ten patients, who had negative PET-CT imaging and were managed conservatively with antibiotics alone and without device removal, had no signs of infection relapse after an average follow-up duration of 13 months. In a recent meta-analysis[41] of 14 studies involving 492 patients, the pooled sensitivity of PET-CT for diagnosis of CIED infection was 83%, and the pooled specificity was 89%. PET-CT demonstrated a higher sensitivity of 96% and specificity of 97% for diagnosis of generator pocket infections. Diagnostic accuracy for lead infections or CIED-IE was lower with pooled sensitivity of 76% and specificity of 83%. Based on these data, PET-CT is a good adjunctive tool for the diagnosis of CIED infection in cases where clinical findings at the generator pocket site are not compelling, and TEE images in cases of suspected lead infection are inconclusive (Fig. 82.4). In addition to diagnosis of CIED infection, PET-CT can identify distant foci of infection or malignancy that may be clinically silent.

Lead tip cultures are frequently used to confirm the diagnosis of CIED-related infective endocarditis.[31,32,42] However, most transvenous leads are extracted percutaneously in current practice, and lead tips may be contaminated during removal through the incision of an infected

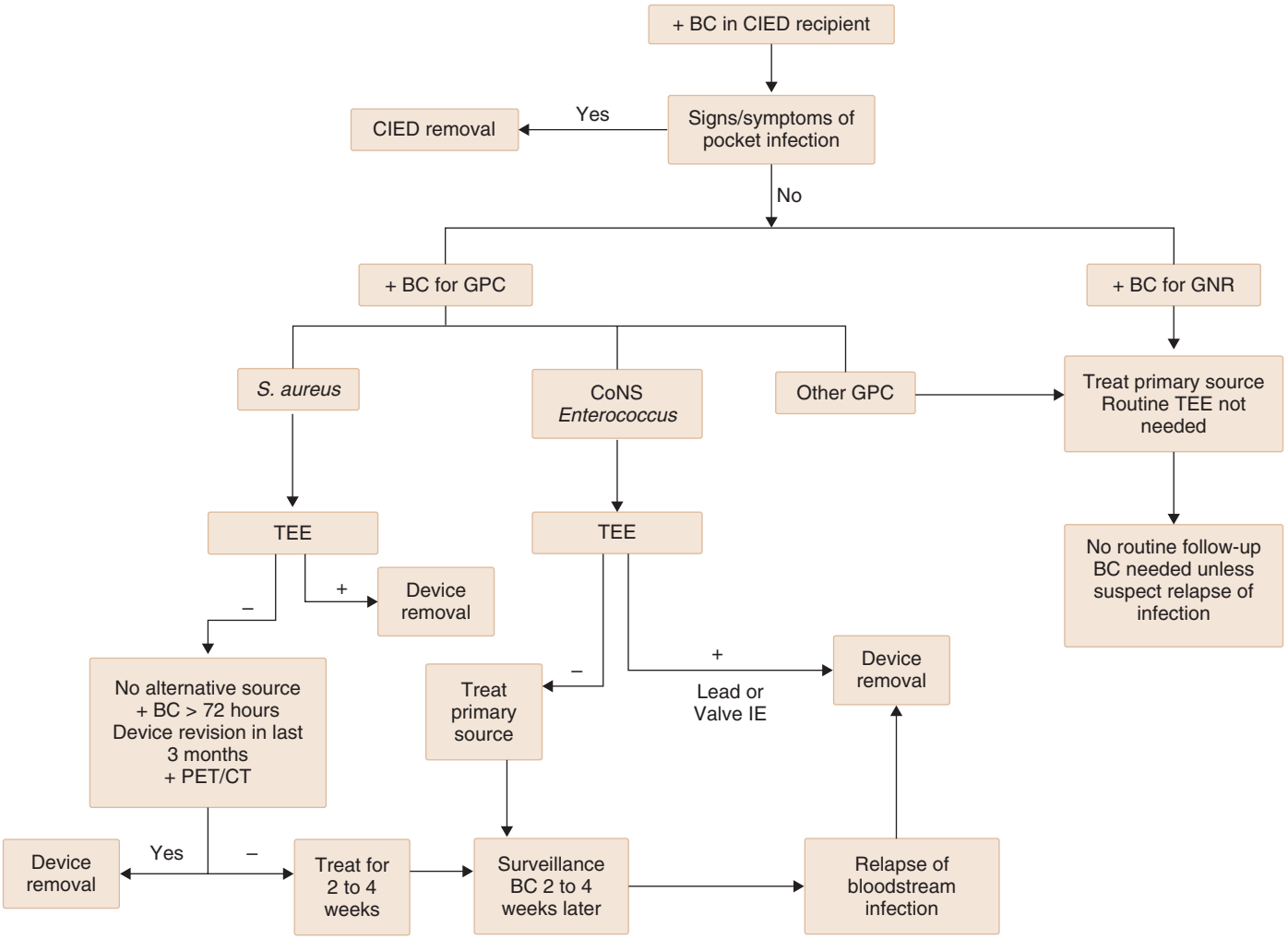

FIG. 82.3 Management of bacteremia in patients with a cardiovascular implantable electronic devices. *BC,* Blood culture; *CIED,* cardiovascular implantable electronic device; *CoNS,* coagulase-negative staphylococci; *CT,* computed tomography; *GNR,* gram-negative rods; *GPC,* gram-positive cocci; *IE,* infective endocarditis; *PET,* positron emission tomography; *TEE,* transesophageal echocardiogram. *(Modified from DeSimone DC, Sohail MR. Management of bacteremia in patients living with cardiovascular implantable electronic devices.* Heart Rhythm. *2016;13:2247–2252.)*

pocket.[30] Lead tip cultures are more reliable if they are extracted using a sterile technique (via a protected sleeve) or if removed from a different incision than that used at the generator pocket site.

Role of Echocardiography in Diagnosis of Cardiovascular Implantable Electronic Device Infection

In addition to identifying possible vegetations on CIED leads (with limitations as discussed earlier), echocardiography is critical in the diagnosis of other complications associated with CIED infection, such as valvular vegetations, perivalvular extension of infection, and abscess formation. The diagnostic superiority of TEE over transthoracic echocardiography (TTE) has been substantiated in multiple studies, with the reported sensitivity of TEE at >95% compared with <50% for TTE.[10,30,43,44] TEE is also helpful in assisting in decision making regarding the most appropriate extraction strategy by providing information regarding vegetation size and attachment of device leads to surrounding venous or cardiac structures.

A limitation, however, is that echocardiography cannot distinguish noninfected lead clots, which can be seen in 1.5% to 48% of noninfected patients, from infected vegetations on leads, depending on the type of tool used to identify the clots. In practice, patients who present with BSI and have a mass attached to a device lead on TEE are presumed to have CIED infection. PET-CT may be marginally helpful in these cases to confirm or exclude a "true" lead infection.

Complications of Cardiovascular Implantable Electronic Device Infection

Complications of CIED infection may include valvular endocarditis (mostly right sided), septic arthritis, spine infection (diskitis, vertebral osteomyelitis, or epidural abscess),[45] sternal wound infection, metastatic abscesses (lung, liver, spleen, brain, renal), and thrombosis of a subclavian vein or superior vena cava. In patients with metastatic abscesses or osteomyelitis it may be difficult to decipher whether an ectopic site is the source of bacteremia with hematogenous seeding of a cardiac device or vice versa.

Management of Cardiovascular Implantable Electronic Device Infection

The primary focus of treatment should be complete removal of the CIED system. Although no prospective, randomized trials have been conducted to evaluate the role of medical (antimicrobial) therapy alone versus a combined medical-surgical treatment approach, data from several retrospective analyses show a clear advantage of complete device removal.[4,26,46,47] For example, the reported mortality rate of CIED-related endocarditis ranges from 31% to 66% if the infected device is retained, compared with 18% or less in patients managed with a combined approach of complete device removal and parenteral antibiotics.[30,31,32] Patients with partial device removal (generator only) or those treated conservatively with antibiotics alone have a higher risk of treatment failure or relapse.[4,26,48] In one investigation of 416 patients with CIED

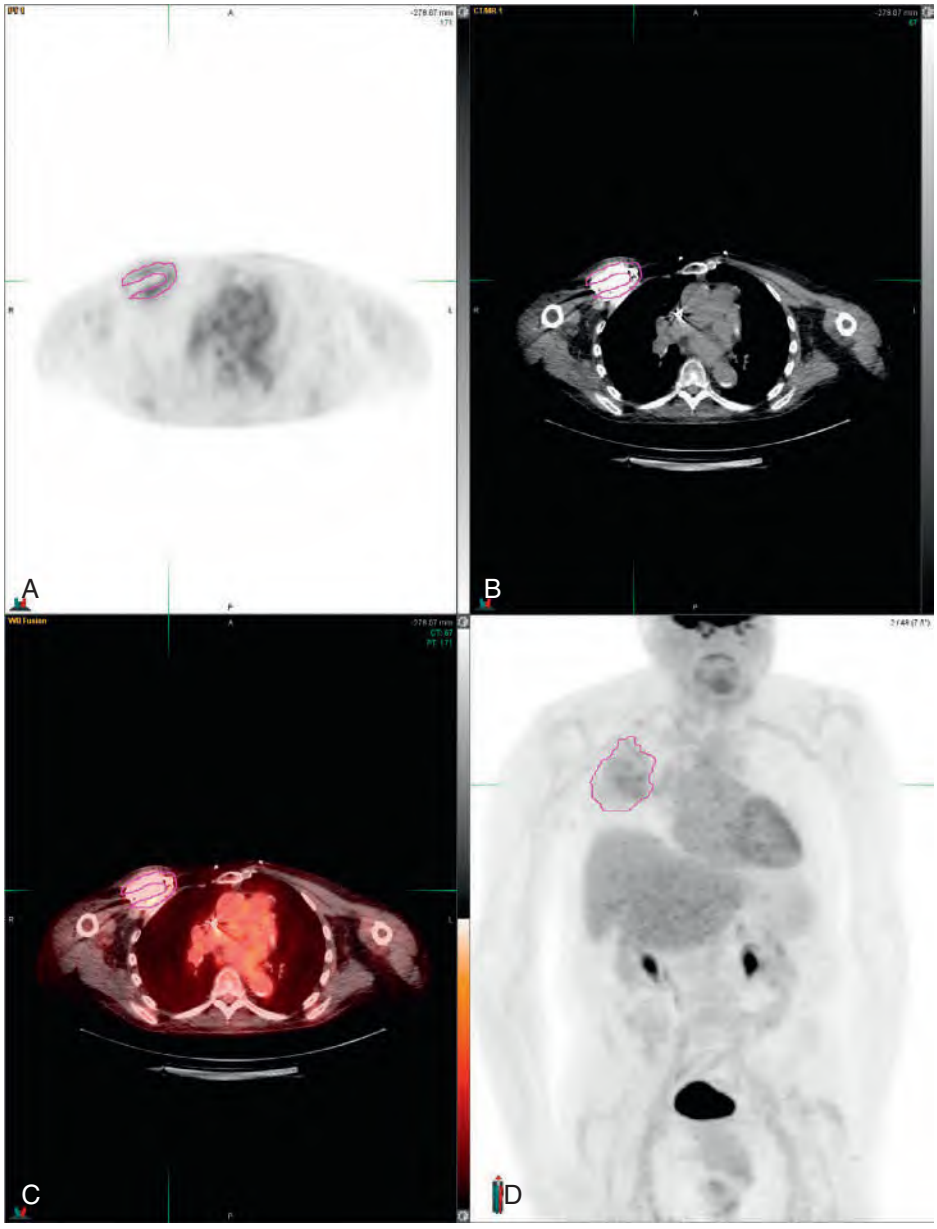

FIG. 82.4 Increased fluorodeoxyglucose activity at cardiovascular implantable electronic device generator pocket consistent with device infection. (A) Axial positron emission tomography. (B) Axial computed tomography. (C) Maximum intensity projection image. (D) Fused images. *(Copyright Mayo Clinic.)*

infection, antimicrobial therapy alone without device removal was associated with a sevenfold increase in 30-day mortality.[49] Moreover, immediate device removal, when compared with delayed extraction or no device removal, was associated with a threefold decrease in 1-year mortality in this analysis.

When planning device removal, three factors must be addressed. First, removal of a lead that is embedded in cardiac tissue can be difficult and potentially dangerous. Complications include tamponade due to tearing or perforation of the myocardial wall, laceration of the superior vena cava or tricuspid valve, hemothorax, fracture of lead fragment requiring surgical intervention, and life-threatening arrhythmias.[4] However, newer techniques, including the use of a locking stylet, photoablation of fibrous attachments with a laser sheath, and minimally invasive video-assisted thoracoscopic techniques, are less invasive and safer methods of device removal compared with open thoracotomy.[4,10]

Second, in cases where larger (>10 mm in diameter) vegetations are attached to infected leads, embolic showering of the pulmonary vasculature with percutaneous lead extraction is a concern. However, data from several studies[4,30,32,43,50] indicate that risk of clinically significant pulmonary emboli and death with percutaneous extraction is low and does not warrant routine surgical removal of leads via thoracotomy in this patient population. Routine screening for subclinical pulmonary emboli using CT or ventilation-perfusion scan is also not recommended.[30] Risks of thoracotomy and need for cardiac bypass (in mostly an older patient population) should be considered before deciding whether a percutaneous or a surgical approach should be used.

Third, the need for ongoing CIED support should be assessed before implanting a new device. The percentage of patients who do not require replacement of a PPM has ranged from 13% to 52%.[4,26,31,46] In patients who are dependent on a device, a temporary system can be placed, whereas BSI is cleared by antimicrobial therapy before implantation of a new device. However, use of temporary wires may increase the risk of new device infection.[18]

Figs. 82.5 and 82.6 summarize the management approach of CIED infection.[51,52] We recommend a two-step exchange in most patients (i.e., complete device removal, followed by replacement CIED, if needed, in a subsequent intervention). Clearance of BSI, if present, and adequate control of infection at the generator pocket site should be achieved

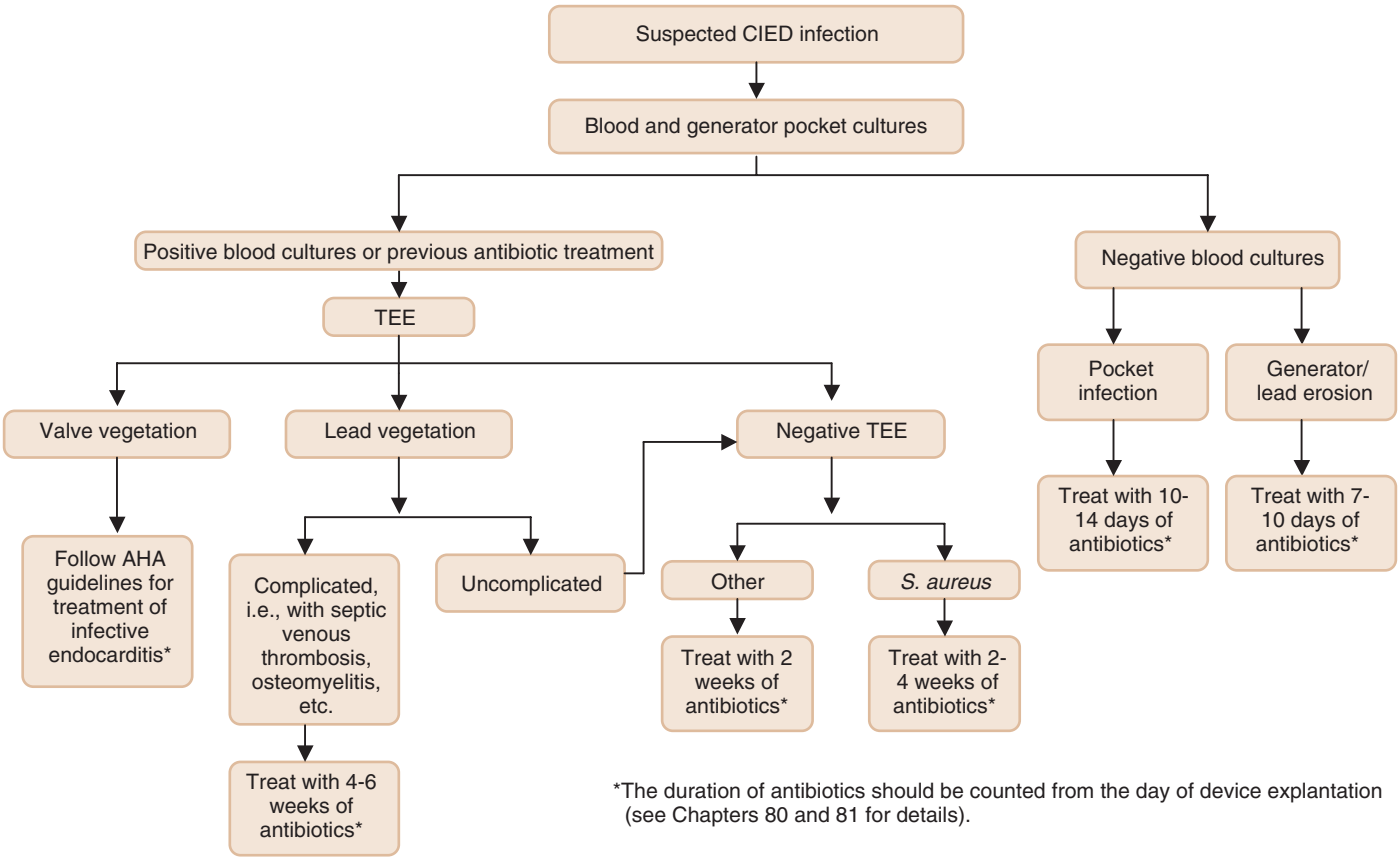

FIG. 82.5 Approach to the management of adults with cardiovascular implantable electronic device *(CIED)* infection. This algorithm applies only to the patients who are managed with complete device removal. *AHA,* American Heart Association; *S. aureus, Staphylococcus aureus; TEE,* transesophageal echocardiogram. *(Modified from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections.* J Am Coll Cardiol. *2007;49:1851–1859.)*

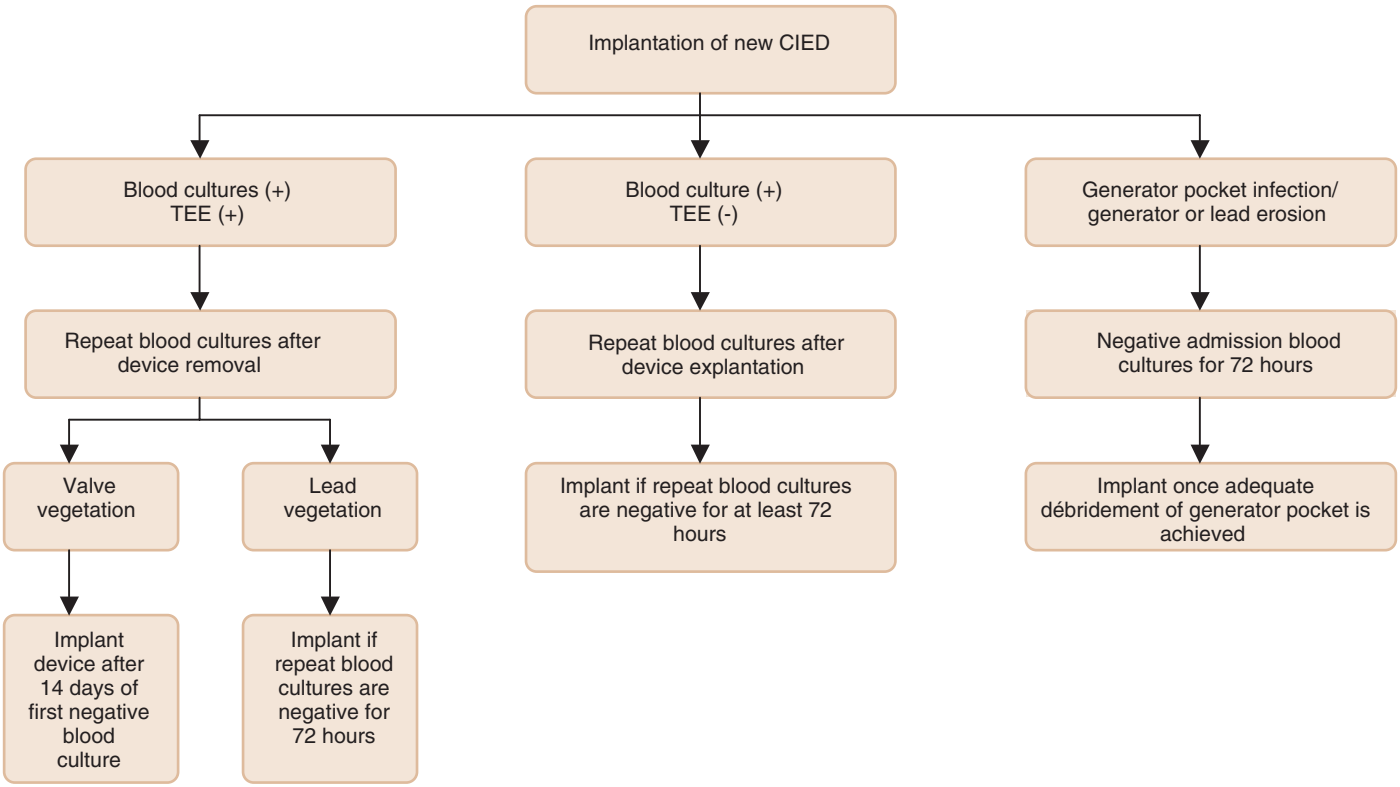

FIG. 82.6 Guidelines for implantation of a new device in patients with cardiovascular implantable electronic device *(CIED)* infection. *TEE,* Transesophageal echocardiogram. *(Modified from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections.* J Am Coll Cardiol. *2007;49:1851–1859.)*

before placement of a new device (see Fig. 82.6). For patients who have BSI at initial presentation, blood cultures should be repeated after device explantation. Patients who have persistently positive blood cultures after device removal should be treated for at least 4 weeks with antibiotics even if a TEE is negative for valve vegetations. For patients who present with generator or lead erosion only, in the absence of clinical evidence of pocket infection, the replacement CIED may be placed immediately after removal of the original device (one-step exchange). The new device should be placed on the contralateral side in patients who have clinical or intraoperative findings consistent with generator pocket infection. Cure rates of more than 95% can be achieved.[4]

The choice and duration of antimicrobial therapy are dictated by pathogen, in vitro antimicrobial susceptibility results, and the presence or absence of concomitant valvular endocarditis. Empirical antibiotics should include coverage for MRSA and CoNS. Intravenous administration of antimicrobials is recommended. If an infected CIED cannot be removed, long-term oral suppressive antibiotics[53,54] (for the life of the CIED) should be administered after an appropriate course of initial induction therapy (see Fig. 82.2).

Prevention

Meticulous attention to aseptic technique is key to preventing microbiologic contamination of CIED generators and leads at the time of implantation. Several clinical studies have demonstrated the efficacy of antibiotic prophylaxis before device implantation.[16,18,55] In a recent large, prospective, randomized, double-blinded, placebo-controlled clinical trial,[56] patients undergoing CIED implantation or generator replacement were randomized to either receive a single dose of cefazolin or placebo for perioperative prophylaxis. In multivariable analysis a lack of antibiotic prophylaxis was an independent predictor of CIED infection ($P = .037$). For patients who are allergic to β-lactam antibiotics or are colonized with MRSA, vancomycin is an acceptable alternative. There are no published data to support the routine use of secondary prophylaxis for patients undergoing dental, respiratory, gastrointestinal (GI), or genitourinary procedures, and the practice is discouraged.[10]

Two recent large clinical trials (PADIT and WRAP-IT) assessed the role of additional interventions to prevent CIED infection compared to current standard of care. In the PADIT trial,[57] incremental approach included preoperative intravenous antibiotics (cefazolin plus vancomycin), intraoperative antimicrobial wash (bacitracin), and postoperative oral antibiotic (cephalexin or cefadroxil) therapy in patients deemed high-risk for CIED infection. However, these additional interventions did not result in a lower rate of CIED infection compared to a single dose of intravenous cefazolin administered preoperatively. WRAP-IT[58] was a randomized clinical trial that compared the use of an antibiotic-impregnated (minocycline and rifampin) envelope to standard of care in CIED recipients deemed at high risk of infection. Use of envelope was associated with 40% relative risk reduction in major CIED infections.

LEFT VENTRICULAR ASSIST DEVICES

Historically, LVADs were used to provide temporary support for patients with end-stage heart failure while awaiting heart transplantation (bridge to transplantation). However, with an increasing prevalence of advanced heart failure and a limited supply of donor organs, LVADs are increasingly being used as long-term myocardial surrogate therapy ("destination therapy"), especially in patients who are ineligible for a heart transplant.[59] With this changing trend, interest is shifting from short-term complications to long-term infection rates and survival. Infection is a major complication of LVAD therapy and was responsible for up to 20% of deaths in one cohort of LVAD recipients.[60]

LVADs are mechanical pumps that are implanted in the thoracic cavity to assist the pumping action of a failing heart. These devices are connected to the heart via two cannulas, pulling blood from the left ventricle and pumping into the aorta (Fig. 82.7). Most LVADs used in contemporary practice (e.g., HeartMate II and Jarvik 2000) are designed as axial flow pumps to provide continuous flow.[61] These devices do not require a mechanical valve, are smaller in size (and therefore less prone to infection), and last longer. These devices are connected to an external battery pack with a driveline. Increasingly, LVADs, which use electromagnetically or hydrodynamically levitated continuous-flow centrifugal pumps (e.g., HeartWare HVAD, Duraheart, Los Angeles) are being implanted in clinical practice. These devices have even simpler mechanics with fewer moving parts.

LVAD therapy is associated with significant infection risk. In the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial,[59] which examined the role of long-term LVAD use as destination therapy, infection and device failure were predominant factors that led to a limited 2-year survival rate of 23%. Within 3 months of LVAD placement, LVAD infection complicated 28% of cases. LVADs that use continuous-flow pumps are at lower risk of infection compared with devices with pulsatile flow pumps.[60,62]

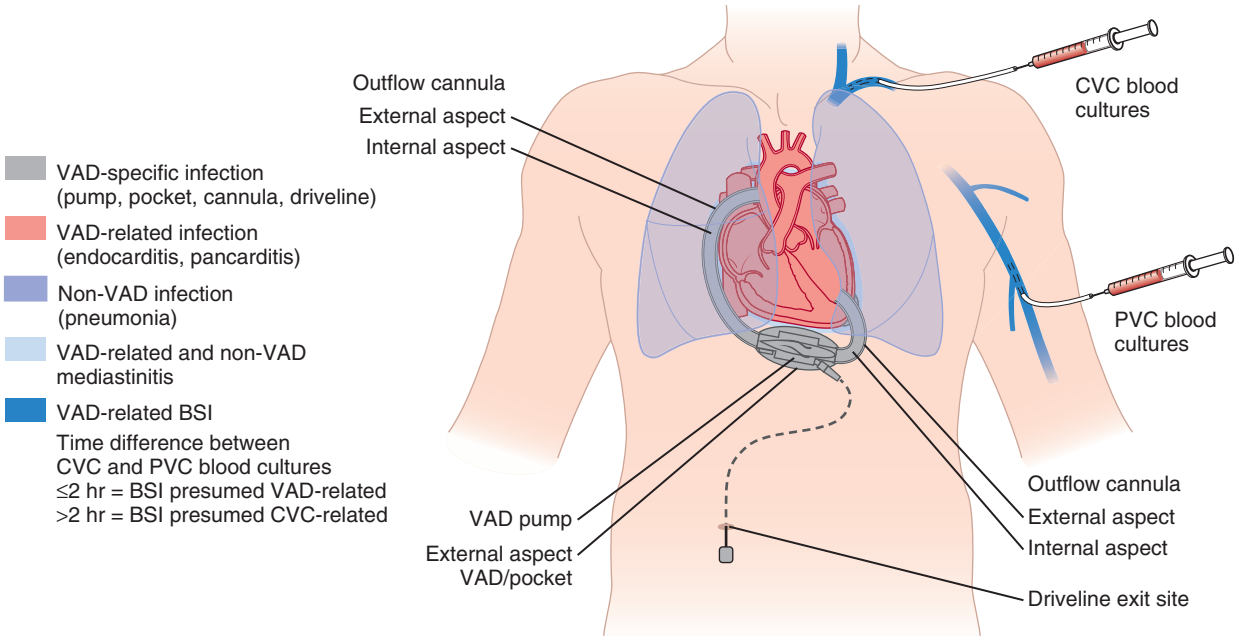

FIG. 82.7 Classification of left ventricular assist device *(VAD)*-associated infections. *BSI,* Bloodstream infection; *CVC,* central venous catheter; *PVC,* peripheral venous catheter. *(Modified from Hannan MM, Husain S, Mattner F, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices.* J Heart Lung Transplant. *2011;30:375–384.)*

Epidemiology of Left Ventricular Assist Device Infections

The risk of infection varies based on duration of LVAD support, with higher rates of infection reported in the destination therapy group compared with patients where LAVD is used as a bridge to transplantation.[64] In one review of LVAD-related complications the incidence of infection was two times higher in patients with an LVAD in place for more than 60 days compared with those with an LVAD for less than 30 days.[65]

The reported rates of infection in LVAD recipients vary from 13% to 80%[14] and depend on multiple factors, including underlying comorbidities, type of device, duration of LVAD support, and study definition of LVAD infection. In a cohort study[66] that included patients with HeartMate devices, the overall rate of surgical site infection was 44 per 100 LVAD implantations or 6.2 infections per 1000 device days. Seven of the patients had superficial infection that involved the driveline incision (19.4 infections/100 LVAD implantations), three patients had sternal infections (8.2 infections/100 LVAD implantations), and six had organ space infections that involved either the LVAD or the preperitoneal pocket that contained the pump (16.7 infections/100 LVAD implantations). Two of the patients also developed mediastinitis.

Risk of LVAD-related BSI was calculated in a retrospective study from the Cleveland Clinic.[67] An LVAD-related BSI was defined as one in which the same pathogen was cultured from the device and the blood and no other source of BSI was identified. Overall, 140 nosocomial BSIs occurred in 104 (49%) of 214 patients (7.9 BSIs/1000 LVAD days); 53 (38%) episodes were device related. Patients with LVAD-related BSI had a higher mortality rate of 58% compared with 42% in patients with LVAD support but no BSI ($P = .07$) in this investigation.

Pathogenesis of Left Ventricular Assist Device Infections

The impact of LVAD implantation on the immune system is speculated to be one factor that predisposes device recipients to infectious complications.[68,69] LVAD implantation can lead to increased susceptibility of circulating CD4 T cells to activation-induced apoptosis, resulting in a progressive decrease in CD4 T-cell count and impaired cell-mediated immunity. This has been postulated that LVAD recipients are at increased risk of infection, including those due to opportunistic pathogens. In one clinical survey[69] LVAD recipients were at increased risk of developing *Candida* infections compared with control subjects (28% vs. 3%; $P = .003$). Dysregulation of the humoral arm of the immune system has also been reported.

Risk Factors for Left Ventricular Assist Device Infections

Duration of LVAD support[64] and documented trauma at the driveline exit site are well-known risk factors associated with device infection.[70] Data from INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), the largest registry of patients who received mechanical circulatory assist devices, suggest that continuous-flow devices have a lower rate of infectious complications compared with LVADs with pulsatile pumps. Risk factors for LVAD-related infection are summarized in Table 82.3.

TABLE 82.3 Risk Factors for Left Ventricular Assist Device Infection

Length and extent of surgery required for device implantation
Reoperation or revision
Hematoma at device pocket site
Persistent local trauma or poor wound healing at driveline exit site
Poor nutritional status of the host
Comorbid conditions (chronic heart failure, renal failure, diabetes mellitus, obesity)
Prolonged hospitalization
Length of time left ventricular assist device is in place
Foreign bodies in other locations (endotraceal tubes, urinary catheters, central venous or arterial catheters, drainage tubes, cardiovascular implantable electronic device)
Immune system dysregulation due to underlying disease or immunosuppressive drugs

Clinical Manifestations of Left Ventricular Assist Device Infections

Infectious complications related to LVADs can be broadly categorized into three types (Fig. 82.7): (1) LVAD-specific infections, infections that are related directly to the device hardware and include pump and cannula infections, pocket infections, and percutaneous driveline infections; (2) LVAD-related infections, which, although they can also occur in patients without LVADs, the presence of an LVAD warrants special management considerations, including valvular endocarditis, BSIs, and mediastinitis; and (3) non-LVAD infections, that is, those not related to LVAD placement and that may include pneumonia, urinary tract infection, and other remote infections.

The most common presentation of LVAD-specific infection is driveline exit site infection. Local inflammatory changes and purulent drainage are frequently seen. Device pocket infections usually present with frank inflammatory changes in the skin and soft tissues overlying a device pocket. Infection of the valves or other blood-contacting surfaces of the LVAD occurs less often. Clinical manifestations of this form of endocardial infection mirror the manifestations of native or prosthetic valve endocarditis. Fever and other signs of systemic inflammatory response may be apparent. Systemic or pulmonary (for devices that assist the right ventricle) embolic phenomena can be seen. Mechanical dysfunction of the LVAD can occur if an obstructing pannus of infection develops within the internal lumen of the inflow or outflow cannulas that are anastomosed into the apex of the left ventricle and ascending aorta, leading to clinical worsening of cardiac function.

Microbiology of Left Ventricular Assist Device Infections

S. aureus and CoNS account for greater than 50% of cases of LVAD-related infections. Enterococcal species, *Enterobacter* spp., and *P. aeruginosa* are other commonly isolated bacterial pathogens in LVAD-related infections.[67,71,72] Because of nosocomial acquisition of these infections, antimicrobial resistance is a common occurrence. Although colonization with *Candida* spp. occurs in up to 39% of patients with LVADs, clinical infection is less frequent.[73] Use of broad-spectrum antibiotics increases this risk. Eradication of infection is difficult due to microbial biofilm formation on prosthetic surfaces.

Management of Left Ventricular Assist Device Infections

Our approach to diagnosis and management of LVAD infection is summarized in Fig. 82.8.[72] Débridement of an infected driveline exit site or device pocket may be helpful to control localized infection in some patients. Vacuum-assisted closure systems can help to facilitate wound healing.[74] For patients with LVAD-related BSI, chronic suppressive antimicrobial therapy, after an induction course, is recommended. Suppressive antibiotics should be continued unless the infected LVAD is removed or the patient undergoes cardiac transplantation. However, earlier LVAD removal is required in some cases to control infection. Of note, LVAD-related infection is not a contraindication to cardiac transplantation.[10,71] In fact, for some patients cardiac transplantation is necessary not only for advanced heart failure but also for removal of the infected device to achieve control of ongoing infection.

Earlier reports suggested that patients with pretransplantation LVAD infection have similar short- (<6 months) and long-term (as long as 3 years) survival rates after cardiac transplantation, compared with noninfected controls.[67,75] However, a subsequent investigation[71] showed a prolonged length of hospitalization and increased early mortality in heart transplant recipients with pretransplantation LVAD-related infection. However, long-term survival rates were comparable between the two groups.

Optimal duration of antimicrobial therapy for LVAD-related BSI in patients who are awaiting heart transplantation is unclear. In one investigation of 76 patients with LVADs,[71] continuous antimicrobial treatment, from the time of initial diagnosis of BSI until transplantation or death, was associated with a lower rate of relapse compared with a limited antibiotic course of 2 to 6 weeks ($P = .003$). Relapses were diagnosed at a median of 12 days (range, 2–89 days) after discontinuation of antimicrobial therapy. All patients who had LVAD-related infection

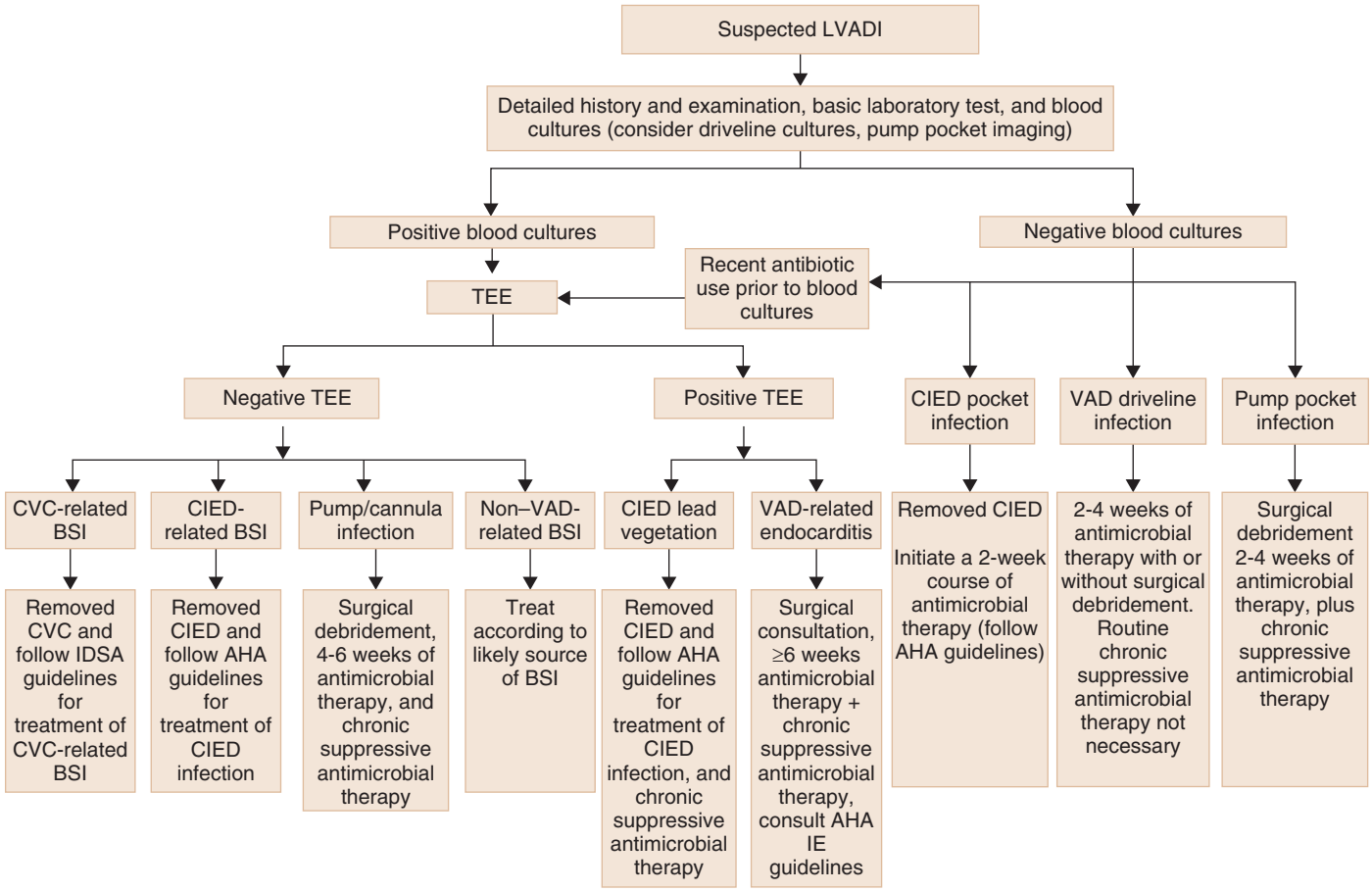

FIG. 82.8 Mayo Clinic guidelines for the management of left ventricular assist device–associated infections *(LVADIs).* These are general guidelines only, and LVADI infection management should be individualized based on clinical presentation and host factors. *AHA,* American Heart Association; *BSI,* bloodstream infection; *CIED,* cardiovascular implantable electronic device; *CVC,* central venous catheter; *IDSA,* Infectious Diseases Society of America; *TEE,* transesophageal echocardiogram; *VAD,* ventricular assist device. *(Modified from Nienaber JJC, Kusne S, Riaz T, et al. Clinical manifestations and management of left ventricular assist device-associated infections.* Clin Infect Dis. *2013;57:1438–1448.)*

due to *S. aureus* and were treated with limited courses of antibiotics experienced relapse. There was no difference in the two groups in terms of posttransplantation mortality, length of hospitalization, or 1-year survival.

Prevention

Several strategies have been advocated to reduce the rate of LVAD-related infections.[76] These include meticulous attention to aseptic techniques at the time of device implantation, use of chlorhexidine for skin preparation, perioperative intranasal mupirocin to diminish *S. aureus* colonization, elimination of percutaneous drivelines with totally implantable LVADs,[77] longer tunneling of the driveline, and immobilization of the driveline exit site using an abdominal binder. Since publication of the REMATCH trial,[59] a majority of LVAD implanters have been using a broad-spectrum antimicrobial regimen, including a β-lactam plus a fluoroquinolone plus an antifungal agent, for surgical site infection prophylaxis. However, a recent investigation from the Mayo Clinic[78] suggested that there was no obvious benefit of using a multidrug regimen as it did not impact infection-free survival or all-cause mortality compared with single-drug regimen. Based on these data, we recommend using a simplified regimen of cefazolin plus vancomycin for routine surgical site infection prophylaxis. Additional agents, such as an antifungal and an agent with gram-negative bacillary coverage, may be considered in patients with preexisting infections before LVAD implant, prolonged hospitalization, and colonization with multidrug-resistant (MDR) organisms.

PROSTHETIC VASCULAR GRAFTS

Despite technical advances in graft design, infection remains a significant complication associated with use of prosthetic vascular grafts and can lead to loss of limb or life. Infections involving the prosthetic vascular grafts can manifest in three distinct ways: (1) perigraft infection or abscess formation, (2) graft exposure due to disruption of the superficial soft tissue layers overlying the prosthesis, and (3) graft erosion or fistula formation involving a mucosal surface. However, these three presentations of graft infection are not mutually exclusive. Moreover, there is a dramatic increase in the use of endovascular grafts and stent grafts, which are at less risk of infection and are addressed later in this chapter.

Epidemiology of Prosthetic Vascular Graft Infection

The rate of prosthetic vascular graft infection (PVGI) varies and depends on the anatomic location of the prosthesis. For aortic grafts limited to the abdomen, graft-related infections occur in 1% or less of recipients. The rate of infection is higher (1.5%–2%) for aortic grafts that extend to the femoral location. Infrainguinal vascular grafts that originate in the groin are at the highest (6%) risk of complicating infection.[10,79,80,81] Reported morbidity (mostly amputations) and mortality rates for peripheral vascular grafts are 41% and 17%, respectively.[82] Prosthetic aortic graft infections have a higher mortality rate (24%–75%). The average 5-year survival rate for aortic graft infections is only 50%.[79,83]

Pathogenesis of Prosthetic Vascular Graft Infection

Several distinct routes of microbial contamination are recognized in vascular graft infections. Microbial seeding of a graft at the time of implantation or in the immediate postoperative period accounts for most of the graft infections. Vascular graft contamination can also occur if there is infection in a contiguous anatomic area, such as bacterial

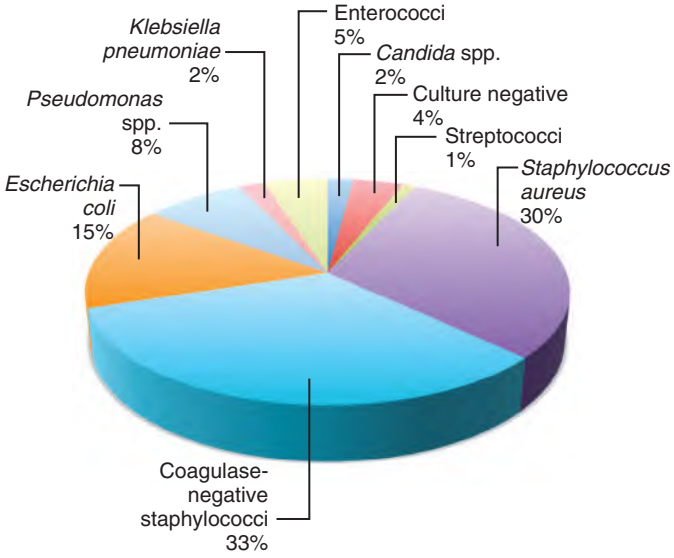

FIG. 82.9 Microbiology of prosthetic vascular graft infections (intraoperative culture results from 119 patients, 68 with aortoiliofemoral and 51 with extracavitary graft infections). *(Data from Bandyk DF, Novotney ML, Back MR, et al. Expanded application of in situ replacement for prosthetic graft infection.* J Vasc Surg. *2001;34:411–420.)*

TABLE 82.4 Risk Factors for Prosthetic Vascular Graft Infection

Emergent surgery
Lack of appropriate antimicrobial prophylaxis in the perioperative period
Groin incision
Bloodstream infection during index hospitalization
History of multiple invasive interventions before or after graft placement
Poor wound healing/infection at surgical site
Contiguous infection in the graft area
Comorbid conditions (diabetes mellitus, chronic renal insufficiency, obesity, immunocompromised host)

colonization of a thrombus in an aneurysmal sac or in atherosclerotic plaques.[83,84] Superficial surgical site infection can also lead to graft infection. Subsequent manipulation of an implanted graft by either surgical or percutaneous procedures can predispose to graft infection. Finally, BSI originating from an anatomically remote site of infection can predispose to hematogenous seeding of vascular grafts. The risk of hematogenous seeding is highest in the early postoperative period and decreases over time because of partial endothelialization of the graft.[84]

Risk Factors for Prosthetic Vascular Graft Infection

Purported risk factors for PVGI are summarized in Table 82.4.[10,79,85–87,88] In a large statewide dataset that included 14,000 patients who underwent aortic aneurysm repair,[88] BSI during the index hospitalization for repair was associated (OR, 4.2) with increased risk of aortic graft infection. In another case-control study[86] that included cases of aortic and peripheral graft infections collected over a 21-year period, groin incision (OR, 4.1) and wound infection (OR, 5.1) were risk factors for PVGI in a multivariable analysis. In one study that included 496 cases with prosthetic femoral artery grafts,[89] redo bypass (hazard ratio [HR], 5.8), active infection at the time of bypass (HR, 5.2), female gender (HR, 4.5), and diabetes mellitus (HR, 4.6) were associated with increased odds of PVGI in multivariable analysis.

Microbiology of Prosthetic Vascular Graft Infection

Staphylococcal species continue to be the predominant pathogens responsible for PVGI (Fig. 82.9). However, less virulent organisms that are normal skin flora account for an increasing portion of PVGI.[86] Pathogens included in this category are CoNS, *Corynebacterium* spp., and *Cutibacterium* (formerly *Propionibacterium) acnes.* PVGI caused by these organisms tend to be delayed and indolent in onset. In contrast, *S. aureus*–related graft infections occur early after graft implantation. In a prospective cohort study that included 85 patients with PVGI, *S. aureus* infection was more frequent in limb grafts compared with aortic grafts.[82] Enterococcal species and anaerobic bacteria, often as part of polymicrobial infection, have also been identified as pathogens of PVGI.[86] *Candida* spp. are an infrequent but difficult-to-treat cause of PVGI.

Clinical Manifestations of Prosthetic Vascular Graft Infection

Timing of onset and clinical presentation of PVGI vary based on location of the graft and virulence of the causative pathogen. Considering that intraoperative or immediate postoperative vascular graft contamination is the mechanism accounting for infection in most cases, clinical evidence of infection should be evident within 1 to 2 months after graft implantation. Although this is generally true for extracavitary (extremity grafts, especially infrainguinal) PVGI, intracavitary (abdominal graft) infections may present several years after placement.

In patients who present with early graft infection (within 3 months of implantation), local inflammatory findings indicating surgical site infection is present. Even when these findings appear superficial, underlying graft infection is nevertheless a consideration. Local complications associated with graft infection may include abscess or sinus tract formation, hemorrhage, graft occlusion, pseudoaneurysm formation, graft exposure, and poor tissue incorporation. Septic emboli and distal tissue ischemia can also occur. Systemic signs of sepsis can accompany the local findings, particularly when more aggressive pathogens, such as *S. aureus,* are present. Fever, chills, and leukocytosis are generally present in the setting of bacteremia or fungemia.

Late graft infection is characterized less often by systemic toxicity. The local stigmata of graft healing complications prevail. These include cutaneous sinus tracts, lack of graft incorporation by surrounding tissue, anastomotic aneurysm, and graft-enteric erosions or the development of fistulas.[90] The formation of cutaneous sinus tracts is an obvious clue that underlying graft infection is present. Poor graft incorporation may not be apparent until intraoperative inspection. The clinical presentation of pseudoaneurysms is variable, ranging from little to no inflammatory response to local pain at the aneurysm site with or without a palpable mass. For one-third of patients[90] the clinical presentation of anastomotic pseudoaneurysm is emergent in regard to threat of life (hemorrhagic shock) or limb (distal ischemia due to graft thrombosis or embolization).

PVGI-related enteric erosions and fistulas may present years after graft placement. They are diagnosed in less than 5% of patients who undergo aortic graft placement. These patients can present with systemic (sepsis) and local (abdominal pain) complaints. The aortic graft most often erodes the third or fourth portion of the duodenum. GI tract bleeding, which ranges from subtle to massive, can present as hematemesis, hematochezia, or melena. Polymicrobial infection, consisting of enteric flora, usually is confirmed with blood and graft and perigraft tissue cultures. A prompt diagnosis of this condition is lifesaving because mortality is universal if the complication is left untreated.

Diagnosis of Prosthetic Vascular Graft Infection

A practical approach to diagnostic workup of prosthetic graft infections is outlined in Fig. 82.10. Even when physical examination findings are suggestive of graft infection, diagnostic imaging is usually performed to confirm the diagnosis and to define extent of infection. Blood cultures may be negative if infection is limited to the extraluminal graft surface. A comparison of various imaging modalities is provided in Table 82.5.[83,85,91] CT is the best tool in the diagnostic evaluation of graft infection. Findings on a CT scan that support vascular graft infection include the presence of perigraft fluid not attributable to recent (≤3 months) graft implantation, increasing perigraft fluid in the early postoperative period, perigraft fluid with fat stranding or gas bubbles, lack of a fat plane between graft and bowel, and anastomotic aneurysms.[79] For less virulent pathogens, particularly CoNS, the inflammatory response may be limited, and the perigraft findings on CT may be minimal to nonexistent. The sensitivity of CT is decreased considerably in patients

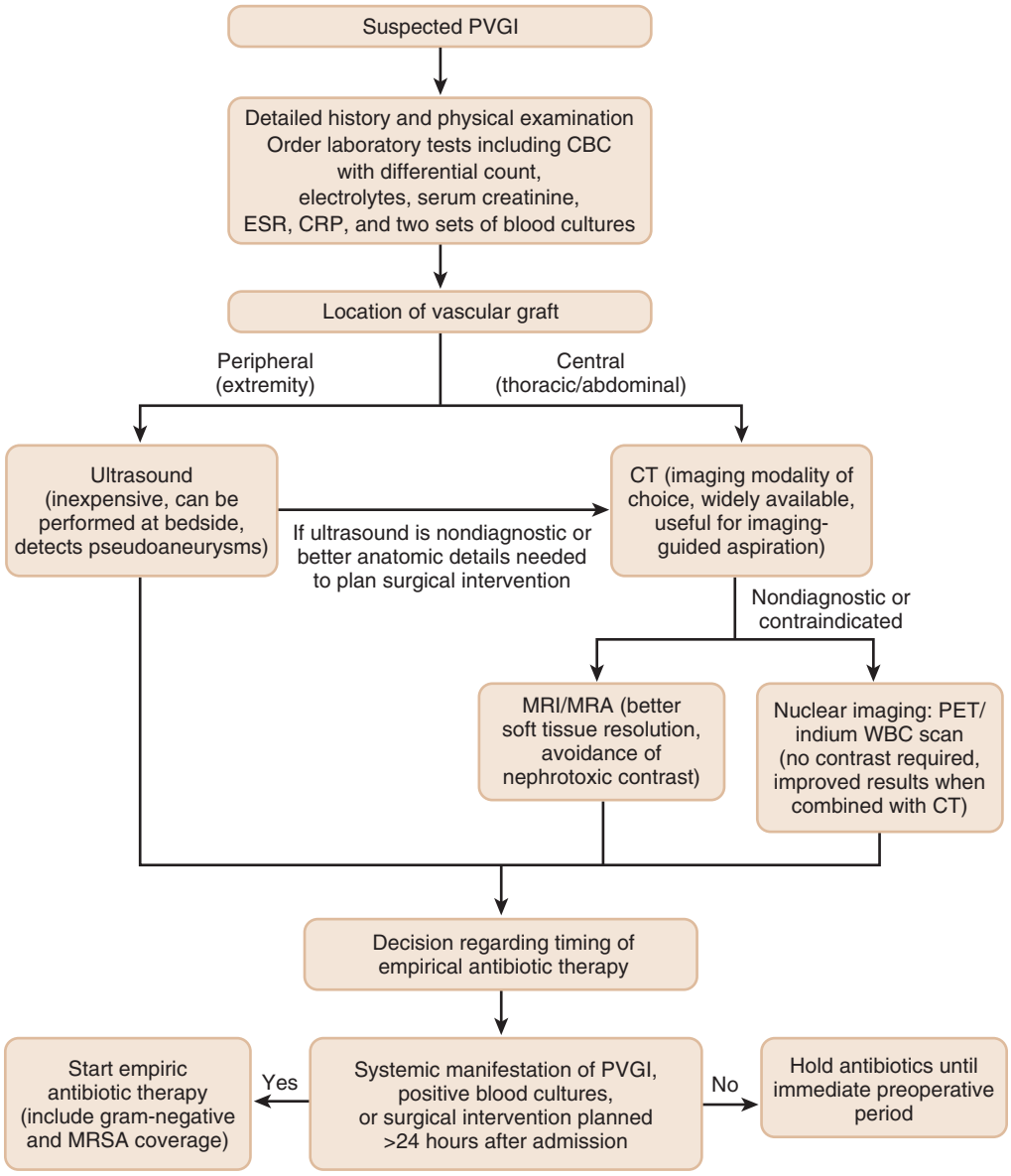

FIG. 82.10 Diagnostic evaluation and initial management of prosthetic vascular graft infections. *CBC,* Complete blood count; *CRP,* C-reactive protein; *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *MRI/MRA,* magnetic resonance imaging/magnetic resonance angiography; *MRSA,* methicillin-resistant *Staphylococcus aureus; PET,* positron emission tomography; *PVGI,* prosthetic vascular graft infection; *WBC,* white blood cell. *(Modified from Nagpal A, Sohail MR. Prosthetic vascular graft infections: a contemporary approach to diagnosis and management.* Curr Infect Dis Rep. *2011;13:317–323.)*

TABLE 82.5 Comparison of Imaging Techniques for Diagnosis of Vascular Graft Infection

COMPUTED TOMOGRAPHY (CT)	MAGNETIC RESONANCE IMAGING (MRI)	ULTRASONOGRAPHY	NUCLEAR MEDICINE IMAGING (INDIUM-LABELED WBC SCAN AND GALLIUM SCAN)
Sensitivity: 95% Specificity: 85% Imaging modality of choice Images may be degraded in the presence of metallic hardware in spine or extremities Administration of potentially nephrotoxic contrast dye	Sensitivity: 68%–85% Specificity: 97%–100% Useful when CT findings are nondiagnostic Better soft tissue resolution More expensive than CT scan Use of nephrotoxic contrast agent is avoided Small risk of nephrogenic fibrosing dermopathy with use of gadolinium in patients with preexisting renal insufficiency	Useful for peripheral vascular grafts to detect pseudoaneurysms Least expensive imaging modality Can be performed at bedside No need for contrast administration	Sensitivity: 73% Specificity: 87% False-positive results in early postoperative period Decreased sensitivity with previous antimicrobial therapy Useful when CT or MRI findings are inconclusive

WBC, White blood cell.

with more indolent infections. In cases where a pseudoaneurysm is not detected on CT, imaging-guided percutaneous aspiration of perigraft fluid should be considered. Fluid should be sent for cytology and microbiologic analysis, including bacterial, fungal, and mycobacterial cultures.

Some of the previously mentioned CT findings of infection are normally seen in the early postoperative period. Perigraft fluid can persist for 3 months after graft implantation. Perigraft air related to graft placement is usually absorbed within 1 week of surgery, although it can persist for as long as 7 weeks.[92]

Magnetic resonance imaging (MRI) may be helpful when CT findings are inconclusive.[80,91,93] MRI is better in visualization of subtle perigraft inflammatory changes than CT. Moreover, MRI is often able to differentiate subacute or chronic hematoma from inflammatory changes in the perigraft area. In one investigation of intracavitary vascular graft infections,[91] MRI had an excellent positive predictive value (95%), but the negative predictive value was low (80%). Indium-labeled WBC scanning had a positive predictive value of 80% and a negative predictive value of 82% compared with MRI in the same investigation. On the basis of these data, MRI is a preferred modality over indium-labeled WBC scanning for the diagnosis of aortic graft infections. However, results are not mutually exclusive, and a combination of imaging techniques may be helpful in difficult-to-diagnose cases. Software-based fusion imaging that combines data obtained from CT angiography (CTA) and WBC scintigraphy may provide a better diagnostic yield compared with a single-imaging modality. In a recent investigation[94] software-based fusion imaging of both modalities resulted in improved sensitivity (94%), specificity (50%), positive predictive value (88%), and negative predictive value (67%).

Endoscopic examination of the GI tract is helpful in cases where a graft enteric erosion or fistula is the suspected source of GI bleeding. Angiography is generally not necessary to diagnose PVGI. However, it may be used to define complex vascular anatomy for planning revascularization.

PET, combined with CT scan (PET-CT), is another emerging modality for the diagnosis of PVGI.[95] In a study that included 39 subjects with graft infection,[39] combined PET-CT had 93% sensitivity and 91% specificity in the diagnosis of vascular graft infection. Positive and negative predictive values were 88% and 96%, respectively. In a more recent prospective study,[96] fluorodeoxyglucose (FDG)-PET had high sensitivity of 93%, specificity of 70%, positive predictive value of 82%, and negative predictive value of 88%. FDG-PET also had excellent interobserver consistency and provided a better diagnostic accuracy than CT for the diagnosis of PVGI.

Management of Prosthetic Vascular Graft Infection

Optimal management of PVGIs is challenging and requires a multidisciplinary team approach with involvement of both medical and surgical subspecialties. Four general principles are followed in the treatment of PVGIs (Table 82.6).[97] In 2016 the American Heart Association issued a scientific statement outlining recommendations for diagnosis and management of vascular graft infections.[98]

TABLE 82.6 General Principles for Management of Prosthetic Vascular Graft Infection

Complete excision of the infected graft material
Extensive débridement of all infected, devitalized tissues in the perigraft area
Revascularization of distal tissues
Microbiologic identification of causative pathogen, followed by appropriate systemic antimicrobial agents for >6 weeks (depending on clinical response and repeat imaging)
Bactericidal antibiotics preferred and combinations often used

In general, complete excision of infected graft and débridement of infected perigraft tissue is necessary to achieve cure of infection. Extraanatomic bypass revascularization and in situ reconstruction are the two main revascularization strategies after resection of infected graft material. The key advantages and disadvantages of both options are summarized in Table 82.7. In cases where extraanatomic bypass is the preferred method of revascularization, the extraanatomic bypass is done first, followed by infected graft excision and local débridement during either the same anesthesia (sequenced approach) or a second surgery at a later date (staged approach).[99] In situ reconstruction through uninfected tissue planes is the second method of revascularization.[100] Three types of grafts are available for use and include antibiotic-bonded prosthetic grafts, fresh and cryopreserved arterial allografts, and autogenous vein grafts. The advantages of the allografts and autogenous vein grafts include the decreased likelihood of new graft infection because native tissue is placed in situ rather than prosthetic material.[85] Autogenous vein grafts also have higher long-term patency rates.[101] However, the disadvantage is the prolongation of the operative time required for vein harvesting.

By tradition, extraanatomic bypass has been touted as the gold standard for the surgical management of PVGI because of the theoretically decreased risk of reinfection by avoiding placement of a new graft in a previously infected tissue bed. However, in a systematic review and meta-analysis,[102] pooled estimates of mean event rates for all outcomes (reinfection, amputation, conduit failure, mortality) favored the use of in situ reconstruction with autogenous veins, rifampin-bonded prostheses, or cryopreserved allografts over extraanatomic bypass revascularization.

Regardless of surgical approach, multiple intraoperative specimens of graft material and perigraft inflammatory tissues should be submitted for bacterial, fungal, and mycobacterial stains and cultures to maximize the yield. Empirical antibiotics should include coverage for CoNS and MRSA.

Conservative management of prosthetic graft infections is associated with high mortality, and this approach should be reserved for a specific situation.[103,104] In cases in which complete excision of the infected graft is not feasible (poor surgical candidate because of multiple comorbid conditions or limited revascularization options), lifelong (for the "life of the graft") suppressive antimicrobial therapy is recommended.

For management purposes PVGI can be classified into intracavitary and extracavitary graft infections. This classification is helpful in guiding surgical management of infected grafts and duration of antimicrobial therapy.

Surgical Management of Extracavitary Prosthetic Vascular Graft Infection

In cases of early (<2 months postoperatively) PVGI, where infection is not complicated by active bleeding and the anastomotic site is not involved, graft preservation rather than graft excision and reconstruction, is a reasonable consideration. However, for late-onset infection (after 2 months postoperatively), graft excision and reconstruction should be considered instead of graft preservation. In cases where infection involves the graft anastomotic site or infection is caused by MRSA, *Pseudomonas*, or MDR microorganisms, or for patients for whom graft

TABLE 82.7 Comparison of In Situ Reconstruction Versus Extraanatomic Bypass Revascularization for Management of Prosthetic Vascular Graft Infection

IN SITU RECONSTRUCTION		EXTRAANATOMIC BYPASS REVASCULARIZATION	
ADVANTAGES	**DISADVANTAGES**	**ADVANTAGES**	**DISADVANTAGES**
Reduced rate of lower extremity amputation Elimination of the need for a second operation Avoidance of creating an aortic stump that could blow out in future Lack of anatomic limitations to placement Shorter operating time when rifampin-bonded prosthetic grafts or arterial allografts are used Reinfection rate: 10% with prosthetic graft reconstruction vs. 3% with autogenous vein replacement	Theoretical risk of increasing chances of new graft infection by placing new prosthetic material or allograft in a previously infected tissue bed	Theoretical reduced risk of new graft infection by avoiding placement of a new prosthetic material or allograft in a previously infected tissue bed	Need for a second procedure if staged operative strategy is used Reduced limb salvage rates (20%–30% lower extremity amputation rate) Aortic stump blowout (20%) 20% reinfection rate

preservation or in situ reconstruction has failed, it is reasonable to perform extraanatomic revascularization, followed by graft excision instead of graft preservation or in situ reconstruction. For patients in whom PVGI is complicated by sinus tract formation or active bleeding, extraanatomic revascularization followed by graft excision is preferred.

Antimicrobial Management of Extracavitary Prosthetic Vascular Graft Infection

In cases where infection is limited to skin or soft tissues without CT findings to suggest graft involvement, a 2- to 4-week trial of antimicrobial therapy with or without surgical débridement is reasonable. For more advanced infection (sinus tract or fistula formation, anastomotic site involvement, or systemic infection), a 4- to 6-week course of parenteral induction antimicrobial therapy, followed by 6 months of oral antimicrobial therapy, is recommended.

Chronic (lifelong) suppressive antimicrobial therapy may be considered for infections caused by MRSA, *Pseudomonas*, MDR organisms, *Candida*, or other fungal species; for those patients who have undergone emergency or multiple surgeries; for patients with graft preservation or in situ reconstruction with extensive perigraft infection; or for patients who are poor candidates for reoperation. The choice of antibiotic depends on in vitro susceptibility testing. Suppressive therapy is usually with oral cephalosporins, penicillin derivatives, tetracyclines, or trimethoprim-sulfamethoxazole. Patients who are conservatively managed should have ultrasound examination every 3 to 6 months for 2 years, followed by lifelong ultrasound examination every 6 to 12 months.

Surgical Management of Intraabdominal Prosthetic Vascular Graft Infection

In general, graft excision and in situ reconstruction with cryopreserved, arterial allograft, or venous autograft or rifampin-bonded synthetic graft is recommended. However, in patients with infection caused by MRSA, *Pseudomonas*, or MDR microorganisms or those with extensive intraabdominal abscess or perigraft purulence, extraanatomic bypass revascularization, followed by graft excision, may be considered.

Antimicrobial Management of Intraabdominal Prosthetic Vascular Graft Infection

A 6-week course of parenteral antimicrobial therapy after surgery is recommended. An additional 3 to 6 months of oral antimicrobial therapy is recommended for cases managed with in situ reconstruction. Lifelong suppressive antimicrobial therapy may be considered in patients with extensive perigraft infection or infection caused by MRSA, *Pseudomonas*, or MDR microorganisms.

Management of Intrathoracic Prosthetic Vascular Graft Infection

In situ repair using cryopreserved arterial allografts, followed by 4 to 6 weeks of parenteral antimicrobial therapy, is recommended. In patients with a high risk of morbidity and mortality, those who cannot tolerate extensive reconstructive surgery, or those with in situ repair using a synthetic graft, lifelong suppressive antimicrobial therapy may be considered.

Prevention

Meticulous attention to aseptic procedures during vascular graft placement is the key to limiting the risk of subsequent graft infection. Administration of perioperative antibiotics is associated with a reduced risk of subsequent graft infection.[87] However, there is no benefit of extending antibiotic prophylaxis beyond 24 hours from graft placement.

HEMODIALYSIS PROSTHETIC VASCULAR GRAFTS

Infection is the second leading cause of death among patients with end-stage renal disease[105] and is often caused by *S. aureus*. Due to extensive health care system exposure and frequent administration of antibiotics in this high-risk population, MDR strains of *S. aureus*, enterococci, and gram-negative bacilli have emerged as a serious problem among these patients.

TABLE 82.8 Risk Factors for Polytetrafluoroethylene Graft Infection

Need for repetitive percutaneous cannulation
Breaks in sterile technique during cannulation
Poor patient hygiene
Prolonged postdialysis bleeding from the graft
Perigraft hematoma formation
Surgical manipulation of graft
Severe pruritus and scratching over needle sites
Human immunodeficiency virus coinfection
Lower extremity (thigh) graft
Bacteremia or fungemia caused by an ectopic site of infection

Epidemiology

Vascular access site infections constitute a major part of infection-related morbidity and mortality in long-term hemodialysis patients. Use of the prosthetic arteriovascular grafts composed of polytetrafluoroethylene (PTFE) is a major contributing factor for access site infections and associated morbidity and mortality.[106,107] These grafts are at higher risk of infection, up to four times higher incidence, compared with the native arteriovenous (AV) fistulas. Therefore PTFE grafts should only be used in cases in which surgical creation of a native AV fistula is not anatomically feasible. The main benefit of vascular grafts is that they do not require maturation, as AV fistulas do, and they can be used for hemodialysis within days of placement. The risk of infection with either tunneled or temporary hemodialysis catheters is highest. In one prospective survey[105] the risks of infection (per 1000 dialysis sessions) in patients with AV grafts (2), tunneled catheters (12.2), or temporary catheters (29.2) were much higher than the risks associated with the use of AV fistulas (0.9).

Risk factors for infection of PTFE grafts are listed in Table 82.8.[107,108]

Clinical Manifestations

Most patients with graft infection present with local inflammatory findings at the graft site. *S. aureus* (53%) and CoNS (20.3%) are the most commonly isolated pathogens.[10] However, occult BSI without local graft inflammatory changes can also be a manifestation of graft infection. An occult presentation is more common in patients with old, nonfunctioning, and thrombosed grafts.[109] Indium-labeled WBC scanning may be helpful in detecting these clinically silent graft infections. In one investigation[110] of occult infection involving such old or thrombosed grafts, the indium-labeled WBC scan showed 100% sensitivity and 75% specificity in detecting graft infection.

Management

Preservation of the vascular access site is a major consideration when making management decisions regarding PTFE graft infections because other potential venous access sites have been frequently exhausted in these patients. Parenteral antimicrobial therapy combined with local débridement is curative in selected cases of early graft infection or exposed vascular graft,[111] and removal of the entire graft is not always necessary. If conservative management is attempted the remaining graft segment should have adequate tissue coverage and close follow-up to ensure resolution of infection is necessary. However, presence of purulence or abscess in the immediate graft area or aneurysmal graft formation mandates graft removal. Old, thrombosed, nonfunctioning grafts should be resected when infection at this nidus is confirmed.

Three to 4 weeks of parenteral antimicrobial therapy, directed by in vitro susceptibility testing, is recommended.[112] In patients with SAB, transesophageal echocardiography should be performed to exclude infective endocarditis.

Prevention

Vascular access site infection is a leading cause of morbidity and mortality in hemodialysis patients. The total annual cost of graft infection-related morbidity in the United States has been projected to be more than $1 billion.[113] The best method to prevent a PTFE graft-related infection is to avoid its use. The National Kidney Foundation[105] and the Fistula

First Project[114] recommend placement of an AV fistula instead of PTFE grafting when anatomically feasible. Cryopreserved vein allografts may be an alternative in some scenarios.[115] Their patency rates are equivalent to that of expanded PTFE, and rates of reinfection are generally low.

Use of intranasal mupirocin to eradicate *S. aureus* colonization may help to reduce the risk of *S. aureus* bacteremia.[116] Prophylactic antibiotics should be administered preoperatively at the time of graft placement and before subsequent surgical graft manipulation, if required. In addition, adherence to infection control practices at the time of graft cannulation is mandatory.

INVASIVE NONSURGICAL CARDIOLOGIC PROCEDURES

The array of invasive nonsurgical cardiologic procedures continues to expand. Three of the more common procedures include percutaneous coronary intervention (PCI), diagnostic cardiac catheterization, and electrophysiologic studies. Most PCI procedures involve stent placement. Although coronary stent infection is exceedingly rare, BSI complicating the procedure has been the topic of numerous reports.[10] Local (groin) and metastatic infectious complications have been highlighted in other citations.

BSI after invasive nonsurgical cardiologic procedures is the most common infectious complication. It can be a manifestation of local vascular or soft tissue infection or a cause of metastatic infection that can result in a variety of syndromes, including infective endocarditis, septic arthritis, and epidural abscess formation.

Epidemiology

The incidence of BSI among patients who undergo invasive nonsurgical cardiologic procedures is low.[117,118] Risk of BSI depends on the duration of the procedure, multiple skin punctures performed, use of multiple balloons, and obesity. The incidence of early (≤36 hours postprocedure) BSI in patients who underwent PCI in a large prospective study was 0.61%.[118] In another study[119] 22,006 procedures that included cases of percutaneous transluminal coronary angioplasty, diagnostic cardiac catheterization, and electrophysiologic studies were reviewed. The overall incidence of BSI during the first 72 hours postprocedure was 0.11%. For PCI the BSI incidence was 0.24%. BSI was detected a median of 1.7 days after the procedure.

In one prospective study that included patients who underwent complex PCI[120] (requiring use of multiple devices in arterial circulation), blood cultures were obtained in all patients immediately and 12 hours after the procedure. Of the 147 patients included in this investigation, 26 (17.7%) had positive blood cultures immediately after PCI, whereas an additional 12% of patients yielded positive blood cultures in the next 12 hours, with femoral sheaths still in place. CoNS were the most commonly isolated organisms. However, none of these episodes of transient BSI was associated with clinical sequelae.

Risk Factors

The purported risk factors for the development of BSI after invasive nonsurgical cardiologic procedures are summarized in Table 82.9.[10] In one investigation[121] independent risk factors for PCI-related bacteremia included duration of the procedure (OR, 2.9), number of catheterizations at the same site (OR, 4.0), difficult vascular access (OR, 14.9), arterial sheath in place for more than 1 day (OR, 6.8), and heart failure (OR, 43.2). In another study[119] the median length of hospital stay was 21 days and 6 days for patients with and without procedure-related BSI, respectively. The overall mortality rate was several-fold higher (8%) among patients who developed postprocedure BSI compared with those who did not (0.009%).

TABLE 82.9 Risk Factors Associated With Bloodstream Infection After Invasive Nonsurgical Cardiologic Procedures

Age >60 years
Duration of the procedure
Repeated punctures at an ipsilateral femoral artery
Difficult vascular access
Inguinal hematoma
Arterial sheath in place for >24 hours
Brachial artery access via a cutdown approach
Heart failure

Clinical Manifestations

Fever and chills are the predominant symptoms of procedure-related BSI. However, fever and chills can occur during or soon after catheterization procedures secondary to noninfectious reasons, such as introduction of foreign proteins or endotoxin. Blood cultures should be obtained to confirm the underlying cause of fever. Local findings of infection in the femoral area are present in patients with femoral artery endarteritis, soft tissue infection, or pseudoaneurysm formation.[10]

Microbiology

S. aureus has been the major pathogen in most case series and characteristically causes the most serious infections. CoNS and enterococci are less commonly reported. In only one case series[119] gram-negative bacilli outnumbered gram-positive isolates as the cause of complicating bacteremia.

Treatment

Management of these cases is similar to that of other catheter-related BSIs.[122]

Prevention

Prevention efforts should be focused on use of meticulous sterile technique and avoidance of the risk factors cited earlier (see Table 82.9). These include avoidance of vascular access by puncturing endovascular grafts; contralateral femoral artery puncture for repeat procedures, especially if a closure device was used during the first procedure; and minimizing duration of indwelling sheaths.[10]

CORONARY ARTERY STENTS

Despite widespread use of coronary stents and the demonstrated risk of transient bacteremia associated with PCI,[123] infection of these stents has been rarely reported. Drug-eluting stents, in theory, may have a higher risk of infection because of impaired local immune response and delayed endothelialization.[124,125,126,127] Among the published cases,[124,125,128] men have predominated, perhaps due to higher rate of atherosclerosis that requires PCI. Symptoms of infection, with rare exception,[125,128] begin within days to less than 1 month after stent placement. Fever, chills, and chest pain are the most frequently reported symptoms. The large majority of infections are caused by *S. aureus*, followed by *P. aeruginosa* and CoNS. Blood cultures are positive in most patients with coronary artery stent infection. Complications may include myocardial abscess, pericardial empyema, aneurysm and pseudoaneurysm formation, coronary artery perforation, and myocardial infarction. Coronary arteriography or cardiac magnetic resonance angiography (MRA) may be required to evaluate for evidence of stent infection if echocardiography and CT are nondiagnostic.

Early-onset stent infections (detected within 10 days of stent placement), are mostly caused by *S. aureus* and should be managed aggressively. If no local complications are detected on imaging, conservative management with antimicrobial therapy and close follow-up may be an option in selected cases.[128] However, late-onset infections (occurring after 10 days of stent placement) or major complications necessitate combined medical and surgical intervention. Surgery includes removal of stent, if possible, and abscess drainage or perforation repair when indicated. The overall mortality rate of coronary artery stent infection among cases reported to date is 46.1% (6/13).[124,125]

PERIPHERAL VASCULAR STENTS

Peripheral vascular stents are being used increasingly for nonsurgical treatment of atherosclerosis complications. Complications of endovascular stent placement include vascular injury, thromboembolism, local delivery site/stent deployment irregularities, and hemorrhage.[129] Infection related to these devices is rare, with an estimated risk being less than 1 in 10,000 cases.[130]

TABLE 82.10 Risk Factors Associated With Peripheral Vascular Stent Infection

Prolonged procedural time
Prolonged use of an indwelling catheter or sheath
Reuse of the same sheath after 24 hours (for thrombolytic therapy)
Local hematoma formation
Multiple interventions on the same or an adjacent site
Use of the same femoral artery for vascular access within 1 week of previous catheterization

Epidemiology

There are limited published data regarding peripheral vascular stent infections. In one review of 65 cases of aortoiliac stent graft infection,[131] 50 had stents placed in the aorta for aneurysm management. In this report estimated prevalence of infection was 0.43% (range, 0.05%–4%). A majority (80%) of patients were male and had multiple comorbid conditions. Almost two-thirds of patients presented more than 4 months after stent graft placement. Clinical manifestations varied and ranged from indolent signs and symptoms to septic embolization and hemorrhagic shock. Aortoenteric fistulas were described in 20 (31%) cases. However, this high rate of fistula formation could be due to case selection and referral biases because only large referral medical centers were included. *S. aureus* was the most commonly isolated pathogen (24 cases, 54.5%).

Proposed risk factors for vascular stent infection are listed in Table 82.10.[10,129,132] However, due to limited number of cases, no risk factors have been validated in a multivariable analysis.

Diagnosis

Blood and operative specimens should be submitted for culture in all cases. CT and angiography can aid in the diagnosis of stent-related infection. The presence of fluid and inflammatory reaction around the stent on a CT scan is suggestive of stent infection. Patients with aortoenteric fistulas typically present with abdominal pain or GI bleeding, or both. Upper GI endoscopy and CTA have been crucial in establishing a diagnosis of this life-threatening complication.

Management and Outcome

The preferred management approach is excision of an infected stent and involved vessel, with extraanatomic revascularization in combination with parenteral antibiotics. In the previously cited review[131] surgical intervention with stent graft excision was done in 50 (82%) of 61 cases in which treatment modalities were described. Reported mortality rate was 14%. Empirical antibiotics should include coverage for *S. aureus,* the most common pathogen isolated.[10,132] Other less frequently reported pathogens include CoNS, *P. aeruginosa,* β-hemolytic streptococci, and, rarely, fungi.[133]

A conservative management strategy using antibiotics alone, without infected stent removal, has been used in a limited number of cases[130,131,132] and is associated with higher failure and mortality rates. This approach should be reserved for patients whose risk of surgery outweighs the potential benefits. In the review cited earlier,[131] conservative management had a higher mortality rate (36%) compared with a combined medical and surgical approach (14% mortality rate; $P = .086$).

Peripheral vascular stent infection can be complicated by pseudoaneurysm formation, arterial necrosis, abscess formation, septic peripheral emboli (requiring limb or digit amputation), and severe sepsis with multiorgan failure. Aortoenteric fistula may develop in patients undergoing endovascular stent-graft repair of abdominal aortic aneurysms.[134] These fistulas generally involve the third or fourth portion of the duodenum. Despite aggressive combined medical and surgical intervention, reported mortality rate has been as high as 40%.[135]

Prevention

Proper sterilization of the insertion site and adherence to other infection control procedures is critically important. Current practice guidelines recommend primary antibiotic prophylaxis at the time of stent deployment. However, secondary prophylaxis for dental, GI, and genitourinary procedures is not recommended.[5]

VASCULAR CLOSURE DEVICES

Percutaneous vascular closure devices (PVCDs) are used for hemostasis of a femoral artery puncture site after catheterization. They increase patient comfort and decrease time to hemostasis and ambulation compared with manual or mechanical compression.

PVCDs can be broadly categorized into two types: those that use various mechanisms of collagen or other substance deposition at an arterial puncture site and others that use a suture to close the arteriotomy site. Complications associated with use of these devices include hematoma, pseudoaneurysm formation, limb ischemia, AV fistula, or access site infection complicated by femoral endarteritis.[136]

Epidemiology and Clinical Manifestations

The reported infectious complication rate ranges from 0.0% to 5.1%. Hematoma formation at the puncture site and the presence of foreign material likely serve as a nidus for infection. In one review of 52 cases of PVCD infections[137] the median incubation time from device insertion to presentation with PVCD-related infection was 8 days (range, 2–29 days). The majority of patients presented with local inflammatory findings at the device deployment site, including pain, erythema, swelling, and drainage. Although fever was reported in only 38% of the cases, blood cultures were positive in the majority (86%) of patients. Infection associated with PVCDs results in localized endarteritis at the insertion site, a risk factor for development of mycotic pseudoaneurysm. In the previously cited review[137] mycotic pseudoaneurysm was diagnosed in 42% of the cases with PVCD infection. Ultrasonography should be performed in suspected cases to confirm the diagnosis.

Microbiology

S. aureus is the single most commonly (up to 75% of the cases) isolated pathogen, followed by gram-negative rods (13%) and CoNS (5%).[137] Other less common pathogens include *Peptostreptococcus, Enterococcus* spp., and *Corynebacterium* spp., frequently in the setting of polymicrobial infection (14% of cases).

Management

Treatment of PVCD-related infection requires surgical débridement in almost all cases, followed by reconstructive surgery in more than 50% of cases.[136,137] Cure rates as high as 90% can be achieved with combined medical and surgical intervention. The reported mortality rate is 6%, and the majority of deaths are due to *S. aureus* sepsis. Choice of antibiotics depends on results of blood and local wound/tissue cultures. Empirical therapy should cover MRSA and gram-negative rods while awaiting culture data. Two to 4 weeks of parenteral therapy is recommended in the majority of cases depending on the causative pathogen (longer therapy recommended for *S. aureus* infections) and clinical response.

Prevention of Percutaneous Vascular Closure Device–Related Infection

Preventive efforts should focus on the use of strict aseptic techniques. There are no clinical trial data on the utility of antibiotic administration at the time of PVCD placement. However, primary prophylaxis has been considered in patients with diabetes mellitus or in those in whom a prosthetic vascular graft puncture site is closed with one of these devices.[10,137] Secondary prophylaxis (e.g., dental procedures) is not recommended.[138]

INTRAAORTIC BALLOON PUMPS

Intraaortic balloon pumps (IABPs) are frequently used for short-term circulatory support in current practice. IABPs are used in a variety of clinical settings, including refractory cardiogenic shock, severe heart failure with reduced ejection fraction, difficulty weaning from cardiopulmonary bypass, refractory myocardial ischemia, and preoperative support in the presence of severe left ventricular dysfunction.[139] Early generations of the IABPs required surgical insertion and removal. However, balloon pumps used in current practice are inserted and removed percutaneously and have lower complication rates compared with early models.

TABLE 82.11 Risk Factors Associated With Intraaortic Balloon Pumps

Emergency insertion in the intensive care unit
Improper preparation of the femoral insertion site
Obesity
Surgical insertion of intraaortic balloon counterpulsation catheters
Duration of intraaortic balloon pump therapy
Presence of additional intravascular monitoring devices
Contaminated water reservoir

Infection is an uncommon but well-recognized complication of IABP insertion. Most infections originate at the insertion site but may track along the pump, resulting in BSI and sepsis. Reported rates of local wound infections and BSI are 5% and 2.2%, respectively.[10] The risk of infection increases with the duration of IABP support.[140] Longer duration of IABP support is associated with higher risk of BSI. In a multivariable analysis risk of IABP-related septicemia increased by an OR of 1.5 for each additional pump day.[141] In another analysis that included 733 patients with IABP insertion by surgical and percutaneous methods,[142] risk of infection was higher (26%) when IABPs were inserted while the patients were in intensive care units, especially in emergency settings, compared with elective placement performed in operating rooms or cardiac catheterization laboratories (12% and 17% infection rate, respectively). Risk factors associated with IABP-related infection are summarized in Table 82.11. Outbreaks of *Pseudomonas cepacia* and *S. marcescens* BSI due to contaminated IABP reservoirs have also been reported.[143,144]

A diagnosis of IABP-related BSI requires isolation of the same organism from blood and local wound cultures. However, most patients are treated presumptively on the basis of local inflammatory findings at the insertion site or positive blood cultures. Local wound débridement and parenteral antibiotics are required in most cases when early removal of IABP is not feasible. The duration of antibiotics is similar to other central catheter-related BSIs. Because of nosocomial acquisition of infection, empirical antibiotics should include coverage of methicillin-resistant staphylococci and MDR gram-negative bacteria while awaiting results of cultures and in vitro susceptibility testing. In a prospective analysis of 60 patients by Crystal and colleagues,[145] IABP-related BSI was not associated with increased mortality.

Preventive efforts should be focused on sterile insertion techniques and adherence to infection control procedures during routine care of the insertion site. Routine use of antibiotic prophylaxis around the time of insertion is not recommended.[10]

VENA CAVA FILTERS

Inferior vena cava (IVC) filters have been in use since the early 1970s, when the Greenfield filter was introduced,[146] and are generally inserted percutaneously via a femoral or jugular approach and positioned infrarenally in most patients. IVC filters are extensively used to prevent pulmonary embolism in patients with thromboembolic disease and a contraindication for or previous failure of anticoagulation.[147]

Although venous thrombosis at the filter site has been frequently reported (20%–40% of the cases), infection of an IVC filter remains a rare complication, with only few suspected cases published to date.[53,148–151] Clinical onset of infection occurred within 10 days of placement in all cases. Infection was confirmed by culture of the explanted device in four cases.[149–151] Blood cultures were positive in five of the six cases, and staphylococcal species were recovered in five patients. Hematogenous seeding of IVC filter with *Candida glabrata* was reported in one case,[151] where patient developed central line–related *C. glabrata* BSI after abdominal surgery for necrotizing pancreatitis. Ultimately, the IVC was removed, and *C. glabrata* was recovered from device cultures. Cure was achieved with device removal and 6 weeks of antifungal therapy.

Removal of an infected IVC filter, followed by 4 weeks of parenteral antimicrobial therapy, is recommended to eradicate infection.[149–151] If the infected IVC filter cannot be removed, long-term antibiotic suppressive therapy is recommended.[53]

DACRON CAROTID PATCHES

Synthetic carotid patches, consisting of either Dacron or PTFE, increase the safety and durability of carotid endarterectomy compared with primary arteriotomy closure. Their use is also associated with reduced risks of stroke, internal carotid thrombosis, and recurrent stenosis as a complication of carotid endarterectomy. Unlike autologous vein patches (mostly harvested from the greater saphenous vein and occasionally from the external jugular vein or common facial vein), synthetic carotid patch do not require a groin incision (to harvest saphenous vein) and do not have the lack of predictability of diameter size that characterizes vein grafts.

Synthetic carotid patch infection is rare.[152,153,154–157,158] The reported rate of infection ranges from 0.26% to 1.76%. The purported risk factors include early postoperative wound complications (hematoma or superficial surgical site infection) and comorbid conditions such as diabetes mellitus.[154,157] Perioperative prophylactic antibiotics are routinely administered for carotid patch placement surgery.[152,154–157,158]

Clinical Manifestations

The time from patch placement to clinical presentation with infection varies, ranging from 10 days to 86 months. However, up to 50% of patients present within 3 months of surgical intervention.[152,154–157,158] Clinical presentation includes fever and localized inflammatory findings at the surgical site, including erythema, warmth, draining sinus, abscess, and pseudoaneurysm formation. Ultrasonography can be helpful in diagnosing pseudoaneurysms. Septic emboli resulting in stroke have also been reported. CT or MRI/MRA may aid in the diagnosis of difficult cases in which florid local manifestations of infection are absent.

S. aureus and *Streptococcus* spp. are the most commonly isolated pathogens in early-onset (<6 months) Dacron carotid patch infections.[152,154–157,158] However, gram-negative bacteria, including *Pseudomonas, Proteus,* and *Bacteroides,* have been occasionally reported. A majority of late-onset (>6 months) carotid patch infections are caused by CoNS.

Management

Resection of the infected foreign material combined with parenteral antibiotics is necessary to eradicate infection. Autologous vein patches or interposition vein grafts are used for reconstruction thereafter. Replacement of an infected prosthetic patch with another Dacron graft should be avoided because it leads to a high rate of reinfection (up to 50% in one series).[155] A 2- to 4-week course of parenteral antibiotics is recommended to treat these infections.

CARDIAC SUTURE LINE INFECTIONS

Left ventriculotomy is performed for several reasons, including resection of aneurysms or scars, antiarrhythmic surgery, and placement of ventricular assist devices. A variety of devices are used to buttress sutures at the line of incision, including autologous or resorbable strips and Teflon pledgets or patches. Despite the high frequency of left ventriculotomy with myocardial suture line support device placement, infection of these devices is rare.[159,160,161] Two published case series[159,160] described 29 patients with cardiac suture line infection. However, this likely represents underreporting because of the difficulty in making a diagnosis due to often prolonged interval (average duration, 16 months) between ventriculotomy and onset of infection stigmata[159,161] and nonspecific clinical presentation. The diagnosis of suture support device infection may not be made until surgical intervention or postmortem examination.

Clinical Manifestations

Three clinical presentations have been appreciated: (1) chest wall or epigastric soft tissue infection, (2) bronchopulmonary infection, and (3) endocardial infection with bacteremia or fungemia. Chest wall or epigastric involvement is seen most commonly and presents as a chronic draining sinus (cardiocutaneous fistula),[161] a subcutaneous mass, or local pain. A syndrome of endocardial infection is the next most common presentation and typically manifests with BSI. If the underlying diagnosis is not appreciated, relapsing bacteremia or fungemia can occur after discontinuation of antimicrobial treatment. Eradication of infection is not achieved until débridement is performed. Bronchopulmonary

presentations (cardiobronchial fistulas) are less common. In this scenario patients present with recurrent hemoptysis, purulent sputum production, bronchiectasis, and pneumonia with or without empyema. Some patients may present with a combination of features that reflects more than one syndrome presentation. Left ventricular false aneurysms commonly develop.[159,160]

Diagnostic evaluation in suspected cases may include echocardiography, CT, and/or left ventricular angiography. Although staphylococcal species account for the majority of cardiac suture line infections, a variety of other organisms, including other skin flora, have been identified.

MANAGEMENT OF CARDIAC SUTURE LINE INFECTIONS

Optimal treatment includes early surgical débridement of infected native and foreign tissues, along with pathogen-specific antimicrobial therapy. Of 29 patients in two case series,[159,160] 23 (79.3%) survived with combined surgical débridement and antimicrobial therapy. In 4 of 6 patients who died, no débridement of the infected ventricular suture line was performed.[159] Preventive strategies include the use of absorbable sutures or autologous pericardium to support a suture line at the time of initial surgery, in addition to strict adherence to infection control procedures.

CLOSURE DEVICE TREATMENT OF PATENT DUCTUS ARTERIOSUS, ATRIAL SEPTAL DEFECT, AND VENTRICULAR SEPTAL DEFECT

Therapeutic cardiac catheterization with placement of closure devices for a variety of congenital defects is being used increasingly with success and avoiding the risks of surgery.[162] Several different devices are in use, and others are under investigation. Overall, complications related to device placement are infrequent, and infectious sequelae have been rare, with scant published reports.[163,164] It can be difficult to determine the interval between device placement and the onset of occlusion device-related infection. Nevertheless, in two reports[163,164] infection occurred less than 3 months after device placement. Pathogens were identified in both cases and included *S. aureus* in one[163] and *Bacillus pumilus*[164] in the other. In both cases device-related vegetations were demonstrated on TTE. After surgical excision of the devices and débridement of infected tissues, followed by administration of parenteral antibiotics over 6 weeks, both infections were eradicated.

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The complete reference list is available online at Expert Consult.

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83 Prevention of Infective Endocarditis

Bruno Hoen, Xavier Duval, and David T. Durack

SHORT VIEW SUMMARY

Definition of the Issue

- Infective endocarditis (IE) continues to cause serious morbidity and mortality; therefore prevention of IE is a priority.

Epidemiology

- The incidence of IE is low, estimated at 3 to 9 cases per 100,000 individuals annually in industrialized countries. However, incidence varies widely according to different patient characteristics, including the prevalence of predisposing cardiac conditions in the population and types of exposures that may give rise to transient bacteremia.
- Contributing factors include aging populations; the steadily increasing number of medical procedures, implants, and prostheses; and the rising frequency of health care–associated infections, especially catheter-related bloodstream infections.

Microbiology

- Not all bacteria are equally capable of adhering to damaged endothelium, as illustrated by the fact that the leading causes of IE are gram-positive bacteria: staphylococci, streptococci, and enterococci.
- These common gram-positive microbes, originating from the oropharynx, the skin, or the gastrointestinal and urinary tracts, all carry surface adhesins that mediate attachment to valvular extracellular host matrix proteins.
- Transient bacteremia due to gram-positive cocci can be induced by common dental or medical procedures, but there also are spontaneous low-grade, asymptomatic bacteremias that originate daily from the oropharynx. Invasive dental procedures may contribute, albeit infrequently, to the development of IE in adults, especially those with prosthetic heart valves.

Interventions to Prevent Infective Endocarditis

- For many years, various prophylactic strategies and guidelines based on antibiotic use have been proposed for patients with cardiac conditions predisposing to IE who undergo invasive procedures that may cause bacteremia. However, because no randomized clinical trials have been performed, proof of efficacy remains lacking. In addition, cost-effectiveness analyses have found conflicting results.
- Consequently, recent guidelines have shifted toward a dramatic reduction in indications for antibiotic prophylaxis of IE. The current approach is to limit antibiotic prophylaxis to individuals at highest risk of IE and highest risk of poor outcome of IE. These categories include patients with a history of IE, a mechanical or a biologic prosthetic valve, or a surgically constructed systemic or pulmonary shunt or conduit.
- For this limited group of high-risk patients, recommended antibiotic prophylaxis regimens remain based on administration of amoxicillin or ampicillin in a single dose administered 30 to 60 minutes before the scheduled procedure in patients with no allergy to penicillins. Patients with allergy to penicillin or ampicillin should receive clindamycin in a single dose of 600 mg in adults and 20 mg/kg in children, orally or intravenously.
- Several studies have now examined the effect of restricting antibiotic prophylaxis on the incidence of IE, with conflicting results. These studies were all observational and therefore cannot establish with certainty a causal link between restriction of antibiotic prophylaxis and increased incidence of IE. Various confounders could account for an increased incidence of IE irrespective of any change in guidelines for antibiotic prophylaxis.
- Beyond antibiotic prophylaxis, other interventions should be considered for prevention of IE. These include maintenance of good general and oral hygiene; prevention of health care–acquired bacteremias; and specific interventions to prevent IE secondary to the implantation of prosthetic valves, cardiac implanted electronic devices, and cardiac assist devices.

Prevention of infective endocarditis (IE) is an important clinical issue because this disease continues to cause serious morbidity and mortality. In developed countries, the annual number of cases has risen appreciably over the past years.[1,2] The incidence of IE in the United States was reported in 2013 to be approximately 12 cases per 100,000 persons per year, more than double previous estimates.[2] Advances in diagnosis and treatment clearly have improved outcomes in some subgroups, yet the overall long-term mortality of IE is only modestly better than it was 50 years ago.[3] Although the causative organism usually can be eradicated with antibiotics, such "microbiologic cure" often does not prevent permanent cardiac valvular damage and other sequelae, such as recurrent IE, which can impair quality of life, necessitate valve surgery, and reduce life span. In recent large series, 75% to 85% of patients survived the active phase of endocardial infection,[2,4] but survival rates at 1 year and longer are notably lower.[5,6] For example, overall survival at 4 years in one series was only 67%.[6] Furthermore, the increasing prevalence of antibiotic resistance among the common gram-positive cocci that cause most cases of endocarditis makes treatment more difficult.[7]

Thus, effective measures to prevent IE are clearly desirable. The most obvious potential intervention is administration of antibiotics, but despite years of study, this long-standing practice has never been proven to be effective in humans.[8] For this reason, the most recent practice guidelines recommend eliminating attempted antibiotic prophylaxis for IE in most settings, or even entirely.[9,10,11]

PATHOGENESIS OF INFECTIVE ENDOCARDITIS IN THE CONTEXT OF PREVENTION

The pathogenesis of IE is reviewed in detail in Chapter 80. The theoretical foundation for interventions intended to prevent IE is based on the following elements of pathogenesis. It is accepted that normal valve endothelium is naturally resistant to colonization by bacteria. In the conventional model of native valve endocarditis, the development of endocarditis results from colonization of previously damaged valve endothelium by bacteria that circulate in the bloodstream and have specific adherence properties. Endothelial damage may result from so-called jet lesions due to turbulent blood flow, or may be provoked by electrodes, catheters, or repeated intravenous injections of particulate matter in intravenous drug users. Chronic inflammation from rheumatic carditis and degenerative valve lesions in the elderly[12] also predispose to IE. Lesions of the valvular endothelium result in the exposure of underlying extracellular matrix proteins, the production of tissue factor,

and the deposition of fibrin and platelets as part of the attempted repair process. The resulting initial nidus of nonbacterial thrombotic endocarditis offers optimal conditions for adherence to some species of circulating bacteria.[13] Not all bacteria are equally capable of adhering to damaged endothelium, as illustrated by the fact that the leading causes of IE are gram-positive bacteria: staphylococci, streptococci, and enterococci.[3,14] These common gram-positive microbes, originating from the oropharynx, the skin, or the gastrointestinal tract, all carry surface adhesins that mediate attachment to extracellular host matrix proteins. In contrast, IE due to gram-negative bacteria is relatively rare.

Low-grade, asymptomatic bacteremia due to gram-positive cocci from the oropharynx occurs commonly, often daily.[15–17] Transient bacteremia can also be induced by common dental or medical procedures.[15,18,19] Studies have confirmed that invasive dental procedures may contribute, albeit infrequently, to the development of IE in adults,[20] especially in those with prosthetic heart valves.[21] Furthermore, health care–associated bacteremias due to gram-positive cocci, especially staphylococci, are common and have become an increasingly important risk factor for IE.[2,3]

ESTIMATION OF THE RISK FOR INFECTIVE ENDOCARDITIS

The incidence of IE is low, estimated at three to nine cases per 100,000 individuals annually in industrialized countries.[3,22–25] However, this incidence depends on the prevalence of predisposing cardiac conditions (PCCs) in the population and the number of factors that may give rise to transient bacteremia. The prevalence of PCCs for which prophylaxis is generally recommended is much higher than formerly thought. Previously unknown PCCs detected with systematic echocardiographic surveys are now estimated to exist in 2.5% (95% CI, 2.2%–2.7%) of the general population of the United States.[26] The prevalence of PCCs increases with age, to 13.3% (95% CI, 11.7%–15.0%) in individuals older than 75 years. The prevalence of previously known PCCs has been estimated to be 1.8% in the United States in the general population[26] and 3.3% in the 25- to 84-year-old French population.[27] Furthermore, it has been estimated that approximately 2.1 at-risk dental procedures are performed per patient per year.[27] The risk of developing IE in patients with PCCs after an at-risk dental "unprotected procedure" appears to be extremely low. A French study estimated the risk to be 1 in 54,300 in adults with native valve PCC, and 1 in 10,700 in adults with prosthetic valves.[27] The risks reported in a US study were even lower (one case of IE per 14 million dental procedures).[28]

Procedures at Risk for Causing Infective Endocarditis

The identification of procedures at risk for causing IE includes a consideration of several factors: (1) the number of different species of IE-inducing pathogens that are colonizing the site involved in an invasive procedure and that might enter the bloodstream, (2) the amount of bleeding induced by the procedure, (3) the frequency of positive blood cultures after a given procedure (Table 83.1), (4) the magnitude of the bacteremia after the procedure (inoculum size), (5) the duration of the bacteremia, and (6) the number of cases of IE that have been reported after any given procedure. However, there is wide variation in the reported frequencies of all these factors. For example, bacteremia is noted in 10% to 95% of patients after tooth extraction, a wide range that probably reflects the heterogeneity of these dental procedures, the varying dental status and immunity of the host, and the detection methods used.[29–33] Given the heterogeneity of these data, it is difficult to clearly establish definitive criteria for risk factors. A better knowledge of the factors predisposing to IE is necessary. Given that transient asymptomatic bacteremias that occur after tooth brushing, flossing, or chewing are common in everyday life, and given the high prevalence of PCCs in the general population, the incidence of IE is astonishingly low. Genetic host susceptibilities allowing or promoting attachment of microorganisms to valvular endothelium probably exist; their identification could allow prophylactic measures to be focused on those patients at highest risk.

On the other hand, the rate of bacteremia after at-risk procedures has been used as a surrogate measure of the risk for IE, and for selecting procedures requiring antibiotic prophylaxis. However, there is no evidence-based method to decide which procedures should be covered by antibiotic prophylaxis because there is no proof that the incidence, the magnitude, or the duration of bacteremia after a procedure increases the risk of IE. Therefore, use of these factors to identify procedures that warrant prophylaxis is somewhat artificial; nevertheless, it is the method usually used. This has resulted in complex and detailed lists of dental and other procedures for which prophylaxis is or is not recommended. The 2006 British Society for Antimicrobial Chemotherapy (BSAC) broke with this practice and introduced the notion of a general classification of "dental procedures involving dento-gingival manipulation" for which antibiotic prophylaxis is indicated.[34] Current guidelines that recommend antibiotic prophylaxis before certain dental procedures specify that antibiotic prophylaxis should be given for "dental procedures requiring the manipulation of the gingival or periapical region or the teeth or perforation of the oral mucosa (except for local anesthesia)."[10,35]

TABLE 83.1 Ranges of Positive Blood Samples After Various Oral Procedures

REFERENCES	ORAL PROCEDURES	POSITIVE BLOOD CULTURES (RANGE), %
172–177	Mastication	17–51
	Toothbrushing or irrigation	0–50
	Flossing	20–60
	Dental examination	17
173, 177–179	Dental polishing	24
	Intraligamentary local anesthetic injection	97
	Matrix band placement	32
	Rubber dam placement	30
	Slow drill	12
	Fast drill	4
29–33, 172, 180, 181	Single dental extraction	18–94
	Multiple dental extraction	10–85
172	Scaling	17–70
172, 182	Periodontal surgery	32–88
172, 182	Endodontic instrumentation	20–42
183	Postoperative suture removal	5
182, 183	Endodontic treatment	42

Preexisting Cardiac Conditions

The risk of occurrence of IE in any given case of PCC is most often indirectly estimated by comparing the frequency of different cardiac diseases in patients with IE versus its frequency in the general population (Table 83.2).[36] It has also been estimated by monitoring cohorts of cardiac patients and calculating the incidence of IE cases in this population, thus determining the lifetime risk of acquisition of IE associated with a specific PCC.[37–41,42,43,44] Recent reports have also used administrative databases to estimate this incidence.[21,45,46]

To determine which patients should receive prophylaxis, it is necessary to choose a threshold above which the risk for IE is considered to be significant. According to this gradation of risk, patients with a history of IE, a mechanical or biologic prosthetic valve, or a surgically constructed systemic or pulmonary shunt or conduit are the patients with the highest incidence of IE and therefore considered at highest risk of developing IE during their lifetime. This risk gradation is now widely accepted.[34,47,48]

The prognosis if IE were to occur in a given case of PCC must also be taken into account when choosing which PCCs should be covered. IE on prosthetic valves and in patients with a previous history of IE have poorer outcomes and higher risk of death. Other characteristics of patients' general health background also have been associated with in-hospital death during IE: old age, diabetes mellitus (primarily insulin-dependent diabetes), immunodeficiency, dialysis, and hepatic insufficiency.[49–52] These considerations were used in most guidelines to identify patients with worse prognosis should they develop IE (Table 83.3). This led US guidelines to recommend antibiotic prophylaxis for

TABLE 83.2 Estimates of Rates and Relative Risk for Infective Endocarditis (IE) Associated With Demographics and Selected Preexisting Cardiac Conditions

RISK FACTOR	RATE OF IE PER 10^5 PERSON-YEARS	RELATIVE RISK
None (reference group)	3–12	1.0
Mitral valve prolapse without murmur	3–12	1
Male gender	8–25	2.5
Age >65 yr	30–120	9
Mitral valve prolapse with murmur, thickening, and/or redundancy	45–180	15
Any cardiac valvular abnormality	50–200	17
Aortic stenosis	130–520	45
Ventricular septal defect (uncorrected)	150–800	50
Ventricular septal defect (corrected)	30–120	10
Congenital heart disease (many types)	15–600	5–55
Chronic rheumatic heart disease	100–400	35
Previous infective endocarditis	110–440	37
Prosthetic cardiac valve	225–900	75

Note that these are approximations based on multiple studies and reviews. These estimates could change with time as new studies are conducted, and they could be subject to significant error. Interpretation of these data should be considered in this context.
Modified from references 2, 36, 141, and 184 and J.M. Steckelberg (personal communication, 2009).

TABLE 83.3 Predisposing Cardiac Conditions According to the Risk to Develop Endocarditis

High-Risk Predisposing Cardiac Conditions

Previous infective endocarditis
Mechanical or biologic prosthetic valves
Surgically constructed systemic or pulmonary shunt or conduit
Complex cyanotic congenital heart disease (single ventricle states, transposition of the great arteries, tetralogy of Fallot)

Moderate-Risk Predisposing Cardiac Conditions

Most other congenital cardiac malformations (except isolated secundum atrial septal defect with no increased risk)
Acquired valvular dysfunction (e.g., rheumatic heart disease)
Hypertrophic cardiomyopathy
Mitral valve prolapse with valvular regurgitation and/or thickened leaflets

IE in cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve.

Indirect Evidence Regarding the Risk for Infective Endocarditis Posed by Dental Procedures and the Efficacy of Prophylaxis

Because the implementation of a very large randomized clinical trial to assess the effectiveness of antibiotic prophylaxis has been regarded as unfeasible to date, indirect evidence has been sought.

Cohort Studies

There are few cohort studies in the literature that estimated the risk of IE after invasive procedures, because the number of patients needed to be enrolled to make such a study possible is very high. Furthermore, the time window during which an IE case could be reasonably considered as the consequence of an invasive procedure is unknown, given the fact that the incubation period between the microbial colonization of the endocardium and the first symptoms is not known precisely, but is likely quite short.[53] In two recent studies based on the analysis of administrative databases and considering the 3 months after dental care as the incubation period, authors did not find a statistically significant reduction of IE incidence in patients receiving antibiotic prophylaxis before dental procedures.[21]

Case-Control Studies

The role of dental procedures in the genesis of IE can also be evaluated indirectly in large series of IE or in case-control studies. In both cases, only a small minority of IE cases due to oral streptococci are preceded by an invasive dental procedure: 2.7% to 5% of cases in several epidemiologic series.[20,21,27,36,54] However, even in the case of a close temporal relationship between a dental procedure and the development of IE, it is not possible to determine with certainty whether the bacteremia that caused IE was induced by the procedure, or caused by dental disease predating the procedure, or due to a spontaneous daily bacteremia. This very low risk level probably explains why some case-control studies failed to identify any clear relationship between the onset of IE and preceding "at-risk" dental procedures, whereas others did; however, none have definitively proven the efficacy of antibiotic prophylaxis.[20,36,54–56] In a recent case-control study, authors reported using a population-attributable risk analysis that indicated that dental procedures within the preceding 3 months accounted for less than 20% of streptococcal IE cases, whereas incorrect and/or lack of oral hygiene habits accounted for two-thirds of them.[20]

Using a case-crossover design in a French administrative database, Tubiana and colleagues reported that the number of invasive dental procedures within the 3 months preceding oral streptococcal IE was significantly higher than during the same preceding control period in individuals with prosthetic cardiac valves (5.1% vs. 3.2%; odds ratio [OR], 1.66; 95% confidence interval [CI], 1.05–2.63).[21] Despite including 137,000 patients with prosthetic valves, the study was not sufficiently powered to prove the efficacy of antibiotic prophylaxis. A similar result has also been reported by others.[46]

In Vitro Antibiotic Susceptibility Studies

It is well known that the frequency and degree of antibiotic resistance among common bacterial pathogens has increased extensively worldwide and continues to increase. This topic is reviewed in Chapter 18 and will not be recapitulated here. However, it is obvious that increased antibiotic resistance among bacteria causing IE would almost certainly further impair the efficacy (if any) of attempted prevention of IE with antibiotics.

Experimental Infective Endocarditis

Studies in animal models have provided an important secondary source of information on the mechanisms and efficacy of prevention of IE. When a polyethylene catheter was passed into the right or left heart chamber of living rabbits, small sterile vegetations composed of platelets and fibrin developed at points of contact between the catheter and endocardium.[57] When staphylococci were placed in the lumen of the catheter, staphylococcal endocarditis resulted. Modifying this experimental model for IE by injecting organisms intravenously after intracardiac catheter placement has provided a convenient in vivo system for examining the efficacy of various antibiotic regimens for the prophylaxis of endocarditis.[58–62] A similar model in rats has also been used extensively to investigate antibiotic prophylaxis.[63,64] Under experimental conditions, the time of onset of IE is known exactly. Another important advantage is that the incidence of infection in untreated animals can be adjusted easily by altering the size of the inoculum; therefore the problem of very low infection rates can be overcome by choosing an inoculum of the test organism that is large enough to infect many or all of the experimental animals. Significant differences among antibiotic regimens being tested for prevention or treatment of IE can then be demonstrated with use of manageable numbers of animals in each group.[64–73]

Later experiments showed that a very-low-inoculum bacteremia, if sufficiently prolonged, also often caused IE in predisposed rats.[74] These

experimental conditions resemble the frequent low-level bacteremias originating from the oral cavity that are known to occur in the normal daily life of humans. They demonstrate that the area under the curve can be as important as the peak level of bacteremia in causing IE.

Early experiments using high inocula compared the efficacy of various antibiotic regimens against viridans-group streptococci in these model systems, proving that penicillin in a high sustained dose could prevent IE; that a synergistic combination of a penicillin plus an aminoglycoside was even more effective in preventing IE caused by viridans-group streptococci or enterococci; and that vancomycin provided an effective alternative to regimens that included penicillins.[58,60,61,69] Other antibiotics proven capable of preventing IE under controlled experimental conditions include ampicillin, amoxicillin,[66,73,75] ampicillin-sulbactam,[71] erythromycin,[73] clindamycin,[70] rifampin,[76] and azithromycin or clarithromycin.[72] In early animal studies, bacteriostatic antibiotics such as tetracycline usually failed to prevent IE, but further experiments have modified the view that bactericidal activity is essential for prophylaxis.[77] Streptomycin proved surprisingly effective in the prevention of experimental IE for some strains of enterococci, even though the concentration of streptomycin in serum was far too low to kill them.[58] Subinhibitory concentrations of certain antibiotics, especially vancomycin, can inhibit the adherence of streptococci to fibrin surfaces in vitro. Other experiments have demonstrated successful prophylaxis for various streptococci with sublethal doses of vancomycin, clindamycin, erythromycin, and even a tetracycline.[69,70,73] Penicillin was less effective in the prevention of experimental streptococcal endocarditis if the strain was tolerant to penicillin (i.e., inhibited but not killed).[78] However, penicillin retained some prophylactic activity even if the strain was so tolerant that bactericidal concentrations of penicillin could not be achieved in serum. These findings all suggest that prevention of IE in animals can sometimes be achieved by antibiotic effects that fall short of total bacterial killing, perhaps by an alteration of surface structures that mediate adherence to fibrin or by other unknown mechanisms. Thus, bactericidal action may be sufficient but not necessary for prevention of endocarditis.

The experimental observation that successful prophylaxis with amoxicillin can be reversed by administration of penicillinase shortly after colonization of the vegetation shows that neither killing of organisms in the bloodstream nor prevention of their adherence to the endocardium is essential for successful antibiotic prophylaxis.[64]

The implications of these extensive experimental findings for humans are uncertain. To place the experimental data in perspective, it should be emphasized that direct extrapolation of findings in animals to humans may not be meaningful. Although experiments in living animals provide a closer simulation of human endocarditis than any in vitro system, there are two important differences. First, a foreign body was present throughout many of these experiments because an intracardiac catheter often was left in place. The presence of a foreign body markedly lowers the inoculum required to initiate infection, and then makes that infection harder to eradicate. Therefore animal models probably simulate patients with prosthetic valves or pacemakers more closely than patients with congenital or rheumatic valvular disease. Second, in many of the experiments, a high inoculum was chosen deliberately to make statistical comparisons possible with a relatively small number of animals. Because both the presence of a foreign body and the use of high inoculum tend to make prevention harder to achieve, it is entirely possible that an antibiotic regimen that failed in animals might succeed in humans. Conversely, any regimen that proved effective under these challenging experimental conditions would be likely to provide a wide margin of effectiveness in clinical use. In summary, studies of prevention in animals have proven beyond doubt that antibiotics can prevent IE in vivo. They have provided insights into the mechanisms whereby different antibiotics and dosage regimens achieve prevention of IE, and they have provided a convenient in vivo method for ranking prophylactic antibiotic regimens in order of efficacy. For example, they support the conclusion that optimal bactericidal regimens, such as a penicillin plus an aminoglycoside or vancomycin, should provide a wider margin of effectiveness than a lower-ranking regimen, such as erythromycin or tetracycline.[60] However, they cannot prove whether any particular antibiotic regimen will or will not prevent endocarditis in humans.

Recent experiments using prolonged, low-inoculum bacteremias in predisposed rats showed that some antiplatelet and antithrombin drugs can prevent IE due to gram-positive cocci.[79] This suggests that long-term antiaggregant and/or anticoagulant therapy, which is already routinely used for some cardiovascular diseases, might also prevent IE.

Going forward, experimental models should continue to be useful for the initial evaluation of novel approaches to prevent IE—for example, new antibiotics, new anticoagulants and antiaggregants, new vaccines, and new interventions to prevent biofilm formation.

POTENTIAL INTERVENTIONS TO PREVENT ENDOCARDITIS

Correction of Predisposing Cardiac Conditions

Adult congenital heart diseases (ACHDs) are well-known predisposing factors for IE. Some congenital abnormalities that predispose to IE may be corrected. Surgical advancements have benefited many patients with ACHD and consequently reduced their risk of IE; on the other hand, prosthetic material inserted at surgery may constitute a nidus that favors attachment of circulating bacteria. In this population, IE incidence has been reported to be 133 cases per 100,000 person-years.[42] Valve-containing prosthetics were independently associated with greater short- and long-term risk after implantation (0–6 months—hazard ratio [HR], 17.29 [95% CI, 7.34–40.70]; 6–12 months—HR, 15.91 [95% CI, 6.76–37.45]; beyond 12 months—HR, 5.26 [95% CI, 3.52–7.86]).[42] Non–valve-containing prosthetics, including valve repair, appear to predispose to IE only in the first 6 months after implantation (HR, 3.34 [95% CI, 1.33–8.41]), but not thereafter.[42] These results are consistent with the findings of other studies that also showed that the incidence of IE in ACHD was lower than in patients with a history of IE or in those with a prosthetic heart valve [42,43,80]

Minimization of Portals of Entry for Microorganisms

Most cases of IE are caused by gram-positive cocci that originate from the skin, the oral cavity, or the gastrointestinal or urinary tracts. Whereas the oral cavity is the portal of entry for oral streptococcal bacteremia, improvement in general oral hygiene is probably responsible in part for the decrease in streptococcal IE in industrialized countries.[81] Invasive dental procedures have been reported to cause higher rates of bacteremia in individuals with poor oral hygiene who undergo tooth extraction.[82] The rate of IE patients with poor orodental status is higher, even in those with IE due to nonoral microorganisms.[20] Conversely, tooth brushing three times daily or more after meals in the absence of invasive dental hygiene such as use of toothpicks, dental water jets, flossing, and interdental brushes has been associated with a decreased risk of streptococcal IE.[20] Given the low rate of IE after invasive dental procedures, improving oral hygiene and eliminating incorrect oral hygiene habits may be the most efficient interventions to reduce the incidence of streptococcal IE.

Cutaneous portals of entry have increased in number as medical progress has increased the number of percutaneous procedures. Venous or arterial catheters are a major source for staphylococcal bacteraemia.[83] *Staphylococcus aureus* bacteremia is associated with all types of catheters, short term or long term, surgically inserted or peripheral, tunneled or nontunneled. The incidence of bloodstream infections as a complication of intravascular catheter use varies considerably with the type of catheter, the frequency of catheter manipulation, and patient-related factors. The highest risk, found by Maki and colleagues in a meta-analysis of 200 prospective studies, was associated with short-term noncuffed and nonmedicated central venous catheters (2.7 per 1000 catheter-days). For long-term cuffed and tunneled hemodialysis catheters, the incidence rate was 1.6 intravascular device–related bloodstream infections per 1000 intravascular device–days.[84] Chronic intravenous access was a common predisposing factor in the International Collaboration on Endocarditis (ICE)–Prospective Cohort Study (PCS), around 10% of IE cases, with evidence of geographic differences. For European countries involved in ICE-PCS, chronic intravenous access accounted for 5% of the predisposing conditions; it accounted for 25% in North America.[14] The infrequent use of native arteriovenous fistulas in the United States

as compared with their more frequent use in Europe (24% vs. 80%) may explain this difference.[85]

Aging of the population is associated with a higher prevalence of colonic tumors, which are a proven portal of entry of *Streptococcus bovis* IE, and to a lesser extent enterococcal IE.[86] The search for portals of entry and their eradication is warranted in IE patients to reduce the rate of recurrent IE episodes.[87]

Prevention of Health Care–Associated Infections

Health care–associated infective endocarditis (HCAIE) today accounts for an increasing proportion of IE cases—currently approximately one-third[3]—and therefore requires specific strategies for prevention. The affected population has medical conditions, interventions, and treatments that may cause bacteremia, and most patients have either degenerative valve disease or no intrinsic cardiac risk factors. The most frequent risk factors for HCAIE are hemodialysis, cancer, diabetes mellitus, and the presence of a cardiovascular implantable electronic device (CIED), but there are many others.[3,88] *S. aureus* is the causative organism in approximately one-third of cases.[3,88] The in-hospital mortality in patients with HCAIE is significantly higher than in those with community-acquired infection (31.1% vs. 20.3%; $P < .01$).[3]

S. aureus is the second most frequent microorganism causing bacteremia in industrialized countries and the first or second most frequent to cause IE, depending on country.[14] Asymptomatic carriage of *S. aureus* has been associated with the occurrence of bacteremia. In the United States, 10% to 20% of the population carries *S. aureus* persistently, and others carry it transiently.[89] Interventions to change practice and improve adherence to preventive procedures such as hand hygiene, barrier precautions, and antisepsis have already significantly reduced rates of central line–associated bloodstream infections.[90]

Administration of Systemic Antibiotics

For many years, various prophylactic strategies and guidelines based on antibiotic use have been proposed for patients with cardiac conditions that predispose to IE who undergo invasive procedures that may cause bacteremia.[10,35] Because no randomized clinical trials have been performed, proof of efficacy remains lacking,[36,55,91] and consequently more recent guidelines have shifted toward a dramatic reduction in indications for antibiotic prophylaxis of IE.[11,35,47,92] An additional reason to reduce or even abandon IE prophylaxis is the demonstration that "everyday low-level bacteremias" that occur after tooth brushing, flossing, or chewing likely far outweigh post–dental procedure bacteremias as a risk for IE.[8,93–96] The capability for a sustained low-level bacteremia—as a surrogate for everyday-life bacteremia—to induce IE has been confirmed experimentally, with 70% to 100% of animals developing IE, depending on the species of microorganism and the inoculum size.[74] On the other hand, when considering the high number of patients with PCCs for IE (2.5% of the general US population, 1.7% of the French population, and 7% of people older than 60 years) who are exposed to daily repeated bacteremia capable of inducing IE, the rarity of IE is striking.[27,95]

As the effectiveness of preventive antibiotic treatment remains to be proven, recommendations originating from different countries diverge widely with regard to the patient population and circumstances in which antibiotic prophylaxis should be administered. Since 2008, antibiotic prophylaxis is no longer recommended in the United Kingdom and Sweden.[97] The 2007 US[9] and the 2009/2015 European guidelines[10,92] recommend antibiotic prophylaxis only in patients with prosthetic heart valves, a history of IE, or congenital cyanotic heart disease who are undergoing invasive dental procedures.

EVOLUTION OF CLINICAL PRACTICE IN PREVENTION OF INFECTIVE ENDOCARDITIS

Historical Trends Over 7 Decades

Early strategies to prevent IE focused on bacteremias that were known to result from dental extractions. Initial trials showed that penicillin reduced the incidence of bacteremia after dental extraction. This led the American Heart Association (AHA) to recommend penicillin prophylaxis for patients with rheumatic heart disease and congenital heart disease in 1954. Between 1954 and 2002, AHA guidelines on prevention of IE were periodically updated, and the range of indications for antibiotic prophylaxis was extended beyond dental procedures to procedures involving the urinary and gastrointestinal tract, if such procedures were known to induce bacteremias. This came to a halt in 2002, when the French IE prophylaxis guidelines dramatically reduced the indications for prophylaxis, limiting them to patients at high risk of IE.[47] Between 2007 and 2009, guidelines in the United States and Europe also restricted the indications for antibiotic prophylaxis of IE.[9,92] Several facts explain this evolution of practice. First, no randomized controlled trial of antibiotic prophylaxis had ever been conducted to confirm the efficacy and assess the risk-benefit ratio of this intervention. Second, substantial evidence was presented that transient bacteremia is common with normal daily activities such as tooth brushing, flossing, and chewing food, which in all likelihood cumulatively contribute more to the risk of IE than brief dental procedures.[35,74,98] Third, the efficacy of antibiotic prophylaxis has been questioned in case-control studies.[36,55,91] Fourth, although rare, side effects including severe and sometimes fatal anaphylaxis can result from antibiotic prophylaxis.[99–102] Finally, widespread antibiotic use contributes to the emergence of antibiotic resistance and affects the microbiome, which may in turn increase the risk of diseases such as diabetes.[103] In an extreme step, the UK National Institute for Health and Care Excellence (NICE) recommended in 2008 that antibiotic prophylaxis be abandoned in all patients for all procedures.[97] It should be emphasized that these changes are not based on any new evidence that antibiotic prophylaxis does not work. Nor are they based on any new evidence that dental and medical procedures do not, on rare occasions, cause IE. The NICE guidelines were based on three primary considerations: First, very few cases of IE are caused by medical or dental procedures[36,54,104]; second, there are no evidence-based data demonstrating efficacy of antibiotic prophylaxis in humans; and third, cost-effectiveness and cost-benefit calculations have not demonstrated convincing benefits.[105,106]

Several studies have now examined the effect of restricting antibiotic prophylaxis on the incidence of IE. In France, where antibiotic prophylaxis was restricted to high-risk subjects in 2002, successive surveys conducted in 1991, 1999, and 2008 showed that the annual incidence of IE was stable at 35, 33, and 32 cases per million, respectively, suggesting no significant change after restriction of antibiotic prophylaxis. Of note, the number of cases caused by oral streptococci was also stable.[107] In the United States, using data from the Rochester Epidemiology Project, De Simone and colleagues found no change in the incidence of IE due to oral streptococci before and after the 2007 guideline change.[108,109,110] In contrast, two nationwide epidemiologic studies from the United States and the United Kingdom brought conflicting results. Using the Nationwide Inpatient Sample, Pant and colleagues identified a statistically significant increase in the incidence of IE caused by streptococci, whereas there was no significant change in the incidence of staphylococcal IE.[111] However, this study did not perform change point analysis to confirm that the incidence change coincided with the guideline change in 2007, and did not have access to antibiotic prophylaxis prescribing data to confirm that this had declined. In addition, enterococci were included in the streptococcal category, so the apparent increase in streptococcal IE might be due in part to rising rates of enterococcal IE.[112]

In the United Kingdom, the first analysis after the 2008 NICE guidelines showed no rising incidence of IE.[1] In 2015, though, an extended analysis from the same group showed that antibiotic prophylaxis dropped from 10,900 prescriptions per month to 2236 prescriptions per month after NICE guidelines were introduced, while in parallel the number of IE cases increased by 0.11 cases per 1 million persons per month, which translates to an excess of about 35 cases per month. Statistical analysis identified June 2008, which was 3 months after implementation of the new guidelines recommending nonuse of antibiotic prophylaxis, as the change point. However, the accuracy of the calculation of the change point date has been criticized,[113] and it was not possible to confirm that these cases were mostly due to oral streptococci because microbiologic data were unavailable.[114] Another study that used the Canadian Institute for Health Information Discharge Abstract Database to identify all hospitalizations between April 2002 and March 2013 in which IE was a primary diagnosis showed that although the incidence

TABLE 83.4 2014 American Heart Association (AHA) and 2015 European Society of Cardiology (ESC) Guidelines for Antibiotic Prophylaxis of Infective Endocarditis (IE)

INDICATION	AHA GUIDELINES 2014	ESC GUIDELINES 2015
Patient population	1. Patients with prosthetic cardiac valves 2. Patients with previous IE 3. Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve 4. Patients with congenital heart disease (CHD), including: a. Unrepaired cyanotic CHD, including palliative shunts and conduits; or b. Completely repaired CHD repaired with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure; or c. Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device	1. Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair 2. Patients with a previous episode of IE 3. Patients with congenital heart disease (CHD): a. Any type of cyanotic CHD b. Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains
Procedure	Dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa	Dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa; the latter does not include local anesthetic injections in noninfected tissues

of IE hospitalizations increased throughout the time period, and slightly more after the AHA guidelines were released in 2007, these guidelines had no significant impact on the incidence of IE hospitalizations.[115] By contrast, a nationwide retrospective trend study conducted in the Netherlands using the national health care insurance database to assess the potential impact of the European Society of Cardiology (ESC) guidelines of 2009 by analyzing changes in the incidence of IE between 2005 and 2011 showed that the incidence of IE increased significantly above the projected historical trend after 2009, especially for the subgroup of streptococcal IE.[116]

Two studies also evaluated the impact of the 2007 AHA guidelines on the overall incidence of IE in children in the United States.[117,118] Both failed to show any impact of the new guidelines, although in one study a significant trend toward increased incidence of IE was observed for oral streptococcal IE in the 10- to 17-year-old group.[118]

Current Guidelines

The data summarized earlier are observational and therefore cannot establish with certainty that there is any causal link between restriction of antibiotic prophylaxis and incidence of IE. Various confounders could account for an increased incidence of IE irrespective of any change in guidelines for antibiotic prophylaxis. The change could be caused by an increased number of individuals at high risk of IE, resulting from population aging, increased numbers of patients with implanted intracardiac devices, or increased prevalence of diabetes mellitus or chronic dialysis.[119] Although a randomized clinical trial aimed at evaluating the efficacy of antibiotic prophylaxis of IE is highly desirable, it is also unlikely to be conducted in the near future, if ever. Therefore the current approach, reflected by both current AHA[120] and ESC[10] guidelines, is to limit antibiotic prophylaxis to individuals at highest risk of IE and highest risk of poor outcome of IE. These guidelines are summarized in Table 83.4. Prophylaxis for gastrointestinal, genitourinary, or orthopedic procedures specifically to prevent IE is no longer recommended, although it might be given to prevent other infections. Dental prophylaxis is recommended only for procedures associated with a high rate of bacteremia in that subgroup of subjects with highest risk of developing IE. This conservative pragmatic approach balances the risks and benefits of individual and population antibiotic use.

Timing, Dosage and Duration of Antibiotic Prophylaxis

Recommended antibiotic prophylaxis regimens for high-risk dental procedures in high-risk patients have not changed recently, still being based on administration of either amoxicillin or ampicillin in a single dose of 2 g in adults and 50 mg/kg in children, administered orally or intravenously 30 to 60 minutes before the scheduled procedure in patients with no allergy to penicillin or ampicillin. Patients with allergy to penicillin or ampicillin should receive clindamycin in a single dose of 600 mg in adults and 20 mg/kg in children, orally or intravenously (Table 83.5).[10]

TABLE 83.5 Regimens for Antibiotic Prophylaxis of Infective Endocarditis During Dental Procedures

CLINICAL SITUATION	ANTIBIOTIC	DOSE FOR ADULTS[b]	DOSAGE FOR CHILDREN[b,c]
Standard oral regimen—for most patients	Amoxicillin	2.0 g PO	50 mg/kg PO
If unable to take oral medication	Ampicillin	2.0 g IM or IV	50 mg/kg IM or IV
If allergic to penicillins	Clindamycin	600 mg PO	20 mg/kg PO
If allergic to penicillins and unable to take oral medication	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

[a]Only for patients with highest risk of adverse outcome of infective endocarditis.
[b]Single dose, 30 to 60 minutes before procedure.
[c]Not to exceed adult dose.

COST-BENEFIT AND COST-EFFECTIVENESS ANALYSES

Cost-benefit and cost-effectiveness analyses must be based on the assumption that prophylaxis is efficacious even though, as previously stated, this has not been proven.[121] Current cost-benefit and cost-effectiveness analyses have been based on data coming from studies with low levels of evidence and have found conflicting results.[105,106,122,123] Given the low price of amoxicillin, ampicillin, or clindamycin in prophylactic doses, and the high morbidity and mortality burden of IE, even a low efficacy of prevention would be cost-effective, provided that the cost of potential antibiotic adverse effects is also low. Data have indicated a very low incidence of adverse reactions to amoxicillin: 0 and 22.6 fatal and nonfatal adverse drug reaction per million prescriptions, respectively,[106] which is much lower than the previously reported rate of 10 to 30 deaths per million prescriptions.[124–126] This would favor the likelihood that antibiotic prophylaxis for high-risk individuals is cost-effective and even cost-saving.[106] However, the possible impact of prophylactic antibiotics on the acquisition of resistant bacteria among the commensal microbiota is uncertain and therefore has not thus far been taken into account in cost-benefit and cost-effectiveness analyses of antibiotic prophylaxis.

SPECIFIC ISSUES IN PREVENTION OF INFECTIVE ENDOCARDITIS

Prevention of Health Care–Associated Infective Endocarditis

In addition to uncertainty regarding the efficacy of antibiotic prophylaxis of IE of dental origin, it should be taken into account that the

epidemiologic profile of IE has changed substantially since the 1960s, with a striking decrease in the proportion of IE due to oral streptococci. Currently, IE occurs most often in relatively elderly patients, with no known predisposing condition in 50% of the cases, and is most often caused by staphylococci—both *S. aureus* and coagulase-negative staphylococci—as a consequence of health care–associated bacteremias.[3,88] Most of these patients with HCAIE have underlying conditions such as diabetes mellitus, chronic hemodialysis, or intracardiac devices.

Efforts should therefore be made to prevent HCAIE, so prevention of health care–acquired bacteremia is a logical target. Reducing the rate of central line–associated bloodstream infections can be achieved with practice-changing interventions.[90,102] Bundled interventions to reduce catheter-related bloodstream infection in high-risk patients, such as those on hemodialysis, could translate to a significant reduction in the incidence of IE.[127]

Prevention of Infective Endocarditis Due to the Implantation of Cardiac Implantable Electronic Devices

Because the incidence of IE in patients with permanent pacemakers is about 10 times higher than in the general population,[128] and even higher in patients with defibrillators,[129] attention should also be paid to the prevention of IE associated with CIEDs, which include permanent pacemakers and implantable defibrillators. The efficacy of antibiotic prophylaxis with cefazolin given before the implantation of a CIED has been demonstrated in a large, randomized, double-blind, placebo-controlled trial that showed a significant difference in favor of the cefazolin arm (cefazolin—2 infections in 314 patients, 0.63%; placebo—11 infections in 335 patients, 3.28%; relative risk [RR], 0.19; $P = .016$).[130] Current guidelines from the AHA,[131] BSAC,[132] and Heart Rhythm Society (HRS)[133] recommend that an antibiotic that has demonstrated in vitro effectiveness against staphylococci be administered before CIED implantation. Either cefazolin or vancomycin can be used, the latter being preferred only in areas with high rates of oxacillin resistance among staphylococci and/or in patients allergic to cephalosporins. Additional preventive measures including a search for and treatment of occult or smoldering infection; intravenous antibiotic prophylaxis; intensive aseptic or antiseptic implantation techniques using double gloving, thorough skin preparation, and antiseptic irrigation of the wound and the inside pocket; skin closure with absorbable sutures; and a postoperative course of antibiotics may even further reduce the incidence of infections in CIED implants.[134] To determine whether such additional measures would further reduce the risk of CIED infection, the Prevention of Arrhythmia Device Infection Trial enrolled more than 12,500 patients who underwent generator change, system upgrade, or new CIED implantation and is now in the follow-up stage.[135]

Prevention of Infective Endocarditis Due to Valvuloplasty and Valve Replacement

Early-onset IE after valve surgery is caused by various microorganisms, including staphylococci, gram-negative bacteria, and rarely fungi (see Chapter 81). No single antibiotic regimen is effective against all these organisms, and the use of broad-spectrum antibiotics may itself predispose to superinfection with resistant organisms. Therefore, antibiotic prophylaxis of IE resulting from valve surgery should be limited to a short course of an antistaphylococcal agent, such as a cephalosporin or vancomycin, given with the primary objective of preventing wound infections and the secondary objective of potentially preventing IE.[9,136]

Postoperative bloodstream infections and prosthetic valve IE due to *Mycobacterium chimaera* were first reported in 2013 in Switzerland,[137] and later reported worldwide.[138] Investigations demonstrated that these were due to contaminated heater-cooler units used for intraoperative extracorporeal circulation.[138] Prevention of these life-threatening infections is based on strict adherence to monitoring and decontamination procedures.[139,140]

Prevention of Infective Endocarditis in Patients With Prosthetic Heart Valves

Extensive clinical experience has established that patients with prosthetic heart valves are at high risk for IE (see Chapters 81 and 82 and Table 83.2).[36,141] The high mortality and morbidity associated with prosthetic valve endocarditis and removal and replacement of infected prosthetic valves make its prevention a priority. Although the incidence of IE after cardiac surgery has decreased significantly in recent years, the risk of early-onset IE (defined as occurring within 60 days after valve replacement) remains approximately 0.3% to 0.5% and thereafter approximates 0.5% to 1% per year (see Chapter 82). It is important to recognize this risk and to take all possible steps to minimize it. Before elective valve replacement, the dental health of every patient should be evaluated and any necessary dental work completed. Postoperatively, the patient should maintain good oral hygiene. Consultation between the patient's dentist and physician is important to ensure appropriate antibiotic prophylaxis for routine dental procedures. Strict attention should be paid to prevention and follow-up of health care–associated infections, especially catheter-related bloodstream infections. In addition, personal "endocarditis prevention cards" have been made available in some countries to be given to patients with prosthetic valves.[47]

Late-onset prosthetic valve endocarditis, defined as onset 60 days or more after the operation, is most likely to be caused by organisms originating from the oral cavity or the skin and reaching the valve via the bloodstream, as for native valve endocarditis. Antibiotic prophylaxis of IE in the setting of dental procedures should therefore be directed primarily against streptococci.

Cardiac Assist Devices and Artificial Hearts

Cardiac assist devices and artificial hearts pose a high risk of infection, which increases with duration of use and often has catastrophic consequences; more than 50% of patients develop a device-related infection in the weeks after implantation, and mortality caused by these infections is also greater than 50%.[142] Multiple strategies to prevent infections have been used and/or recommended. Unfortunately, the paucity of clinical studies of such strategies makes assessment of their efficacy difficult.[143] Systemic antibiotics are routinely given before and up to 48 to 72 hours postoperatively.[144] There is no standard regimen for antibiotic prophylaxis. Vancomycin, levofloxacin, and rifampicin were used in the original REMATCH study.[145] Different antibiotic regimens have subsequently been used. In a survey of centers performing ventricular assist device (VAD) surgery, most centers used a three- to four-drug regimen that included vancomycin, rifampicin, fluconazole, and an antibiotic active against gram-negative bacteria.[146]

Cardiac Transplantation

Although cardiac transplantation in itself is not an indication for IE prophylaxis, patients with valvulopathy after transplantation are at increased risk for IE and also at high risk for an adverse outcome if IE develops, with mortality as high as 80%. Therefore the AHA recommends that such patients receive antibiotic prophylaxis when an invasive dental procedure at risk for causing IE is performed.[9]

Medical Diagnostic Procedures

Common diagnostic procedures, such as bronchoscopy, gastrointestinal endoscopy, imaging studies with contrast enhancement, biopsies, and transesophageal echocardiography, may occasionally induce bacteremia but carry minimal risk for causing IE.[147] Therefore administration of antibiotics to prevent IE during such procedures is no longer recommended.[9,10,92]

Invasive Procedures Involving Infected or Nonsterile Sites

Incisions, biopsies, or other invasive procedures involving skin, soft tissues, or other sites in the presence of active bacterial infection can cause bacteremia and, rarely, IE. Examples include instrumentation of the urinary tract during infection, device infections, and dermatologic procedures. Many such patients would be treated with antibiotics anyway, irrespective of any consideration of prevention of IE. In such a setting, it appears reasonable to choose an antibiotic regimen that could prevent IE in those susceptible patients with highest risk of adverse outcome from IE (see Table 83.3). If so, the choice of antibiotic would be dictated by the bacterial species most likely to be involved—*S.*

aureus for skin and soft tissue infections and enterococci for urinary tract infections.

Body piercing and tattooing are a cause for concern, particularly for individuals with increased susceptibility for the acquisition of IE. Case reports of IE after piercing and tattooing are increasing, particularly when piercing involves the tongue.[148,149] Patients should be informed about the hazards of piercing and tattooing, and these procedures should be discouraged not only in highest-risk patients, but also in those with native valve disease. If undertaken, procedures should be performed under sterile conditions, although antibiotic prophylaxis is not recommended.[10]

Prophylaxis of Infective Endocarditis for Children

Antibiotic prophylaxis of IE is currently recommended by the AHA only for those children with underlying conditions that are more likely to have an adverse outcome of IE, just as in other age groups (see Table 83.3). The AHA guidelines of 2014 have been endorsed by the American Academy of Pediatric Dentistry,[150] which issued new guidelines in 2017. These are essentially similar with regard to indications and antibiotic regimens to be used for antibiotic prophylaxis of IE.[151] If used, appropriate adjustment of antibiotic dosage for children is required (see Table 83.5).[151]

Anticoagulant Therapy

The initial nonbacterial thrombotic lesions that can develop on the surface of an endothelial lesion may also be targets for prophylaxis of IE, using antiplatelet and/or antithrombin agents. It has been shown in an animal model that a combination of aspirin plus ticlopidine, as well as abciximab, prevented IE due to *Streptococcus gordonii* and *S. aureus*. Dabigatran also showed efficacy against IE due to *S. aureus* but not to *S. gordonii,* but acenocoumarol was ineffective.[79] Aspirin plus ticlopidine protected rats from IE due to *Enterococcus faecalis* and *Streptococcus gallolyticus.*[152] Antiplatelet and direct antithrombin agents may therefore be useful in the prophylaxis of IE in humans, and their efficacy should be further evaluated.[153] In particular, the potential dual benefit of dabigatran should be evaluated for patients with prosthetic valves, who require lifelong anticoagulation and in whom *S. aureus* IE is associated with high mortality. Although the concept seems potentially promising, to date no guidelines have recommended antithrombotic interventions to prevent IE.

Medicolegal Liability Issues

In the past, issues related to prophylaxis of endocarditis have frequently led to allegations of professional negligence, especially in the United States and the United Kingdom.[154,155] The most common allegation concerns failure to provide antibiotic prophylaxis to a patient with a PCC who develops IE after a dental procedure. However, it is impossible to prove that any single procedure known to cause bacteremia was the proximate cause in a case of IE, or that the failure of a physician or dentist to administer antibiotics was the proximate cause of acquisition of IE in an individual patient. Another common issue arises from the lack of definitive data on the upper limit for the incubation period of IE,[53] although a review of case reports indicates that the incubation period for streptococcal IE does not exceed 2 weeks in most cases.[53]

Recently, two widows in the United Kingdom whose husbands died from IE after dental scaling petitioned NICE, which then significantly altered its guidelines by adding a single word to the main recommendation, which now reads "Antibiotic prophylaxis against IE is not recommended *routinely* for people undergoing dental procedures."[156] The addition of the word *routinely* clearly implies that in individual cases, antibiotic prophylaxis may be appropriate. This subtle modification also places a new burden on UK clinicians, who now must identify patients at increased risk of IE, explain the risk and the ways in which it can be reduced, including antibiotic prophylaxis, and then help them decide whether they want antibiotic prophylaxis or not.[157]

A reasonable standard of care requires that health care professionals dealing with this question be aware of the risk factors for IE, and of current practice guidelines. They should inform susceptible patients of the risk—albeit small—that they may develop IE, and of the measures that they and their health care providers can take to reduce this risk, as described in this chapter. In view of the recent guidelines that strictly limit or eliminate antibiotic prophylaxis for IE, an informed decision by a health care professional not to prescribe antibiotic prophylaxis should not be construed as negligence, whatever the clinical outcome.

NEW HORIZONS FOR ANTIBIOTIC PROPHYLAXIS OF INFECTIVE ENDOCARDITIS

Oral Hygiene

It has been shown that poor oral hygiene is associated with a higher risk of bacteremia due to IE-causing organisms.[82] Therefore, conventional wisdom has promoted high oral hygiene standards as a way to prevent IE in at-risk patients. It is known that tooth brushing induces bacteremia[98] and may be associated with an increased risk of oral streptococcal IE. Nevertheless, it seems likely that in the long term, regular daily tooth brushing would be better than no tooth brushing in minimizing the risk of IE. Likewise, other dental hygiene procedures such as scaling and flossing have been shown to induce bacteremia, but little is known regarding the risk of IE associated with these two procedures. This risk has been estimated through an assessor-blinded case-control study in which cases and controls had definite IE caused either by oral streptococci or by nonoral pathogens, respectively. This study showed that in adjusted analysis, cases were more likely than controls to use toothpicks, dental water jets, or interdental and/or dental brushes, and to have had dental procedures during the prior 3 months, whereas they were less likely to brush their teeth after meals.[20]

Because oral health is of particular importance in patients with heart valve abnormalities owing to the risk of IE, a multidisciplinary working group reviewed the literature to propose individualized approaches for the evaluation and management of orodental status in patients with valvular disease at risk of IE. The main consequence of such management is the decrease in the number of contraindicated dental procedures. Conservative dental procedures can be performed before elective valvular interventions and during follow-up, even in patients at high risk of IE. Implant placement is no longer contraindicated in patients at high risk of IE, but the decision should take into account general and local factors associated with a risk of infectious complications and implant failure.[158]

"Big Data" as a Vehicle to Assess the Usefulness of Infective Endocarditis Prevention Measures

Recently a nationwide population-based cohort study using the French national health insurance administrative data linked with the national hospital discharge database assessed the relationship between invasive dental procedures and IE due to oral streptococci among people with prosthetic heart valves. The cohort included 138,876 adults with prosthetic heart valves (285,034 person-years), 69,303 of whom (49.9%) underwent at least one dental procedure. Among the 396,615 dental procedures performed, 103,463 (26.0%) were invasive and therefore presented a possible indication for antibiotic prophylaxis, which was performed in 52,280 (50.5%). With a median follow-up of 1.7 years, 267 people developed IE due to oral streptococci (incidence rate, 93.7 per 100,000 person-years; 95% CI, 82.4–104.9). Compared with nonexposure periods, no significantly increased rate of oral streptococcal IE endocarditis was observed during the 3 months after an invasive dental procedure (RR, 1.25; 95% CI, 0.82–1.82; $P = .26$) and after an invasive dental procedure without antibiotic prophylaxis (RR, 1.57; 95% CI, 0.90–2.53; $P = .08$).[21] Beyond the main conclusion—that the risk of IE after invasive dental procedures is low even in patients with prosthetic heart valves and could therefore be reduced only marginally by antibiotic prophylaxis—this study highlighted the potential opportunity to use existing "big data" to conduct a randomized, registry-based trial to assess the efficacy and usefulness of antibiotic prophylaxis of IE in humans, in a feasible and affordable fashion. Such registry-based randomized clinical trials on other issues have been conducted successfully in recent years, providing answers that would not have been obtained otherwise.[159,160,161,162]

Novel Approaches

Given the difficulty of curing device-related IE caused by biofilm-forming strains of multidrug-resistant *S. aureus,* novel strategies must be identified,

both for preventing and for treating this life-threatening condition. For prevention, targeting the inhibition of bacterial adhesion to both living and inert surfaces at the initial stage, thus reducing the chances of further development and establishment of biofilms, might be possible. Inhibition of bacterial adhesion at the time of intracardiac device insertion could be key and may be achieved through use of implants coated with various adhesion inhibitors. To date antibiotic-, silver ion–, or silver nanoparticle–coated implants, which can inhibit biofilm formation in vitro, have failed to prove to be both effective and well tolerated in humans. Indeed, enthusiasm for antibacterial coatings has been tempered by experience with the Silzone valve (St. Jude Medical, St. Paul, MN), which had a silver-coated sewing ring but had to be recalled within 3 years of its release in 1997 owing to an increased risk of thrombosis and paravalvular leaks.[163,164] However, novel strategies to target adherence are currently being evaluated.[165]

Future prevention strategies may also include vaccines. Human studies using vaccines targeting causes of IE have been aimed at *S. aureus, Pseudomonas aeruginosa,* and group B streptococci. Two candidate *S. aureus* vaccines evaluated in phase III clinical trials failed to demonstrate efficacy, with one failing to reach an efficacy end point of prevention of *S. aureus* bacteremia in patients undergoing hemodialysis,[166] and another leading to increased mortality in patients undergoing median sternotomy who developed staphylococcal infection.[167] Despite these negative results, other candidate *S. aureus* vaccines are currently being evaluated in humans. A new composite vaccine targeting five components of *S. aureus* has been shown to be highly protective in mouse models,[168] as has a recombinant *Lactococcus lactis* expressing ClfA or FnbpA in rats.[169] The rapid and robust human functional immune responses induced by other candidate vaccines support their further development for the prevention of *S. aureus* disease in adults.[170,171]

CONCLUSION

Although many relevant factors have changed or evolved over time, prevention of IE remains important today. Because no randomized clinical trial to confirm the efficacy and safety of antibiotic prophylaxis has ever been conducted, it is likely that the debate around indications for antibiotic prophylaxis of IE will continue for years to come. In the meantime, it is reasonable to recommend antibiotic prophylaxis for patients at high risk of IE and its complications before they undergo high-risk dental procedures. All patients at risk should maintain good oral hygiene. Prevention of HCAIE should also be targeted, through prevention of health care–associated bacteremias and antibiotic prophylaxis before the implantation of cardiac implantable electronic devices. Prevention of *S. aureus* IE has become a priority; in the future this might be achieved with a vaccine, and candidate *S. aureus* vaccines are currently being evaluated in humans.

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The complete reference list is available online at Expert Consult.

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84 Myocarditis and Pericarditis

Kirk U. Knowlton, Jeffrey L. Anderson, Maria C. Savoia, and Michael N. Oxman

SHORT VIEW SUMMARY

MYOCARDITIS

- Inflammation of the myocardium, which is clinically manifested by chest pain, arrhythmias, and congestive heart failure (CHF), individually or in combination

Etiologic Agents

- Most commonly associated with viral infections, particularly enteroviruses, adenoviruses, human herpesvirus 6, and dengue viruses (see Table 84.1)
- Occasionally caused by bacteria, as a result of bacteremia, direct extension from a contiguous focus, or a bacterial toxin
- Caused by *Trypanosoma cruzi,* the cause of Chagas' disease, which is prevalent in South and Central America

Diagnosis

- In the setting of clinical suspicion, elevation of cardiac enzymes, electrocardiographic changes (nonspecific), echocardiography, and cardiac magnetic resonance imaging are helpful.
- Evidence of coincident viral infection, by culture, detection of viral DNA or RNA in peripheral samples or serology, is circumstantial.
- Endomyocardial biopsy can provide a definitive diagnosis, but sampling errors limit its utility.

Treatment

- Supportive care and management of CHF are essential.
- The benefit of immunosuppressive therapy is not established.
- The efficacy of intravenous immunoglobulin therapy is also not established.

PERICARDITIS

- Inflammation of the pericardium is clinically manifested by chest pain, pericardial friction rub, and pericardial effusion. These may be present individually or in combination. Monitoring for cardiac tamponade is important.

Etiologic Agents

- Enteroviruses are most common, but other viruses may sometimes be responsible (see Table 84.3).
- Bacteria rarely may cause purulent pericarditis, usually as a complication of pneumonia.
- *Mycobacterium tuberculosis* can cause pericarditis, usually as a complication of pulmonary tuberculosis. This is a major problem in Africa in association with acquired immunodeficiency syndrome.

Diagnosis

- Etiology is often undetermined in individual cases.
- Pericardiocentesis may yield an etiologic agent but is negative in the majority of patients.
- Evidence of viral infection by detection in peripheral samples or by serology provides only circumstantial evidence of possible etiology.
- Percutaneous pericardial biopsy or pericardiotomy with biopsy and drainage increase the diagnostic yield.

Treatment

- For presumed viral or idiopathic pericarditis, analgesic treatment with nonsteroidal antiinflammatory drugs (NSAIDs), together with bed rest, is often successful in relieving symptoms. NSAIDs are generally continued for 1 to 2 weeks or until symptoms resolve.
- Colchicine given with NSAIDs has been found to improve rate of recovery and reduce recurrence.
- Purulent pericarditis usually requires drainage in addition to appropriate antibiotics.
- Tuberculous pericarditis requires appropriate antituberculous therapy (see Chapter 249); concomitant administration of corticosteroids reduces the development of constrictive pericarditis and the need for repeated pericardiocentesis.

Inflammatory processes affecting the heart frequently involve both the myocardium (myocarditis) and the pericardium (pericarditis). However, involvement of one or the other usually predominates, and the syndromes of myocarditis and pericarditis are sufficiently distinct in clinical presentation, etiology, and pathophysiology to warrant separate consideration.

MYOCARDITIS

Myocarditis, literally "inflammation of the myocardium," is a protean disease with a wide variety of infectious (Table 84.1) and noninfectious (Table 84.2) causes. Postmortem examinations reveal evidence of previously unsuspected myocarditis in 1% to 4% of unselected cases,[1–3] with a higher incidence in young persons who have died suddenly.[4–7] The advent of modern molecular diagnostics has revealed that there are forms of infectious viral heart disease that do not appear to be associated with a typical inflammatory infiltrate.[8] Hence the term "myocarditis" may not literally describe the full gamut of infectious diseases of the myocardium. However, in clinical practice and in this chapter the term *myocarditis* is used to describe a range of infectious and inflammatory heart diseases that affect cardiac muscle and function, either directly or indirectly. This chapter focuses on infectious causes of myocarditis, recognizing that the etiologic agent remains unidentified in a significant percentage of patients.

The diagnosis of infectious myocarditis is usually considered when unexplained heart failure, chest pain, or arrhythmias occur after an upper respiratory tract infection or another presumed viral infection, or in the setting of a systemic febrile illness.[9] In many cases, however, the antecedent systemic illness is mild or long forgotten. In addition, myocarditis has been found histologically in 10% to 20% of cases of idiopathic dilated cardiomyopathy (DCM).[10–12] Because of the wide spectrum of clinical presentations, the frequent occurrence of asymptomatic cases, the paucity of noninvasive biologic markers, the limited sensitivity of histopathologic diagnosis, and problems with the laboratory identification of etiologic agents, the true incidence of myocarditis and infection-mediated cardiomyopathy may be significantly underestimated.[13,14]

In myocarditis the inflammatory process may affect myocytes, vascular elements, the conduction system, autonomic nerves, or the interstitium. In addition, it is not unusual for both the pericardium and myocardium to be affected at the same time. One or more of at least four mechanisms appears to be involved in the pathogenesis of myocarditis: (1) direct damage to cardiomyocytes by an infectious agent; (2) damage to myocytes

TABLE 84.1 Infectious Causes of Myocarditis

Viruses

Coxsackie B viruses[12,26,29,30,34–37,220,243,247,287–300,302–304,308,389,391,392,527–529]
Coxsackie A viruses[26,29,30,34,37,244,251,287,290,308,390]
Adenoviruses[8,27,28,248,249,251,287,530–533]
Echoviruses[26,287,534–536]
Nonpolio enteroviruses[8,12,26,37,287–289,291,292,302,369,528,530,537,538]
Parvovirus B19[28,32,41,539–543]
Polioviruses[24,544,545]
Rabies virus[546–548]
Mumps virus[19,549–551]
Rubeola (measles) virus[21–23]
Influenza A and B viruses[20,552–555]
Rubella virus[556,557]
Dengue viruses[44,558,559]
Chikungunya virus[559]
Yellow fever virus[560]
Argentine hemorrhagic fever virus (Junin virus)[560,561]
Bolivian hemorrhagic fever virus (Machupo virus)[561]
Lymphocytic choriomeningitis virus[562]
Lassa fever virus[563–565]
Varicella-zoster virus[566–574]
Human cytomegalovirus[26,59,297,575–580]
Epstein-Barr virus[8,581–588]
Human herpesvirus 6[589,590]
Herpes simplex virus[26,250,591,592]
Variola virus[593]
Vaccinia virus[594–598]
Hepatitis B virus[599–601]
Hepatitis C virus[602–604]
Respiratory syncytial virus[26,605,606]
Human immunodeficiency virus[52–54,59–61,65,66,69–72,166,477,607]

Bacteria and Rickettsiae

Brucella[91,392]
Campylobacter[88–90]
Corynebacterium diphtheriae[75–77]
Clostridium perfringens[78,79]
Francisella tularensis[92,93]
Neisseria meningitidis[82–84]
Salmonella[85–87]
Shigella[608]
Streptococcus pyogenes[94,95]
Staphylococcus aureus[96]
Listeria monocytogenes[98,99]
Vibrio cholerae[609]
Mycobacterium tuberculosis[101,610,611]
Legionella pneumophila[102]
Mycoplasma pneumoniae[103–107]
Chlamydia psittaci[108,109]
Chlamydia pneumoniae[108,110,111]
Rickettsia rickettsii[81,112]
Rickettsia prowazekii[81,113]
Rickettsia (Orientia) tsutsugamushi[81,114,115]
Coxiella burnetii[612,613]
Ehrlichia[614,615]
Borrelia burgdorferi[118–127]
Tropheryma whippelii[616]
Ureaplasma spp.[617]

Fungi

Aspergillus[150–155]
Candida spp.[150–152,156,157]
Blastomyces[465]
Coccidioides immitis[151,461]
Cryptococcus neoformans[151,152,158,159]
Histoplasma capsulatum[457]

Parasites[618]

Trypanosoma cruzi[128,129,135–137,223,224,619,620]
Trypanosoma gambiense[139]
Trypanosoma rhodesiense[139]
Trichinella spiralis[140–142]
Toxoplasma gondii[143–149]
Toxocara canis[621,622]

TABLE 84.2 Noninfectious Causes of Myocarditis

Checkpoint inhibitors[306]
Collagen vascular disease[285,623]
- Systemic lupus erythematosus[624]
- Systemic sclerosis[625–627]
- Rheumatoid arthritis[628,629]
- Dermatomyositis/polymyositis[630,631]
- Still's disease[632]

Thyrotoxicosis[285]
Thrombotic thrombocytopenic purpura[633]
Pheochromocytoma[623]
Peripartum[634]
Radiation induced[635–637]
Drug induced (directly toxic)[285,623,638]
- Cocaine
- Alcohol
- Emetine
- Catecholamines
- Arsenic
- Lead
- Cyclophosphamide
- Daunorubicin
- Adriamycin

Drug induced (hypersensitivity)[623,639]
- Methyldopa
- Sulfonamides
- Tetracycline

Scorpion, wasp, and spider stings[623,640]
Etiologic agents not yet identified
- Kawasaki disease[641]
- Giant cell myocarditis[642]
- Sarcoid[643,644]

because of a generalized cytokine or cell-mediated immune response; (3) cytotoxicity caused by viral antigen-specific immune reactions directed against infected cells; or (4) cytotoxicity caused by a circulating toxin. Damage to the vascular endothelium may also result in indirect myocardial injury.[15,16] Research has revealed the complexity of the mechanisms involved in cardiac myocyte injury, especially injury caused by enteroviruses, and has also suggested targets for intervention (Fig. 84.1).[17,18]

Etiologic Agents

Almost every infectious agent is capable of causing myocarditis (see Table 84.1), but viruses are the most important infectious causes of myocarditis in the United States and Western Europe, and many cases of idiopathic myocarditis are assumed to be viral in origin. Long before the era of modern virology, pericardial and myocardial involvement was recognized during outbreaks of mumps,[19] influenza,[20] measles,[21–23] poliomyelitis,[24] and enterovirus-associated pleurodynia.[25] Adenoviruses,[8,26–28] enteroviruses,[29,30] and parvovirus B19[8,26,31–33] have been implicated as major causes of myocarditis. Among the enteroviruses, some of the most commonly identified are group B coxsackieviruses,[12,34–37] and their presence in biopsy samples of patients with myocarditis has been shown by direct immunostaining.[38]

A study using real-time polymerase chain reaction (PCR) and reverse-transcription PCR (RT-PCR) assays to identify viruses in myocardial tissue from 624 children and adults with acute myocarditis and 149 with DCM reported adenoviruses in 23% of the patients with acute myocarditis and 12% of the patients with DCM. Enterovirus genomes were detected in 14% of the patients with acute myocarditis and in 8% of the patients with DCM. In addition, human cytomegalovirus (HCMV), parvovirus B19 (PVB19), influenza A virus, Epstein-Barr virus (EBV), herpes simplex virus (HSV), and respiratory syncytial virus were each identified in a small number of the patients with acute myocarditis but not in any with DCM.[26] A similar study of myocardial tissue from 245 adults with "idiopathic" DCM identified viral genomes in 67.4%, PVB19 in 51.4%, human herpesvirus 6 (HHV-6) in 21.6%, enteroviruses in 9.4%, adenoviruses in 1.6%, EBV in 2%, and HCMV in 0.8%; 27.3% of the positive samples had multiple agents.[8] In a similar study of cardiac tissue obtained by endomyocardial biopsy (EMB) from 24 consecutive patients with acute myocarditis with chest pain in whom myocardial infarction was excluded, 12 (50%) were positive for PVB19, 3 for an enterovirus, and 2 for an adenovirus.[32] Four of the 6 patients in whom coronary spasm could be induced were PVB19 positive. Only 1 of the 24 (1 of 3 that were enterovirus positive) had histopathologic evidence of myocarditis according to the Dallas Criteria (see later).

The marked increase in the detection of PVB19 and HHV-6 in patients with acute myocarditis or DCM during the past decades is noteworthy.[8,26,28,32] However, given the high prevalence of PVB19 and HHV-6

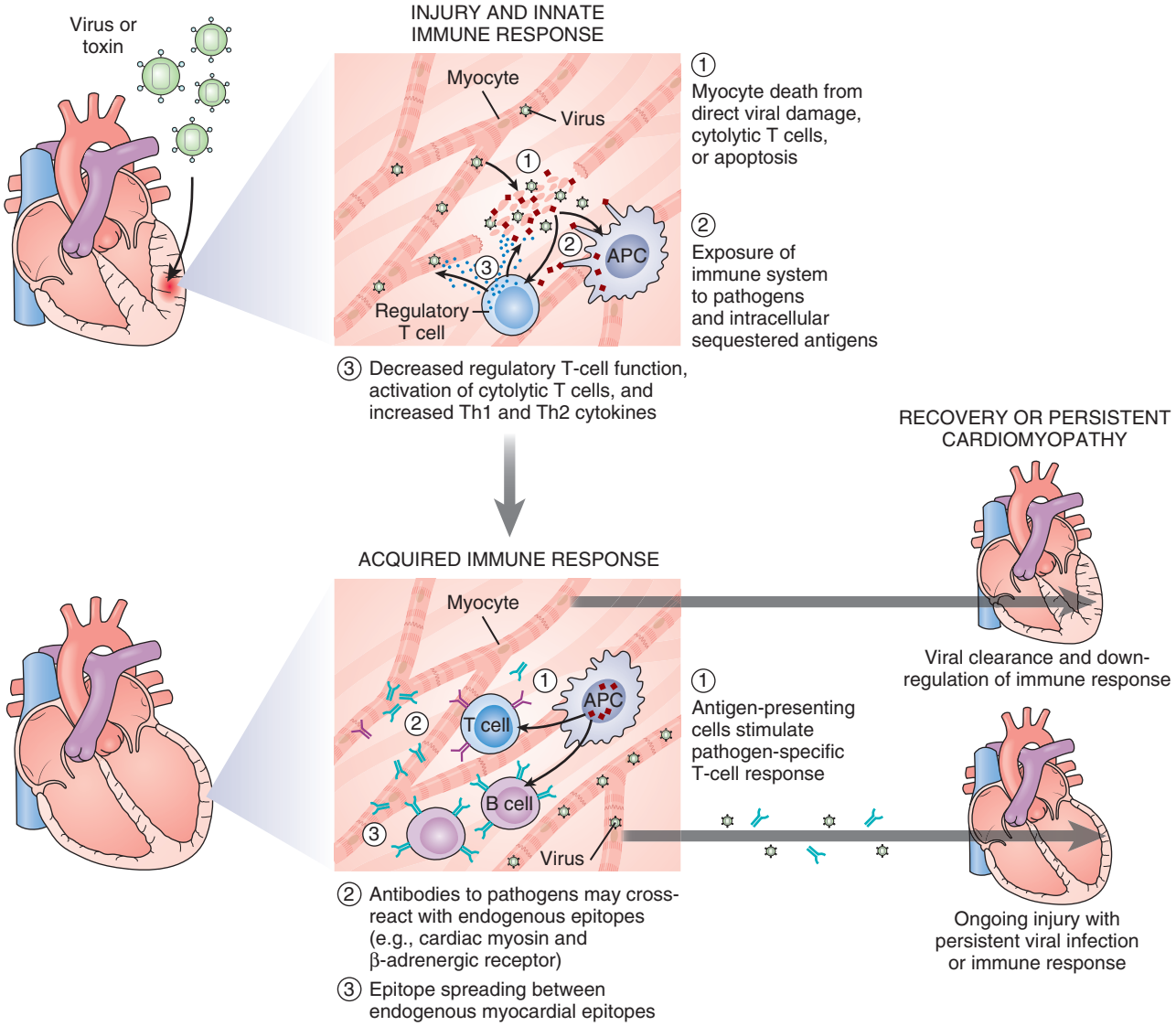

FIG. 84.1 Summary of the cellular and molecular pathogenesis of viral and autoimmune myocarditis, derived primarily from animal models. Three stages are summarized. Acute injury from direct viral infection and innate immune reaction leads to myocardial damage. Specific immunity mediated by T lymphocytes and antibodies is directed against the pathogen and potential endogenous heart epitopes. The pathogen may be cleared, and the immune reaction may decrease with improvement in cardiac function and few sequelae. In some patients persistent virus and inflammation contribute to chronic cardiomyopathy. *APC,* Antigen-presenting cell. *(Modified from Cooper LT. Myocarditis.* N Engl J Med. *2009;360:1526–1538.)*

in the general population, their pathogenic role remains to be proven. For example, in one study PVB19 was detectable by immunohistologic analysis in 65% of patients with acute myocarditis, 35% of patients with DCM, and 8% of noninflamed control hearts. PVB19 load was then assessed by genome copy numbers in the samples that were positive for PVB19 on immunohistologic analysis. PVB19 load was higher in patients with acute myocarditis, followed by those with DCM, and lowest in the patients with normal hearts without inflammation.[39] Viral RNA replicative intermediates were only detected in patients with inflamed hearts. It is important to note that in this study and others, PVB19 was found in endothelial cells and not myocardial cells. Verdonschot and colleagues[40] recently provided a comprehensive review of the relevance of cardiac PVB19 in myocarditis and dilated cardiomyopathy. Recognizing the controversy regarding the exact role of PVB19 in myocarditis, they conclude that PVB19 may be etiologically relevant when the viral load is high and PVB19 is actively replicating and in the presence of other cardiotropic viruses. An alternative possibility is that the presence of PVB19 may be a marker of inflammation. It is important to recognize that, especially with highly prevalent viruses, such as PVB19, HHV-6, and even HCMV and EBV, viral genomes detected in myocardial tissue by sensitive assays may have been carried into the myocardium by infiltrating inflammatory cells and have played no role in the etiology of the myocarditis or DCM.

There is also considerable temporal and geographic variation in the prevalence of infections caused by various adenoviruses and enteroviruses, as well as marked seasonal variation in the prevalence of infections caused by these and other viruses. Moreover, the prevalence of infections caused by some viruses, for example, adenoviruses and PVB19, is greater in children than in adults.[12,26,27,41] In consequence, the relative frequency with which different viruses are identified in acute myocarditis and DCM can be expected to vary from study to study and over time.

Dengue is the most prevalent mosquito-borne virus infection worldwide. It is caused by one of four distinct but antigenically related members of the Flaviviridae family, designated dengue virus serotypes 1 through 4.[42,43] The female *Aedes aegyptus* is the primary vector of dengue; *Aedes albopictus,* a secondary vector in Asia that is tolerant to temperatures below freezing, has spread to North America and Europe.[42] Dengue is endemic in more than 100 countries on every continent except Antarctica; approximately half the world's population is at risk of dengue virus infection, and more than a million cases occur each

year. Since 2010, local transmission has been reported in several countries in Europe and in China, and the disease is now endemic in Florida and the southern United States along the Mexican border. In 2012, more than 1.6 million cases of dengue were reported in the Americas.[42]

Dengue has been reported to cause a variety of cardiac manifestations, ranging from transient arrhythmias to cardiogenic shock and fatal myocarditis.[44–47] Cardiac myocyte necrosis has been observed as a result of direct dengue virus infection, and vascular endothelial cells also appear to be susceptible to infection.[48–50] Some dengue virus infections mimic acute myocardial infarction.[51]

Human immunodeficiency virus (HIV) infection, in advanced stages with high virus titers, is associated with a high incidence of cardiomyopathy. An incidence of cardiomyopathy of more than 50% has been documented in HIV-infected patients during their lifetime,[52–58] and evaluations of patients with acquired immunodeficiency syndrome (AIDS) have shown that cardiac dysfunction is highest in those with the most advanced disease.[59–61] However, many of these observations were made before implementation of antiretroviral therapy (ART). With the improved survival of HIV-infected patients associated with ART, the incidence of heart disease has increased, reflecting a higher incidence of coronary artery rather than myocardial disease. As might be expected, in areas such as sub-Saharan Africa, where ART is not widely administered, there is a significantly higher incidence of cardiomyopathy and myocarditis than that seen in developed parts of the world.[62,63] In developed countries in patients taking antiretrovirals, diastolic dysfunction is more common than systolic dysfunction.[64]

Although it is well accepted that HIV-infected patients can develop cardiomyopathy, the pathogenesis is not clear. Myocytes lack CD4 receptors, and despite the fact that HIV has been cultured from EMB samples[65–67] and identified by Southern blot analysis,[66,68] data are not convincing that HIV directly infects cardiac myocytes to induce cardiac dysfunction. The isolation of other known cardiotropic viruses from AIDS patients is frequently reported.[61,67,69,70] Malnutrition may also be a factor contributing to cardiac dysfunction in AIDS, and malnutrition and wasting are important independent predictors of cardiac morbidity and mortality.[71,72] Autoantibodies against myocardial proteins have been identified in some AIDS patients with cardiac dysfunction.[58] Immune dysregulation and cytokine production by infected monocytes and macrophages may be responsible for some cardiac pathology.[73,74]

Other viruses that have been implicated as causes of myocarditis or myopericarditis are listed in Table 84.1.

Nonviral Pathogens That Cause Myocarditis

Many nonviral pathogens cause myocarditis. For example, myocarditis is the most common cause of death in diphtheria[75–77]; the toxin produced by *Corynebacterium diphtheriae* severely damages the myocardium and conduction system. The cardiac damage seen in patients with *Clostridium perfringens* infection may be the result of toxin, metastatic abscess formation, or both.[78,79] The immunologically mediated carditis associated with acute rheumatic fever[80] is discussed in Chapter 198.

Invasion of the bloodstream by any bacterial pathogen may result in metastatic foci in the myocardium,[81] and myocarditis has been recognized in the course of meningococcemia,[82–84] salmonellosis,[85–87] *Campylobacter* infection,[88–90] brucellosis,[91] tularemia,[92,93] and bacteremias caused by streptococci,[94,95] staphylococci,[96,97] and *Listeria monocytogenes.*[98–100] More commonly, bacteria invade the myocardium as a complication of endocarditis by contiguous spread from infected valvular tissue or via septic embolization of the coronary arteries.[81,96,97]

Tuberculous myocarditis can occur without systemic symptoms and can be responsible for sudden cardiac death, especially in young people.[101] However, most tuberculous infections of the heart involve the pericardium (see later).

Myocarditis is a rare complication during *Legionella* infection.[102] It has also been observed in the course of *Mycoplasma pneumoniae,*[103–107] *Chlamydia psittaci*,[108,109] and *Chlamydia pneumoniae*[108,110,111] infections, and is commonly seen in rickettsial infections,[81,112–115] especially scrub typhus.[81,114,115] Approximately 10% to 16% of patients with Lyme disease develop cardiac abnormalities, most commonly conduction system disturbances (for review, see references 117–119). A recent pathology series showed direct myocardial involvement with *Borrelia burgdorferi.*[116] Lyme carditis usually resolves completely with no long-term sequelae, although cases of fulminant myocarditis have been reported.[117–127]

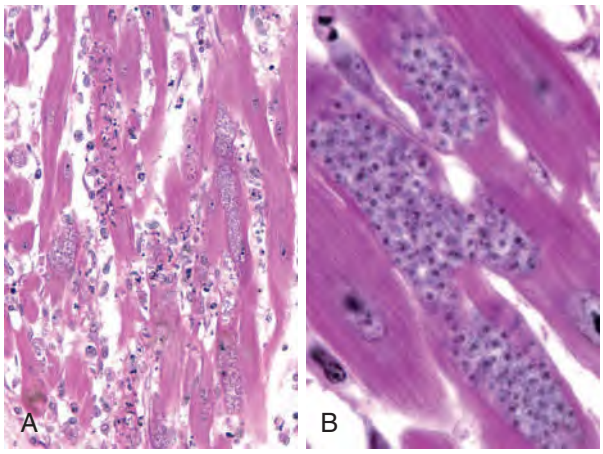

FIG. 84.2 *Trypanosoma cruzi* amastigotes in cardiac muscle stained with hematoxylin and eosin. Low-power magnification (A) and high-power magnification (B). Amastigotes are observed within cardiac myocytes. (Courtesy John T. Sullivan, University of San Francisco.)

In South America a principal agent responsible for myocarditis and heart failure is *Trypanosoma cruzi,* the protozoan that causes Chagas' disease (Fig. 84.2). This is discussed in greater detail in Chapter 276. Chagas' disease is a common cause of DCM worldwide, but the incidence in endemic areas is decreasing substantially.[128–131] In the 1980s it was estimated that there were 17 million people who were infected; these estimates had fallen to 5.7 million people by 2010.[128,131,132] Although the incidence is decreasing in endemic areas, there has been an increase in developed, nonendemic areas due to immigration.[128] The triatome vector that transmits the parasite is found in Texas and, although rare, autochthonous vector-borne transmission of *T. cruzi* in Texas has been reported.[133,134] Initial infection by *T. cruzi* is often asymptomatic or accompanied by a low-grade febrile illness. However, a subset of patients develop an acute illness complicated by myocarditis.[129,135,136] Myocarditis is the principal manifestation of chronic Chagas' disease, which occurs in approximately 30% to 40% of infected individuals. These patients typically have cardiomegaly with congestive heart failure (CHF) and a high incidence of thinning and bulging of the ventricular apex. The cardiomyopathy is often associated with conduction disturbances.[128,136–138] *Trypanosoma gambiense* and *Trypanosoma rhodesiense,* the agents of African trypanosomiasis, may also affect the heart with similar results, but central nervous system findings usually predominate in infections with those agents.[139]

Myocarditis is also observed in trichinosis[140–142] and is responsible for the occasional deaths that occur in severe infections. Myocarditis is common in disseminated toxoplasmosis,[143–149] and systemic aspergillosis and candidiasis may also involve the heart.[150–157]

In immunocompromised patients, myocarditis occurs as a consequence of a number of disseminated infections. Cryptococcal, *Toxoplasma,* and *Aspergillus* myocarditis have been reported in patients with AIDS.[145–147,155,158,159]

Pathology and Pathogenesis

Most of our knowledge about the pathogenesis of viral myocarditis comes from studies of coxsackievirus B3 (CVB3) and encephalomyocarditis virus infection in murine models. Susceptibility to CVB3-induced myocarditis in mice is age dependent and genetically determined, and mechanisms of injury vary in different mouse strains.[160–164] Myocardial pathology also depends on the infectious agent, the pathogenic mechanism involved, and the duration of the process. Fung and colleagues[165] describe the broad spectrum of myocarditis and evolving knowledge of the pathogenic role of viruses and other mechanisms of disease, in an ongoing effort to identify and evaluate new therapeutic interventions.

Early in many viral infections in humans, scattered hypereosinophilic myofibers, widespread edema, and only a few inflammatory cells may

be present. Later, loss of striation, nuclear degeneration, and fragmentation of myofibers can be seen. Degenerating or partially necrotic myofibers are usually surrounded by natural killer (NK) cells and macrophages, and later by T lymphocytes. The types of lymphocytes and macrophages that are present vary depending on the etiologic agent and the stage of infection.[166–169] Polymorphonuclear leukocytes are occasionally seen.[4] Return to normal cardiac function usually precedes resolution of the histologic abnormalities.[170] The acute process may resolve completely; healing and chronicity are reflected by the development of interstitial fibrosis and loss of myofibers.[171]

Coxsackieviruses and adenoviruses both use the coxsackievirus and adenovirus receptor (CAR) for cell entry.[172] Cardiac-specific deletion of CAR protects mice from development of contractile dysfunction and inflammation in the heart on infection with CVB3.[173,174] Immunohistochemical analysis revealed higher levels of expression of CAR in the hearts of patients with DCM, although no cause-and-effect relationship between CAR expression and DCM was established.[175]

Direct viral cytotoxicity plays a role in myocardial damage in mice and humans,[3,4,176,177] and prolonged viral persistence in the myocardium is associated with development of DCM. This notion was further supported by a clinical study of patients with biopsy-proven viral myocarditis in which prolonged viral persistence was associated with persistent immune cell infiltration in the myocardium and worsening of cardiac function on follow-up echocardiographic examination.[178]

At the molecular level, cytotoxicity by CVB3 can be partially explained by its production of protease 2A. This viral protease, the normal function of which is to cleave the viral polyprotein, also cleaves the subsarcolemmal protein dystrophin at a specific site. This destabilizes the dystrophin-glycoprotein complex, thereby facilitating viral propagation in the heart and causing cardiac myocyte dysfunction.[179–182] Knockin mutation of a protease 2A cleavage site in dystrophin that inhibits protease 2A cleavage decreases viral titer, disruption of the cell membrane, and severity of myocarditis.[183] Enteroviral proteases can cleave other host proteins that may have a direct effect on virus-mediated pathogenesis.[165] It has also been demonstrated that inducible, transgenic expression of CVB protease 2A alone in the myocardium can induce a cardiomyopathy that is associated with disruption of the sarcolemmal membrane.[184] It is also possible that loss of dystrophin in patients with Duchenne muscular dystrophy leads to increased susceptibility to myocarditis and, subsequently, to cardiomyopathy. There are studies showing that magnetic resonance imaging (MRI) or histologic evidence of myocardial inflammation in patients with Duchenne muscular dystrophy portends a higher risk of developing heart failure.[185] Recently, it has been shown in patients with acute myocarditis that there is a higher incidence of homozygous or compound heterozygous mutations in genes that have been implicated in cardiomyopathy, including several cytoskeletal genes, which provides additional insight into the mechanisms associated with increased susceptibility to myocarditis in humans.[186]

The pathogenesis of any viral infection is tightly linked to host immune responses. On one hand, inability to mount effective immune responses to myocardial infection can lead to increased viral replication, viral persistence, chronic infection, or a combination of these that may lead to DCM.[178] On the other hand, excessive activation of the immune system can cause immunopathologic myocardial damage and result in cardiomyopathy.

Host response to a pathogen is characterized by an early innate immune response, which is followed by an adaptive, antigen-specific immune response that includes antibodies and antigen-specific lymphocytes. Because the innate immune response is not antigen specific, it occurs more quickly and can be characterized by activation of a cytokine response and infiltration of NK cells. The innate immune response involves the activity of Toll-like receptors (TLRs), interferons (IFNs), Janus kinase–signal transducer and activator of transcription signaling pathway (JAK-STAT), and interleukins (ILs).[165]

The members of TLR family, also known as sentinels of the immune system, are implicated in the development of viral myocarditis. Mice lacking TLR3 have significantly higher mortality after infection with enteroviruses.[187] Genetic analysis of 57 patients with biopsy-proven myocarditis or DCM with biopsies positive for enterovirus RNA revealed a higher frequency of certain TLR3 mutations when compared with healthy matched control subjects.[188] Infection of stable cell lines expressing mutant TLR3 had minimal effect on induction of type I IFN when compared with the cells expressing wild-type TLR3. However, viral titers in supernatants from infected mutant TLR3-expressing cells were found to be significantly higher than in supernatants from cells expressing wild-type TLR3.

Several rodent experiments have highlighted the role of IFNs as the first line of defense against cardiotropic viruses.[189,190] Indirect evidence has also suggested that deficiency in IFN production predisposes to development of DCM after infection with cardiotropic viruses. One study found that stimulation by staphylococcal enterotoxin B elicited a smaller subset of IFN-γ–producing peripheral CD4 lymphocytes in patients with DCM when compared with healthy donors.[191]

IL-1, tumor necrosis factor (TNF), and bacterial lipopolysaccharide all enhance autoimmune injury and cause resistant mice to become susceptible to viral myocarditis.[192] Data demonstrating enhanced expression of intracellular adhesion molecule (ICAM)-1 in murine myocytes, as well as both type I and type II major histocompatibility complex (MHC) antigens in human myocarditis, also support the theory that autoimmunity can play a role in the development of viral myocarditis.[193–196]

Adaptive immunity comes into play at later stages of viral myocarditis, late in the first week and during the second week after infection. Activated lymphocytes help eliminate infected cardiomyocytes but can also cause "an innocent bystander effect" with excessive tissue damage, leading to cardiomyopathy. Cytotoxic T cells recognize both infected and uninfected myocytes, and their presence correlates with the degree of myocardial damage.[197–200] Variants of CVB3 that do not evoke cytotoxic T cells directed against both infected and uninfected myocytes fail to cause myocarditis, even though they are similar to myocarditic strains in their ability to replicate and stimulate neutralizing antibodies.[201] Mice lacking *p56lck*, a tyrosine kinase essential for T-cell activation, are protected against CVB3 myocarditis. After acquiring CVB3 infection, animals heterozygous for *p56lck* developed histopathologic changes consistent with DCM, whereas *p56lck*-deficient mice maintained normal cardiac structure.[202] However, it should be noted that in mice with severe combined immunodeficiency that lack mature B and T cells, there is an increase in CVB3-induced cardiomyocyte injury.[176] IL-17–producing Th17 cells are also implicated in the development of myocarditis.[203,204] A survival benefit and decreased inflammatory cell infiltration have been observed in the myocardium of mice that received allogeneic transplantation of regulatory T cells that limit CD4 activation and prevent inflammation before infection with CVB3.[205]

Mice and humans infected with CVB3 have been shown to develop autoimmune heart-reactive antibodies,[206–208] which may contribute to myocyte destruction.[162,209–213] Zhang and colleagues[214] demonstrated that a live-attenuated variant of CVB3 was able to protect mice against infection with the cardiovirulent wild-type strain. The attenuated virus was able to induce neutralizing antibodies, but, in contrast to wild-type virus, the attenuated virus failed to induce significant levels of antibody against cardiac myosin. In mice, susceptibility to damage from antimyosin antibodies is strain specific and appears to involve a genetically determined difference in target-organ sensitivity.[215] Antibodies to cardiac myosin that cross-react with β1-adrenergic receptors can contribute to cardiomyocyte apoptosis.[216,217] Of note, Huber and associates[218] have described three monoclonal antibodies to group A *Streptococcus* that also bind to various cardiac antigens and neutralize a myocarditic strain of CVB3.

Studies in mice have demonstrated increased virulence of CVB3 in selenium-deficient mice, which suggests that "oxidative stress" may contribute to myocardial damage.[219] The identification of CVB viruses in the myocardium in patients with Keshan syndrome, a form of myocarditis prevalent in a selenium-deficient region of China,[220] suggests that this murine model may have direct relevance to myocarditis in humans. Nonsteroidal antiinflammatory agents may also have deleterious effects,[221] perhaps through inhibition of IFN production.[222]

The immune response has been shown to have a significant role in Chagas' disease. In acute Chagas' disease pathologic examination often reveals parasites within cardiac myocytes. When rupture of the cysts occurs, there is a marked inflammatory infiltrate consisting of lymphocytes, plasma cells, macrophages, and some eosinophils.[135,151] In chronic

Chagas' disease the heart is often enlarged and flabby. Aneurysm formation may be present at the apex. The conduction system is often involved, and this is reflected by a high frequency of rhythm disturbances. Microscopic examination reveals focal mononuclear cell infiltrates and fibrosis.[135,151,223,224] At this stage parasites can be identified in only 25% of patients.[224] Epitopes shared by *T. cruzi* and cardiac myocytes and recognized by cytotoxic T cells may play an important role in the progression of myocarditis late in the disease.[129,225]

Myocardial microabscesses, affecting both myocytes and the conducting system, may occur in the course of systemic bacterial infections with organisms such as *Staphylococcus aureus,* but heart failure is rarely a direct consequence of such lesions.[96,97] In experimental animals *Borrelia burgdorferi* has a predilection for connective tissue in the heart base, and disease severity correlates with the number of spirochetes found.[226,227] Mouse models suggest that infection with *B. burgdorferi* has a different pathogenesis than enterovirus myocarditis; injury is independent of class II MHC–T-cell interactions and results from the response of macrophages to the spirochetes.[228]

Rickettsia and most fungi produce vasculitic lesions with surrounding inflammation. Damage to myocytes may be caused by the adjacent inflammatory process or may reflect anoxia caused by occlusion of small blood vessels.

Diphtheria toxin inhibits cellular protein synthesis. This results in hyaline degeneration and necrosis of myocardial fibers with a secondary inflammatory response.[4,76]

Clinical Manifestations

Patients with myocarditis may be asymptomatic with subacute infection, or they may have a rapidly progressive fatal disease[14,229–231] with a full range of presentations in between.[232] Myocarditis is often classified as fulminant, acute, or chronic.

The diagnosis of infectious myocarditis is usually considered when a person develops unexplained heart failure, chest pain or arrhythmias, or when cardiac abnormalities occur in the course of a recognized systemic infection. Although the diagnosis is made more commonly in pediatric and young adult populations, it is not exclusive to these groups. Fever, malaise, arthralgias, or upper respiratory tract symptoms may precede or accompany coxsackievirus myocarditis,[233–235] but these symptoms are not specific nor are they required to make the diagnosis.[13,236] Supraventricular tachycardia and ventricular extra systoles are common, and, on occasion, atrioventricular block may occur.[237,238] Arrhythmias may provide early evidence of involvement of the conduction system and may be responsible for the occurrence of sudden death in patients with myocarditis. Myocarditis may mimic acute myocardial infarction,[239–242] but care should be taken not to mistake myocardial infarction occurring in a patient with infection for myocarditis.[243] In fulminant and acute myocarditis there may be a low-level elevation of cardiac enzymes that remains elevated for several days.[244,245] Symptomatic pericarditis may or may not also be present.

Diagnosis

Recognizing myocarditis in clinical practice is particularly challenging due to the absence of a sensitive and specific gold standard for diagnosis.[13,14,231,236,246] Therefore it has been difficult to precisely assess the diagnostic value of different clinicopathologic symptoms and signs. Consequently, the diagnosis of myocarditis requires a high index of suspicion. In infants, myocarditis is often just one manifestation of a widespread fulminant systemic infection. Involvement of the lungs, liver, and central nervous system; disseminated intravascular coagulation; and circulatory collapse may obscure the clinical signs of cardiac disease.[247–250] Recognition of myocarditis can also present difficulties in older children and adults when it occurs as part of an overwhelming systemic infection. When sought, however, signs of cardiac dysfunction may be apparent. As stated previously, the diagnosis of myocarditis is generally entertained when a patient presents with new-onset heart failure or with more nonspecific symptoms, such as unexplained chest pain or arrhythmias.

Elevation in biomarkers of necrosis may occur, but such elevation is neither highly sensitive nor specific without additional information. Elevations of cardiac troponins occur more frequently than do elevations of the muscle-brain (MB) fraction of creatine kinase (CK-MB), although the CK-MB is often elevated in the serum of patients with acute myocarditis and significant ST-segment elevation.[251,252] In one study only 34% (18/53) of those with biopsy-proven myocarditis had increased serum troponin levels, as did 11% (4/5) of patients evaluated for possible myocarditis in which the biopsy was negative for myocarditis.[245] A more recent analysis of patients with a troponin-positive episode of chest pain and unobstructed coronary arteries was evaluated with cardiac MRI. The most common underlying cause for the troponin elevation was myocarditis (50%).[253] Another study looked at young adults between ages 18 and 40 years who presented with chest pain and elevated troponin: 59.2% were diagnosed with myocarditis, whereas 37.5% had myocardial infarction.[254] In a pediatric population elevated troponin in the first 72 hours after hospitalization for viral myocarditis was associated with the need for extracorporeal membrane oxygenation.[255] The sensitivity of the newest high-sensitivity troponin assays for myocarditis remains to be determined. Various heart-reactive antibodies have been detected in patients with myocarditis, and their persistence at high titer appears to be a poor prognostic sign.

Various electrocardiographic changes may be present with myocarditis, although they are nonspecific unless there is concomitant pericarditis. The changes that may be seen include nonspecific ST-segment and T-wave abnormalities, sinus tachycardia, ventricular and supraventricular arrhythmias, and atrioventricular or intraventricular conduction disturbances. The degree of ST-segment elevation and the extent and duration of later T-wave inversion have been reported to correlate with myocardial enzyme release and therefore with the amount of cell necrosis.[234,235,237,252,256] The presence of Q waves in addition to ST-segment elevation may herald a rapidly fatal course, and abnormal QRS complexes and left bundle branch block have been correlated with an increased risk of sudden cardiac death and the need for cardiac transplantation.[257,258]

Echocardiography is a key tool in the diagnosis and management of myocarditis, even though many of its findings are nonspecific. It allows careful assessment of ventricular chamber size and function and helps exclude other causes of cardiomyopathy, such as valvular disease and hypertrophic cardiomyopathy. It is also useful for detecting pericardial effusion, ventricular thrombus, aneurysm, and right ventricular involvement.[259] Contractility in acute myocarditis may range from normal to severely compromised, and, because the dysfunction is relatively acute, the ventricular chamber may not be greatly enlarged. Thus fulminant myocarditis is associated with a severe decrease in cardiac function but relatively normal ventricular diastolic dimension and, sometimes, even increased septal thickness due to inflammation and edema.[260] In general, ventricular dysfunction associated with myocarditis is global; however, myocardial involvement can be focal in nature and can present with regional wall motion abnormalities that are difficult to differentiate from myocardial ischemia. In a small study of patients with biopsy-proven myocarditis, echocardiographic evidence of right ventricular dysfunction was the strongest predictor of death or the need for cardiac transplantation.[261]

Repeated echocardiographic examinations may be used to monitor the resolution or progression of myocarditis. Persistent wall motion abnormalities and ventricular dilation suggest the development of DCM.

Cardiac magnetic resonance (CMR) imaging has become a valuable tool for the noninvasive diagnosis of myocarditis. Several techniques have been developed to improve the sensitivity and specificity of CMR imaging for the diagnosis of myocarditis. T2-weighted CMR imaging allows visualization of myocardial edema.[262,263] Early T1-weighted gadolinium enhancement (EGE) can detect hyperemia and myocardial inflammation.[262,264–266] Late gadolinium enhancement (LGE) can identify areas of necrosis and fibrosis, and it has been found to be a useful technique for diagnosing this type of injury in myocarditis.[262,267–270]

In the case of myocarditis LGE is usually observed in subepicardial regions or the midwall of the left ventricle. Subendocardial sparing distinguishes myocarditic patterns of LGE from ischemic injury. In myocarditis LGE tends to be more extensive and is frequently distributed in noncontiguous patches that often involve the lateral wall (Fig. 84.3).[267,271] In a recent study the presence of LGE was strongly predictive of cardiac mortality.[272] Proposed "Lake Louise Criteria" for CMR

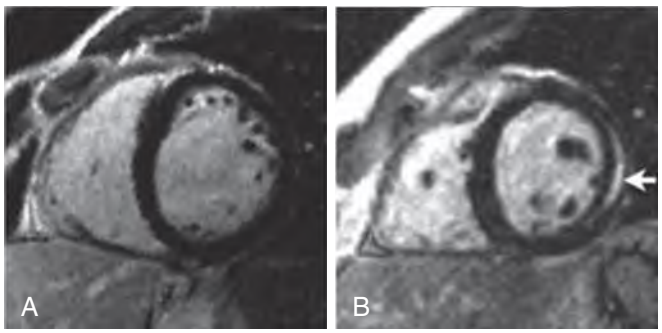

FIG. 84.3 Late gadolinium enhancement magnetic resonance images of the heart. (A) Normal myocardium. (B) Regional, subepicardial enhancement of the lateral wall *(arrow). (Modified from Friedrich MG, Sechtum U, Schulz-Menger A, et al. Cardiovascular magnetic resonance in myocarditis.* J Am Coll Cardiol. *2009;53:1475–1487.)*

image–based diagnosis of myocarditis recommend using a combination of all three MRI sequences (T2-weighted images, EGE, and LGE) in evaluation of patients with suspected myocarditis.[9]

On the basis of these criteria in the setting of clinically suspected acute myocarditis, at least two of the following should be present to confirm the diagnosis:

- Regional or global myocardial signal intensity increase in T2-weighted images, indicating tissue edema
- Increased global myocardial EGE in T1-weighted images
- Presence of at least one focal lesion with nonischemic regional distribution of LGE.

Lurz and colleagues[273,274] assessed the sensitivity and specificity of these criteria by comparing CMR imaging with EMB in patients with suspected acute myocarditis (symptom duration <14 days) and chronic myocarditis (symptom duration >14 days). They found that CMR imaging diagnostic performance is good in patients with suspected acute myocarditis (sensitivity, 81%; specificity, 71%; and diagnostic accuracy, 79%). These indicators are even better in patients with "infarct-like myocarditis" (elevated troponin levels, chest pain, and ST-segment elevation), with sensitivity, specificity, and diagnostic accuracy of 86%, 75%, and 84%, respectively. In contrast, diagnostic performance of CMR imaging in suspected chronic myocarditis was found to be unsatisfactory.[273]

More recently, the MyoRacer-Trial[274] assessed the diagnostic performance of comprehensive CMR imaging in 129 patients with suspected myocarditis, with biventricular endomyocardial biopsy serving as the gold standard. As defined by the area under the concentration-time curve (AUC), T1 (0.82) and T2 mapping (0.81) performed well for patients with acute symptoms ($N = 61$) and were superior to the older Lake Louise criteria (AUC, 0.56). For those with chronic symptoms ($N = 68$), T2 mapping alone yielded an acceptable AUC (0.77). Luetkens and colleagues[275] tested enhanced CMR techniques to improve the diagnostic yield for acute myocarditis. Imaging was performed in 34 patients and 50 control subjects. Clinical validation rather than endomyocardial biopsy was used for diagnosis. AUCs for native T1 (0.92–0.95) and T2 relaxation times (0.92) were excellent and when combined exceeded that of classic Lake Louise criteria (AUC, 0.99 vs. 0.90, $P = .008$). These results also support quantitative CMR parameters, especially using native mapping techniques, as a means of advancing the noninvasive diagnosis of myocarditis.[275]

EMB continues to be an important technique for the diagnosis of myocarditis. In 1986 a panel defined what are known as the "Dallas criteria" for making the diagnosis of myocarditis from EMB samples.[276] These criteria require an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event (Fig. 84.4). Borderline myocarditis is diagnosed in the presence of a less intense inflammatory infiltrate and does not require light microscopic evidence of myocyte necrosis. Both sampling error and variability in interpretation limit the usefulness of the Dallas criteria in clinical practice.[246] For example, postmortem analysis of hearts from patients who died of

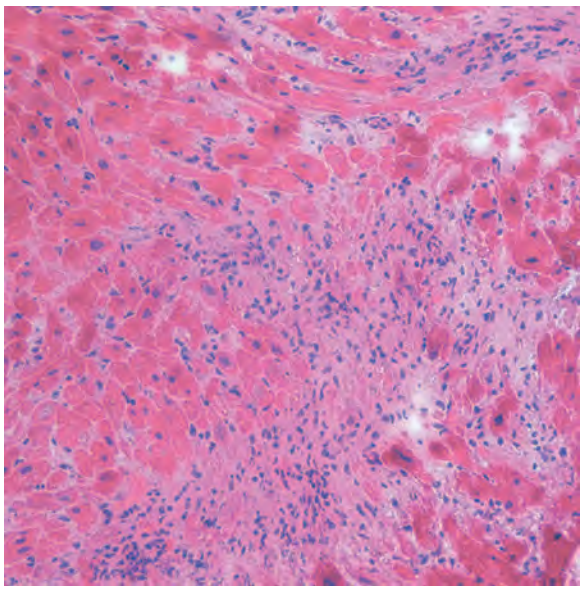

FIG. 84.4 Coxsackievirus myocarditis with extensive infiltration of mononuclear cells and myocyte necrosis. *(Modified from Badorff C, Knowlton KU. Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside.* Med Microbiol Immunol. *2004;193:121–126.)*

myocarditis demonstrated that a single biopsy met Dallas criteria in only 25% of hearts, and five biopsies only made the diagnosis in approximately two-thirds of the hearts,[277,278] which is a reflection of the focal nature of the inflammatory response. Alternative criteria based on cell-specific immunoperoxidase stains for surface antigens on immune cells offer higher sensitivity and may have prognostic value.[196,279,280]

Although there are regional differences in the use of EMB and differences of opinion regarding its usefulness, EMB continues to have a role in establishing the diagnosis of myocarditis in new-onset heart failure.[281] Guidelines published under the auspices of the major cardiovascular and heart failure societies in 2007 recommend EMB for the following:

1. "Unexplained, new-onset heart failure of less than 2 weeks' duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise.
2. Unexplained new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular (AV) heart block, or failure to respond to usual care within 1 to 2 weeks."[281]

The European community has favored more liberal recommendations regarding the indications for EMB. They recommend EMB for essentially all patients suspected of having myocarditis.[282] Complications from right ventricular EMB are generally minor and can occur in up to 6% of cases. Serious adverse consequences (i.e., death, tamponade, perforation) occur in less than 1% if the operator is experienced.[268,283–285] In a study of 4221 patients who underwent EMB from 1983–2013, the overall complication rate was 0.33% for left ventricular EMB (LVEMB) and 0.45% for right ventricular EMB (RVEMB) and decreased over time, with LVEMB having a comparable or better diagnostic yield.[286]

Isolation of a virus that has been shown to be strongly associated with myocarditis or cardiomyopathy from the myocardium or demonstration of viral proteins or nucleic acids in the myocardium provides supportive evidence that virus infection is the cause of the cardiomyopathy. However, except for neonatal myocarditis or myocarditis occurring in immunocompromised patients or in some cases of fulminant myocarditis, viruses are rarely isolated from cardiac tissue.[14,26,34,231,287] To date, diagnosis of viral myocarditis has generally been based on the isolation of virus from another site (e.g., stool), the demonstration of a fourfold or greater rise in antibody titer from acute to convalescent sera, or the demonstration of a high titer of virus-specific immunoglobulin

M antibody in serum.[a] At best, such data provide only circumstantial evidence of causation of myocarditis and must be interpreted with caution because of the prevalence of asymptomatic infections by the same agents that cause myocarditis. In a prospective study 26% of patients without myocarditis had serologic evidence of infection with agents known to cause myocarditis.[237] These traditional methods have failed to provide a specific diagnosis in most patients with myocarditis of presumed viral origin.

The use of molecular techniques for the detection, amplification, and identification of viral nucleic acids in cardiac tissue obtained by EMB is now providing interesting, but somewhat confusing, data on the viral etiology of myocarditis and DCM.[b] Cloned DNA fragments complementary to different regions of the enterovirus genome have served as either type-specific or broadly cross-reactive hybridization probes, and PCR primers capable of detecting or amplifying nucleic acid sequences of a specific virus (e.g., CVB3) or most enteroviruses or adenoviruses permit the detection of viral genomes with unprecedented sensitivity. In situ hybridization, although somewhat less sensitive than PCR, has the advantage of identifying the specific cells that are infected, whereas PCR can increase the sensitivity of the assay to between 1 and 10 viral genomes per milligram of tissue. Overall, enterovirus RNA has been detected by these techniques in approximately 25% of specimens from patients with myocarditis and in about 15% of specimens from patients with DCM. Similar figures have been reported for adenovirus DNA.[8,12,28]

Results from individual studies have varied markedly, however. A large proportion of cases in which coxsackieviruses were implicated serologically did not give positive results by in situ hybridization.[290,295] Furthermore, the cells that contained enterovirus RNA were often not in areas of myocarditis,[290] and in some studies enterovirus RNA was also detected by PCR in cardiac tissue from control patients with a variety of other conditions but not from noncardiac control tissues.[292] These results raise a number of difficult questions, including the specificity of the assays, the sensitivity and validity of the histopathologic assessments, and the pathogenic significance of enterovirus RNA in the absence of inflammation or necrosis. The interpretation of such results is even more problematic when the viruses in question are members of the Herpesviridae or Parvoviridae families, which regularly persist in normal persons and which may even be present in the blood.[297–300] However, the presence of coxsackie B virus genomes within cardiac myocytes that can induce DCM in the absence of both virus replication and immune activation suggests that the mere presence of enterovirus RNA in the heart may have pathogenic significance.[301] In some studies the presence of enterovirus RNA in patients with myocarditis or DCM has been associated with a favorable prognosis,[302] but in others, patients with demonstrated enterovirus RNA have had a poor outcome.[296,303] Coupling PCR with mass spectrometry analysis has recently provided a method to rapidly detect and semiquantify common viruses in cardiac tissue and is capable of identifying 84 human viruses in one assay.[304]

The limitations of current diagnostic strategies underline the importance of identifying novel biomarkers for the diagnosis of viral myocarditis. Several contemporary observational patient registries of nonischemic cardiomyopathies have been assembled or proposed. Their purpose is to carefully characterize patient phenotypes, bank blood and tissue samples, and realize the potential to link clinical, DNA, and "-omic" markers to long-term outcomes. Information from several of these complementary efforts should lead to improved diagnosis, prognosis, and treatment of nonischemic cardiomyopathies, including myocarditis and other inflammatory cardiomyopathies.[305]

A wide variety of noninfectious diseases and agents may mimic infectious myocarditis and produce identical clinical syndromes (see Table 84.2). Of importance, fulminant and acute myocarditis have been associated with the use of novel checkpoint inhibitors as chemotherapeutic agents in patients with malignancies.[306,307]

Treatment

Because there is a lack of specific therapies for myocarditis of various etiologies, the mainstay of therapy for myocarditis is supportive care and standard management of heart failure (HF). With that treatment many patients with viral myocarditis recover.[308–310]

Management of HF secondary to myocarditis includes agents that inhibit angiotensin signaling, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, chronic β-blocker therapy, aldosterone antagonists and diuretics for volume overload, as well as device-based therapy when indicated. However, it should be noted that the effectiveness of these therapies has not been proven in patients with myocarditis, and recommendations are derived from therapeutic recommendations for CHF in general. For this reason animal models of myocarditis provide valuable insight. In mice infected with either CVB3 or encephalomyocarditis virus, treatment with captopril, an angiotensin-converting enzyme inhibitor used in the treatment of heart failure from a variety of causes, reduced inflammation and enhanced survival. A nonspecific β-blocker has also been shown to be beneficial in mouse myocarditis.[311] However, digitalis worsened murine myocarditis.[312] Captopril has also been shown to ameliorate myocarditis in a mouse model of Chagas' disease.[313] Calcium channel blockers have improved murine myocarditis, but the application of these therapies is not well established in patients.[314–316]

Fulminant myocarditis is defined by the presence of cardiogenic shock and therefore requires aggressive therapy aimed at hemodynamic support. This usually includes inotropic agents to maintain cardiac output and blood pressure and, in extreme cases, support with a ventricular assist device. Aggressive support is crucial because long-term survival and recovery from this disease is reported to be greater than 90%, despite its severity on presentation.[229,317] Transplantation may be required if improvement does not occur with circulatory support by a ventricular assist device. However, sufficient time should be given to permit spontaneous recovery before considering cardiac transplantation because the long-term prognosis is generally good.[294,309,317–319]

Given the presence of a marked inflammatory infiltrate in the heart in most cases of myocarditis, considerable attention has focused on therapies aimed at inhibiting the immune system. Early in experimental CVB3 infection in mouse models, indomethacin, salicylates, and ibuprofen all increase viral replication and mortality.[221,320–322] No controlled data regarding their use in patients with myocarditis are available.

Administration of glucocorticoids during the acute phase of viral myocarditis is not established, and the deleterious effects of these drugs have been clearly demonstrated in the acute phase of coxsackievirus infection in mice.[323,324] In some uncontrolled trials patients with myocarditis proved by EMB or with positive gallium scans and who were given immunosuppressive agents showed improvement,[325–328] but, with the exception of a methodologically flawed trial in children,[329] controlled trials have failed to show benefit from treatment with prednisone alone or in combination with cyclosporine.[330–333] The largest controlled trial to date, which compared conventional therapy for CHF with conventional therapy plus prednisone and cyclosporine, failed to show benefit from immunosuppression.[330] A subset analysis of immunologic data from this study suggests that an early immune response may improve outcome, whereas an inadequate early immune response may predispose to viral persistence and chronic immunologic damage.[330]

As knowledge of the pathogenesis of viral myocarditis increases and our ability to rapidly identify the etiologic agents improves, subgroups that might benefit from immunosuppressive therapy may emerge. An example is the clearly beneficial effect of immunosuppression on giant cell myocarditis.[334] In the first randomized, placebo-controlled trial in patients with virus-negative myocarditis, in which EMBs were analyzed for the presence of inflammation and molecular analyses excluded virus infection, combination therapy with prednisone and azathioprine improved LV dimensions and ejection fraction compared with placebo.[335]

Data from mice and uncontrolled studies in humans suggest a beneficial role of immunoglobulins containing antibodies to the causative virus in the treatment of viral myocarditis and DCM. In mouse models of myocarditis induced by CVB3 and encephalomyocarditis virus, immunoglobulin administration suppressed myocardial damage and increased survival in association with a reduction in levels of proinflammatory cytokines and adhesion molecules, including TNF, IFN-γ, IL-6, and ICAM-1.[336,337] Maisch and colleagues[338] demonstrated improvement of hemodynamic function and the eradication of virus after hyperimmune

[a]References 19, 21–23, 25, 29, 30, 34, 35, 81, 233, 288.
[b]References 1, 8, 12, 13, 20, 26, 27, 251, 282, 287–296.

globulin treatment of patients with CMV myocarditis. An uncontrolled study in patients with idiopathic cardiomyopathy and an EMB-proven high PVB19 viral load demonstrated mild improvement in LV ejection fraction with intravenous immune globulin (IVIG) therapy.[339] Another small uncontrolled trial showed significantly improved ejection fractions in 10 patients with new-onset DCM or myocarditis who had New York Heart Association (NYHA) class III/IV heart failure with immunoglobulin administration.[340] However, a placebo-controlled study in adults with acute-onset DCM failed to demonstrate any benefit of treatment with IVIG.[341] Because there are only limited data from randomized trials of immunoglobulin treatment of myocarditis, some experts have concluded that "there are insufficient data from methodologically strong studies to recommend routine use of IVIG for acute myocarditis."[342]

Promising data suggest the efficacy of IFN treatment of viral myocarditis. Studies in mice[343,344] and anecdotal reports in patients[345–347] suggest potential benefit, although a small, single-center, matched-cohort trial demonstrated no significant difference in results between patients receiving IFN and control subjects.[348] A randomized, partially blinded phase II trial of IFN-β1b in patients with biopsy-proven chronic viral cardiomyopathy (CVC) showed that "IFN-β1b treatment resulted in virus clearance or a reduction in virus load, with favorable effects on quality of life, NYHA functional class, and patient global self-assessment in patients with CVC." The therapy was reported as safe. The patients' EMBs were all positive for enterovirus, adenovirus, or parvovirus B19.[349] A subsequent, small study reported that IFN-β therapy improved survival and clearance of enterovirus in patients who were PCR positive for enterovirus on EMB.[350]

Additional data suggest that immunoadsorption therapy might be beneficial in patients with myocarditis and inflammatory cardiomyopathy. Controlled randomized studies demonstrated improved cardiac index in patients with DCM, with elimination of anticardiac antibodies by immunoadsorption.[351,352] In an uncontrolled trial improvement in exercise capacity and decrease in B-type natriuretic peptide levels were reported in patients with DCM after immunoadsorption therapy.[353,354] Bulut and colleagues[355] reported an increase in LV ejection fraction and a decrease in LV end-diastolic dimension after this therapy. These data are intriguing, although larger randomized, controlled clinical trials are necessary to prove the benefit of immunoadsorption therapy. Currently, there is an ongoing trial (NCT00558584) enrolling 200 patients with DCM to assess the effect of immunoadsorption on LV ejection fraction.

Ganciclovir has been used successfully in the treatment of severe CMV infections, including myocarditis.[356] No antiviral drugs with efficacy against the enteroviruses are commercially available at this time. Pleconaril, an experimental agent active against most members of the Picornaviridae family, including enteroviruses, has shown some benefit in clinical trials (see Chapter 48) but was not approved due to side effects.[357–359] Pleconaril integrates into the picornavirus capsid and prevents the virus from attaching to cellular receptors and uncoating to release its RNA into the cell cytoplasm. WIN54954, an earlier compound in the same family, had potent antiviral effects in mouse models of CVB3 myocarditis,[360–363] but adverse effects limited its development.

Heymans and colleagues[232] have provided an excellent recent perspective on the current status of and new approaches to myocarditis and inflammatory cardiomyopathy.

Inhibition of the IL-1β pathway has garnered significant recent attention, with impressive therapeutic outcomes in two other inflammatory cardiovascular conditions: coronary artery disease (Canakinumab Antiinflammatory Thrombosis Outcomes Study [CANTOS])[364] and pericarditis (Anakinra-Treatment of Recurrent Idiopathic Pericarditis [AIRTRIP trial]).[365] Evidence suggests that this pathway also is involved in acute myocarditis. The French ACTION Study Group recently initiated a double-blind, randomized phase IIb clinical trial of anakinra (a recombinant IL-1 receptor antagonist), 100 mg, or placebo, given subcutaneously once daily until hospital discharge (maximum, 14 days), in addition to standard care, for acute myocarditis with follow-up over 6 months. Enrollment target is 120 patients, with a start date of May 30, 2017 and an estimated completion date of June 15, 2021.[366]

Exercise has been shown to increase mortality in murine models of CVB3 myocarditis and to worsen wall motion abnormalities in humans with myocarditis.[29,233,367,368] Thus bed rest is generally recommended in cases of acute myocarditis.

Prevention

The most effective means of preventing myocarditis is to eliminate its causes. To the extent that they have eliminated the diseases, vaccines against diphtheria, poliomyelitis, variola, measles, mumps, rubella, varicella, hepatitis virus A and B, influenza A and B, *Haemophilus influenzae* type b, *Streptococcus pneumoniae,* and *Neisseria meningitidis* have eliminated myocarditis caused by these infectious agents. The fact that most cases of myocarditis and DCM in North America and Europe are caused by a limited group of viral pathogens, namely CVB, adenoviruses, and perhaps parvovirus B19, should make it possible to markedly reduce the incidence of myocarditis and DCM in these regions. A safe and effective vaccine against the coxsackie B viruses could be produced with the same technique currently used to produce inactivated polio vaccine. A safe and effective live-oral adenovirus vaccine is currently administered to US military recruits, and a multivalent adenovirus vaccine capable of markedly reducing the incidence of myocarditis and DCM caused by adenoviruses is feasible. Although no vaccine is currently available for parvovirus B19, vaccines have been produced against animal parvoviruses, and the technology is readily available. The major impediments are cost and the relatively small fraction of infections by these agents that result in myocarditis or DCM. However, DCM occurs with an estimated annual incidence of 2 to 8 cases per 100,000, causes significant morbidity and mortality, and is the major reason for cardiac transplantation in the United States and Europe. This should provide sufficient rationale for considering vaccine development.

In addition to vaccination, proper nutrition with adequate selenium is thought to have had a beneficial effect, at least in the Keshan province in China, where selenium deficiency is prevalent.[219,369] It is notable that myocarditis and pericarditis is rare after live vaccination in adults.[370]

PERICARDITIS

Pericarditis (inflammation of the pericardium) may be caused by any of a wide variety of infectious and noninfectious processes. Pericarditis is generally classified as acute, recurrent, or chronic. This chapter focuses primarily on the etiologies of pericarditis, with less emphasis on these different presentations because the different infectious etiologies can contribute to all classifications.[371] Pericarditis may be clinically silent or may result in severe hemodynamic compromise and death. In 1892 Sir William Osler called attention to the frequency with which pericarditis was overlooked by the practitioner,[372] and series indicate that this is still true today.[373–384] Advances in medicine, including antibiotic therapy, cardiac surgery, hemodialysis, cancer chemotherapy, and organ transplantation, as well as the current epidemic of HIV infection and AIDS, have altered the etiologic spectrum of pericarditis over the course of the 20th century and into the 21st. Idiopathic and viral pericarditis now predominate and usually result in a benign, self-limited disease. Purulent bacterial pericarditis and tuberculous pericarditis are now less common, but they still cause significant morbidity and mortality and present a formidable diagnostic challenge. Imazio and colleagues[385] reviewed the evaluation and treatment of pericarditis with a focus on recent therapeutic strategies.

Etiologic Agents

Because of the difficulty in establishing a specific diagnosis, the cause of acute, self-limited pericarditis is never determined in most cases, and the disease is classified as idiopathic. In some series idiopathic pericarditis accounted for 40% to 86% of patients hospitalized with acute pericarditis.[376–382,386] Idiopathic pericarditis continues to account for a large percentage of cases, even when histology, cytology, viral PCR, and bacterial and fungal sequencing are performed on pericardial specimens.[387] There are no clinical or epidemiologic features that distinguish idiopathic pericarditis from acute pericarditis of proven viral origin. Thus, it is likely that viral infections are responsible for many, if not most, cases of acute pericarditis presently classified as idiopathic.

Most viruses infecting the heart can affect both the myocardium and the pericardium (see previous discussion). Of the many viruses associated with heart disease, the enteroviruses, especially the coxsackieviruses, are

most frequently implicated in pericarditis.[35,381,388–390] The association of myopericarditis with coxsackieviruses was first demonstrated in neonates with overwhelming, fatal systemic infections.[391] Pericarditis has also been recognized in the setting of epidemic coxsackievirus infections.[392] A century ago cases of acute benign pericarditis were recognized during epidemics of Bornholm disease (epidemic pleurodynia), and it was postulated that the etiologic agent of the two diseases was the same.[25,392] Subsequently, the group B coxsackieviruses were shown to be the principal cause of epidemic pleurodynia, and their etiologic role in the associated cases of pericarditis was well established.[392]

Coxsackieviruses have only rarely been isolated from pericardial fluid,[383,384,390] and, as with myocarditis, most diagnoses have been based on the isolation of virus from other body sites (e.g., stool) or the demonstration of a fourfold or greater rise in antibody titer after the acute illness, or both.[383,384,390,393–396] A number of other viruses have also been shown to cause pericarditis, but symptomatic involvement of the pericardium is uncommon. When it occurs, it is often a manifestation of severe disseminated infection. Viruses known to cause pericarditis are listed in Table 84.3.

A wide variety of bacteria can cause pericarditis. In the preantibiotic era, purulent pericarditis occurred primarily as a complication of pneumonia in previously healthy children and adults.[373,375–377,397,398] Of the 425 cases of purulent pericarditis reported in 1961 by Boyle and colleagues,[397] 43% were associated with pleuropulmonary infections. *S. pneumoniae* and *S. aureus* accounted for more than half of the cases. With the advent of antibiotics the incidence of purulent pericarditis decreased markedly. Although staphylococci and streptococci are still etiologic in a substantial number of cases,[374,399–407] the incidence of pneumococcal pericarditis has declined substantially, and gram-negative bacilli have assumed a much more important role.[373–375,398,408–416] Patients with purulent pericarditis are now often older and have an underlying predisposing condition.[373–377,398] Recent reports emphasized the importance of anaerobic bacteria, such as *Actinomyces, Prevotella, Fusobacteria, Peptostreptococcus*, and *Propionibacterium,* in pericarditis complicating esophageal perforation and mediastinitis from head and neck infections,[417–422] but anaerobes can also seed the pericardium via the bloodstream.[419–421] Purulent pericarditis may occur as a complication of meningococcal meningitis or fulminant meningococcemia, but *N. meningitidis,* especially serogroup C, also causes primary pericarditis.[423–425] A reactive, culture-negative pericarditis, presumably of immune origin, may also occur after successful treatment of meningococcal infection at another site.[423,424] *Neisseria gonorrhoeae* may also cause pericarditis, which may be either purulent or reactive.[426,427] *M. pneumoniae* can cause pericarditis; although it is uncommon, this manifestation has been observed in almost 1% of patients hospitalized with *M. pneumoniae* infection.[106,107,428,429] *Legionella pneumophila* has been isolated from pericardial fluid,[430–432] and pericarditis has occurred in association with pneumonia[430–434] and endocarditis.[435] Pericarditis has been observed in children and adults with Lyme disease, but myocarditis is a more common manifestation of *B. burgdorferi* infection.[119,436]

Bacterial infections account for proportionately more pericarditis in children; *S. aureus, H. influenzae,* and *N. meningitidis* are the most common etiologic agents.[437–440] Childhood immunization with *H. influenzae* type b conjugate vaccine has markedly reduced the frequency of *H. influenzae* type b infection in children, and this should result in a comparable reduction in the incidence of *H. influenzae* type b pericarditis.

Acute or chronic pericarditis is reported to occur in approximately 1% of patients with pulmonary tuberculosis.[441] Before the AIDS epidemic, because of the declining incidence of primary tuberculosis and the use of effective chemotherapy, *Mycobacterium tuberculosis* accounted for less than 5% of cases of acute pericarditis in Europe and North America.[441–445] In contrast, tuberculous pericarditis is a major cause of heart disease in Africa[62,231,446–448] and in patients with AIDS.[449–451] Diagnosis is difficult and mortality remains high.[442,443] *M. tuberculosis* continues to be an important treatable cause of chronic pericardial effusion and constrictive pericarditis (see Chapter 249).[444,446–448,452–456]

Primary pathogenic fungi are infrequently recognized as a cause of pericarditis. However, in large outbreaks pericarditis occurred in 6% of patients with acute symptomatic histoplasmosis.[457,458] In most it appeared to represent a sterile inflammatory response to infection in adjacent mediastinal lymph nodes and resolved spontaneously without specific therapy. In disseminated histoplasmosis the pericardium itself may be infected with *Histoplasma capsulatum*.[457,458] Pericarditis is rarely recognized in acute coccidioidomycosis.[459] Spontaneously resolving cases resembling those seen in acute histoplasmosis have been described,[460] but most reported cases have occurred in the setting of disseminated coccidioidomycosis and represent *Coccidioides immitis* infection of the heart.[461–464] Pericarditis caused by *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans,* and other fungi occurs as a consequence of disseminated infection, by direct extension or after surgery, primarily in severely debilitated and immunocompromised patients, especially those with prolonged neutropenia who are receiving multiple courses of antibiotics.[150–152,398,465–474]

Before the introduction of potent antiretroviral therapy, pericarditis was the most frequent cardiac manifestation of HIV and AIDS. Pericardial effusions, most of which are asymptomatic, occur in 10% to 50% of

TABLE 84.3 Infectious Causes of Pericarditis

Viruses

Coxsackie A viruses[30,308]
Coxsackie B viruses[12,27,35,247,388,389,391,392,528,529,538]
Echoviruses[534–536]
Nonpolio enteroviruses
Adenoviruses[482]
Mumps virus[19,549,645]
Influenza A and B viruses[20,552–555,646]
Lymphocytic choriomeningitis virus[562]
Lassa fever virus[563–565]
Varicella-zoster virus[647]
Human cytomegalovirus[648–652]
Epstein-Barr virus[581,587]
Herpes simplex virus[653,654]
Human herpesvirus 6[655]
Variola (smallpox) virus[593]
Vaccinia virus[594–596,656]
Hepatitis B virus[600]
Human immunodeficiency virus[52,54–57,59,60,70,71]

Bacteria and Rickettsia

Streptococcus pneumoniae[397–400]
Other streptococcal species[94,401–405,657,658]
Staphylococcus aureus[96,97,373,397,398,406,407]
Neisseria meningitidis[83,84,423–425]
Neisseria gonorrhoeae[426,427]
Haemophilus influenzae[437–440]
Salmonella[85–87,408,409]
Yersinia[410]
Francisella tularensis[411,412,659]
Pseudomonas[413]
Campylobacter[414,415]
Brucella[416]
Listeria monocytogenes[99,660]
Nocardia[661]
Actinomyces[417,418]
Other anaerobic bacteria[419–422]
Corynebacterium diphtheriae[662]
Mycobacterium tuberculosis[442–453]
Nontuberculous mycobacteria[477–480,663]
Legionella pneumophila[430–435]
Mycoplasma pneumoniae[106,107,428,664,665]
Coxiella burnetii[666]
Chlamydia[108]
Borrelia burgdorferi[118,119,122,125,436]

Fungi

Aspergillus[150–152,466,667–669]
Candida spp.[150–152,467]
Blastomyces[465]
Coccidioides immitis[461,468,469]
Cryptococcus neoformans[151,152]
Histoplasma capsulatum[457]

Parasites[618]

Entamoeba histolytica[670–672]
Toxoplasma gondii[673,674]
Toxocara canis[675]
Schistosoma[676]

patients with AIDS,[52,59,451,475] but in a recent study of 802 HIV-infected outpatients, 85% of whom were receiving antiretroviral therapy, only 2 had effusions on echocardiography.[476]

Although most pericardial effusions are idiopathic, two-thirds of the cases with tamponade are caused by infection or neoplasm; *M. tuberculosis* and nontuberculous mycobacteria, particularly *Mycobacterium avium-intracellulare* complex and *Mycobacterium kansasii,* are responsible for 30% to 50%, and a wide variety of viral, bacterial, and fungal agents have also been isolated from the pericardial fluid.[52,59,451,475,477–484] Malignant effusions have also been observed, primarily EBV-associated lymphomas and Kaposi sarcoma.[c] As with myocarditis, pericardial effusions in HIV-infected patients are associated with advanced stages of infection.[451,481,482,484] The rare parasitic causes of pericarditis are referenced in Table 84.3.

Pathology, Pathogenesis, and Pathophysiology

The pericardium has two opposing mesothelial surfaces. The parietal pericardium forms a flask-shaped sac that encloses the heart and origins of the great vessels. It consists of a 1-mm-thick layer of dense collagen lined by a single layer of mesothelial cells that are covered by microvilli. The mesothelial cell layer is reflected onto the epicardial surface of the heart to form the visceral pericardium. The parietal pericardium has firm attachments to the sternum, diaphragm, and adventitia of the great vessels. The function of the normal pericardium has been a matter of considerable investigation and speculation.[485] It normally contains 15 to 50 mL of clear fluid, which may act as a lubricant. The pericardium reacts to acute injury by exuding fluid, fibrin, and cells in various combinations.[454,482,485,486] Acute pericarditis may resolve completely or progress to fibrous thickening, with or without constriction.

Cardiotropic viruses usually spread to the myocardium and pericardium hematogenously. Inflammation occurs in both visceral and parietal portions; effusion may develop and may be serous, serofibrinous, or serosanguineous. Concomitant myocarditis may or may not be evident. Although most patients with viral pericarditis recover completely, some have repeated disabling recurrences.[377,486–489] The pathophysiology of these recurrences has not been established, but it probably involves immunologic mechanisms and not recurrent or persistent virus replication. Acute pericarditis can cause a pericardial effusion that, in a small percentage of patients, causes pericardial tamponade. Rarely, viral pericarditis leads to constriction as a late complication.[396]

Bacterial pericarditis results from (1) spread from a contiguous focus of infection within the chest, either de novo or after surgery or trauma; (2) spread from a focus of infection within the heart, most commonly from endocarditis; (3) hematogenous infection; or (4) direct inoculation as a result of penetrating injury or cardiothoracic surgery. The incidence of purulent pericarditis arising from a contiguous pneumonia has steadily decreased and now usually occurs only when there has been significant delay in antibiotic therapy.[373,375,398,399] Pericarditis after cardiothoracic or esophageal surgery often occurs in patients with sternal wound infections or mediastinitis[373,398] and may be overlooked. Mortality is high. Pericarditis not infrequently accompanies fatal endocarditis,[96,97,490] especially that caused by *S. aureus*.[96] It often results from extension of a perivalvular abscess into the pericardium.[96,97,490] However, pericardial effusions in endocarditis may also be hemorrhagic or sympathetic and sterile.[490] The presence of preexisting nonbacterial pericardial effusion may predispose to the development of purulent pericarditis in bacteremic patients. Although the pericardial fluid may initially be clear,[397,398] it is usually grossly purulent and may be loculated by the time the disease is clinically apparent. Subsequent organization with adhesions, obliteration of the pericardial space, and calcification may occur and result in constrictive pericarditis.

Tuberculous pericarditis may develop from a hematogenous focus present from the time of primary infection; as a result of lymphatic spread from peritracheal, peribronchial, or mediastinal lymph nodes; or by contiguous spread from a focus of infection in lung or pleura. Four pathologic stages in tuberculous pericarditis have been described.[443,453] In the first stage there is diffuse fibrin deposition and granulomas with viable mycobacteria (Fig. 84.5). Second, a serous or serosanguineous pericardial effusion then develops, usually quite slowly and often without symptoms. Lymphocytes, monocytes, and plasma cells replace the polymorphonuclear cells that are present early in infection. In the third stage the effusion is absorbed, the pericardium thickens, granulomas proliferate, and a thick coat of fibrin is deposited on the parietal pericardium. Acid-fast bacilli become difficult to find as dense fibrous tissue and collagen are deposited. In stage 4, which is associated with constriction, the pericardial space is obliterated by dense adhesions, the parietal pericardium is markedly thickened, and many granulomas are replaced by fibrous tissue. This is often followed by the accumulation of cholesterol crystals and calcification. Constrictive pericarditis may develop in up to 50% of patients with tuberculous pericarditis despite the use of antituberculous chemotherapy.[d] Although the incidence of tuberculosis has declined, it remains an important cause of constrictive pericarditis, especially in developing countries.[446–448,454]

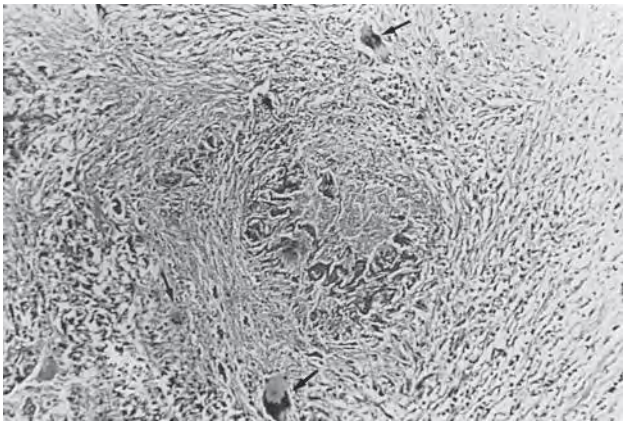

FIG. 84.5 Tuberculous pericarditis, with a typical granuloma in the pericardium. There is central necrosis with aggregates of epithelioid cells at the periphery. Several multinucleated giant cells *(arrows)* are present (original magnification, ×40). *(From Bloor CM. Pericarditis and myocarditis. In: Bloor CM, ed.* Cardiac Pathology. *Philadelphia: JB Lippincott; 1978:265–295.)*

The host inflammatory response is important in the pathogenesis of pericarditis. Xu and colleagues[492] recently updated the scientific understanding of pericarditis, distinguishing between autoinflammatory and autoimmune pericarditis. Activation of the inflammasome underlies autoinflammatory pericarditis. Viruses represent a common activator of the inflammasome, with activation triggering the release of cytokines, including IL-1, which recruit neutrophils and macrophages. Treatment with IL-1β antagonists, such as colchicine and anakinra, have proven to be clinically effective. In autoimmune pericarditis, pericardial inflammatory activity correlates with the severity of the underlying systemic autoimmune disease. Autoimmune pericarditis is characterized by a type I IFN signature. With either type of pericarditis, pericardial delayed hyperenhancement on MRI suggests ongoing inflammation and represents a target for treatment.

Regardless of the cause, if fluid accumulates rapidly in the pericardium and intrapericardial pressure rises, cardiac tamponade may result. Tamponade implies a progressive limitation of ventricular diastolic filling, with resultant reduction in stroke volume and cardiac output. In a series of medical patients with early cardiac tamponade, the cause was infectious in 12.5%, noninfectious in 74%, and undetermined in the remainder.[493] However, the proportion of cases that are idiopathic, associated with infection, or associated with other causes (e.g., cardiac surgery) depends upon the population studied.[374,378,393,450,451]

Clinical Manifestations

The presentation of acute pericarditis varies depending on the cause. However, chest pain, pericardial friction rub, typical electrocardiographic (ECG) changes, and pericardial effusion are the most typical clinical manifestations.[494] Even though the clinical suspicion of pericarditis may

[c]References 52, 59, 451, 475, 481, 482, 484.

[d]References 442–444, 446, 448, 452–454, 456, 491.

be high, it is important to consider the possibility of other causes of chest pain, including coronary artery disease. As the sensitivity of biomarkers of myocardial injury increases, it is likely that a greater proportion of patients with manifestations of pericarditis will also have evidence of myopericarditis as manifested by elevations in troponin I or T.

In viral or idiopathic pericarditis, chest pain is an important feature. This pain is often retrosternal, radiating to the shoulder and neck, and typically is aggravated by breathing, swallowing, and lying supine. In Smith's review of CVB heart disease in adults,[389] 67% of patients had chest pain. Fever was present in 59%. A concurrent or prodromal flulike illness with malaise, arthralgias, myalgias, and occasionally cough with sputum was present in 36%.

Bacterial pericarditis usually develops during the course of a severe systemic infection.[373–375,398] The patient is usually acutely ill, fever is almost always present, and dyspnea is common. However, chest pain is reported by only one-third of patients with purulent pericarditis, and a pericardial friction rub, pathognomonic of pericarditis, is likewise present in only about one-third.[373–375] The symptoms and signs of pericarditis that are present (i.e., fever, dyspnea, and tachycardia) are often attributed to the underlying disease. In consequence, purulent pericarditis is recognized in many patients only at necropsy or after severe hemodynamic compromise has developed.[373–375,482]

Tuberculous pericarditis most often has an insidious onset. Chest pain is present in 39% to 76%,[443,452,454,456] but it may be vague in nature. Weight loss, night sweats, cough, and dyspnea are common. Pericardial effusions in HIV-infected patients are usually asymptomatic, or they may be overlooked in those with severe intercurrent illness.[451,481,484]

The classic physical finding in acute pericarditis is the three-component pericardial friction rub, which reflects cardiac motion during atrial systole, ventricular systole, and rapid ventricular filling in early diastole. This three-component rub was present in 50% of patients with acute pericarditis reported by Spodick.[495] The ventricular systolic component is often the loudest and most frequently appreciated. Rubs are often evanescent and may vary in quality; they are characteristically high pitched, scratching, or grating. In the presence of significant pericardial effusion there may be jugular venous distention—the most common physical finding in acute cardiac tamponade. Enlargement of the cardiac silhouette usually does not occur until at least 250 mL of fluid have accumulated in the pericardial space[482]; if fluid accumulates rapidly, tamponade may occur without detectable enlargement of the cardiac silhouette. A pulsus paradoxus of more than 10 mm Hg, an elevated jugular venous pulse, and a prominent *x* descent with loss of the *y* descent in the jugular venous pressure may be present. Dyspnea is common, but signs of left-sided heart failure are usually absent in cardiac tamponade, and clear lung fields may help to differentiate tamponade from cardiogenic shock.

Constrictive pericarditis, with or without pericardial effusion, is observed in 10% to 20% of patients who present with clinical tamponade.[378] In recent series[378,496] half of the cases of constrictive pericarditis were idiopathic, and most of the others were associated with previous cardiac surgery, thoracic radiation, neoplasms, or tuberculosis. In a series of 26 patients with surgically proven constrictive pericarditis, 18% were found to have no increase in pericardial thickness.[496]

Although the pericardium produces no electrical activity, the ECG is abnormal in 90% of patients with acute pericarditis,[482,486,497] reflecting diffuse sub epicardial inflammation. Characteristic electrocardiographic changes are seen in approximately 50% of patients.[486,497] Early in pericarditis, ST-segment elevation without change in QRS morphology typically occurs in multiple leads. Several days later the ST segment returns to baseline, and there is T-wave flattening. During these early stages there may also be depression of the PR segment. In contrast to myocardial infarction the T-wave inversions in pericarditis usually do not occur until after the ST segment has returned to baseline. These T-wave inversions may last for weeks or months. Large pericardial effusions may be associated with reduced QRS voltage and electrical alternans. Sinus tachycardia is common, but the presence of other arrhythmias suggests preexisting underlying heart disease or significant myocardial involvement.[498]

Echocardiography has proved to be an extremely useful tool for diagnosis of pericardial effusion. The size of the effusion can be roughly quantitated, and early hemodynamic compromise can often be detected.[482] In addition, the echocardiogram can determine whether the ventricular function is compromised, as might occur in myopericarditis. Computed tomography has been useful in demonstrating pericardial thickening and, in some cases, in differentiating an uncomplicated transudate from a high-density exudate.[499,500] In addition, MRI techniques can easily detect pericardial fluid, pericardial thickening, and abnormal ventricular septal motion,[501,502] but they have no particular advantage over echocardiography.

TABLE 84.4 Major Noninfectious Causes of Acute Pericarditis

- Acute myocardial infarction[482,677–679]
- Cardiac injury[482]
  - Trauma (penetrating or blunt)[680]
  - Myocardial infarction (Dressler) syndrome[681]
  - Postpericardiotomy[512,680,682]
- Uremia[683–686]
- Neoplasia[482]
  - Primary
  - Metastatic
- Irradiation[482,635–637]
- Dissecting aortic aneurysm[687]
- Sarcoid[482,644]
- Collagen vascular diseases[482,631]
  - Systemic lupus erythematosus[624]
  - Systemic sclerosis/scleroderma[626,627]
  - Rheumatoid arthritis[628,629,688]
  - Rheumatic fever[482]
- Immunoglobulin G4–related disease[689]
- Inflammatory bowel disease[690]
- Myxedema[691]
- Drug induced[482]
  - Procainamide
  - Hydralazine

Diagnosis

A wide variety of agents and diseases can cause pericarditis and pericardial effusion (see Tables 84.3 and 84.4). Low-grade fever is common in many. A careful history, knowledge of the clinical setting in which the pericarditis occurs, and a search for clues outside the cardiovascular system are helpful in establishing a diagnosis. In a young person without underlying illness who presents with acute pericardial pain, the most likely diagnosis is viral or idiopathic pericarditis. However, establishing a specific viral diagnosis is difficult, costly, and often possible only in retrospect. Virus isolation can be attempted from throat and stool, and acute and convalescent sera can be tested for antibodies to potential pathogens (e.g., coxsackie B viruses and any other enteroviruses prevalent locally at the time), but these approaches frequently fail to yield a specific diagnosis. Viruses are rarely isolated from pericardial fluid, even in patients in whom the diagnosis of viral myocarditis is highly probable. The application of PCR technology using pathogen-specific primers and probes[503] for the detection of the genomes of pathogens in pericardial fluid, pericardial biopsy specimens, and, perhaps, peripheral blood could increase the proportion of patients with pericarditis in whom an etiologic diagnosis is established. However, the etiology of the pericarditis remains undetermined in the great majority of patients.

If the clinical suspicion of viral or idiopathic pericarditis is strong in an otherwise healthy patient with uncomplicated pericarditis, pericardiocentesis or other invasive procedures add little diagnostically[445] and carry a small but definite risk.[504] After excluding patients with postpericardiotomy syndrome, myocardial infarction, renal failure, known neoplastic disease, trauma, and irradiation, Soler-Soler and colleagues[380] prospectively evaluated 256 immunocompetent patients with primary acute pericardial disease. After thorough diagnostic evaluation, 221 (86%) were thought to have acute idiopathic pericarditis. Unsuspected neoplastic pericarditis was found in 12 (5%), tuberculosis in 11 (4%), and collagen vascular disease in 4 patients. Purulent pericarditis and viral pericarditis were each found in 3 patients, and *Toxoplasma gondii* infection was found in 4. The diagnostic yield was substantial when pericardiocentesis or pericardiectomy with biopsy was done to relieve cardiac tamponade (28% and 54%, respectively) but led to a specific etiology in only 5% and 4%, respectively, when these

procedures were done solely for the purpose of diagnosis. The authors concluded that the presence of a pericardial effusion per se is not an indication for an invasive procedure; in patients with pericardial effusion that has persisted for longer than 3 weeks, an invasive procedure may be indicated. In a similar study of patients with large (>20-mm echo-free space in diastole) pericardial effusions without tamponade physiology or suspected purulent pericarditis, the diagnostic yield for pericardiocentesis or surgery was only 7%.[505]

Among those observed expectantly without a drainage procedure, no patient developed tamponade or died as a result of pericardial disease; moderate or large effusions persisted in only 2 of 45 patients.[505] Similarly, small asymptomatic pericardial effusions in patients with HIV infection do not routinely require diagnostic evaluation.[451] In a study of 13 patients with AIDS who underwent surgical pericardial drainage, Kaposi sarcoma was found in 3 (all with preexisting extracardiac lesions), but no other specific causes were identified.[506] However, in patients who are symptomatic, about two-thirds of cases are caused by potentially treatable infections or neoplasms.[451]

When an invasive procedure is necessary for diagnosis, pericardiotomy with biopsy and drainage is preferable to pericardiocentesis because of greater diagnostic yield and fewer complications.[482] Pericardiocentesis alone establishes a specific etiologic diagnosis in 20% to 25% of cases; the availability of both fluid and tissue improves this yield to 54%.[445,456,505] The technique of percutaneous pericardial biopsy is an alternative to surgery for obtaining tissue, and it appears to be safe and effective in patients with a thickened pericardium.[507,508] Noninfectious diseases predominate as causes of significant pericardial effusion and cardiac tamponade,[e] but bacterial and tuberculous effusions are more likely to have serious hemodynamic consequences.[373,374,451,504] Untreated purulent pericarditis is usually rapidly fatal.[373–375,397,398,454] In acutely ill patients in whom purulent pericarditis is suspected, the diagnosis should be pursued quickly and aggressively.

Treatment

Bed rest, symptomatic therapy for pain, and careful monitoring for the development of hemodynamic compromise have been the mainstays of treatment for presumed viral or idiopathic pericarditis. Nonsteroidal antiinflammatory agents are often successful in relieving symptoms in acute pericarditis. Therapy is generally continued for 1 to 2 weeks or longer if symptoms fail to resolve. Discontinuation of therapy is generally tapered to avoid recurrence.[509,510] In addition to these therapies, colchicine has become a key part of pericarditis therapy.[385] A 2013 multicenter, double-blind, placebo-controlled trial compared placebo versus the administration of colchicine during a first attack of acute pericarditis. The dose was 0.5 mg twice daily for patients weighing more than 70 kg and once a day for those less than 70 kg. Usual therapy with aspirin or ibuprofen was included in both arms. The study found that the primary outcome of persistent or recurrent pericarditis occurred in 37.5% of the placebo group compared with 16.7% in the treated group. Colchicine also reduced the rate of symptom persistence at 72 hours, reduced the rate of hospitalization, and increased the rate of remission at 1 week.[511] Two subsequent meta-analyses confirmed the effectiveness of colchicine as adjunctive therapy to NSAIDs in reducing the number of recurrences of pericarditis.[512,513] Because myocarditis often accompanies viral pericarditis and steroids enhance myocardial injury during active virus replication, we believe that steroids should be avoided during the acute pericarditis and may predispose to recurrent episodes.[513] Steroids and other immunosuppressive agents have been used to treat debilitating recurrences of idiopathic pericarditis when other choices are limited, but controlled trials are lacking and serious adverse effects with these regimens are more common.[514,515]

Recurrent pericarditis still presents an ongoing challenge. The AIRTRIP trial used a double-blind, placebo-controlled, randomized withdrawal design to test the therapeutic potential of anakinra. Twenty-one patients who initially responded to a 2-month course of anakinra were randomized to continue daily subcutaneous drug ($n = 11$) or switch to placebo ($n = 10$) for 6 months or until a recurrence of pericarditis. Pericarditis recurred in 9 of 10 placebo patients and 2 of 11 patients continued on anakinra ($P < .001$). Injection site rashes were the most common adverse effect. The promise of IL-1 β blockade in recurrent or persistent pericarditis deserves further assessment in larger and longer-term studies.[365]

Surgical drainage of the pericardium, in addition to appropriate antibiotic therapy, is essential in almost all patients with purulent pericarditis.[397–399,420] Initial pericardiocentesis may be lifesaving, but fluid often reaccumulates and constriction can develop rapidly.[438,444–448] There is little rationale for irrigating the pericardium with antibiotics because penetration of antibiotics from blood is excellent.[516] With early diagnosis and aggressive therapy, *H. influenzae* pericarditis in young patients has a good prognosis.[438] However, overall mortality in bacterial pericarditis remains high (30%), especially when it develops after surgery or occurs in the course of endocarditis.[96,97,397–399,490,517] A retrospective review has suggested that fibrinolysis may have a role in preventing the late complications of purulent bacterial pericarditis as a less invasive alternative to pericardiectomy.[518]

Antituberculous therapy has reduced the mortality of tuberculous pericarditis substantially.[514] However, constrictive pericarditis may develop in 20% to 50% of patients despite appropriate treatment,[442–444,446–448,452,453,491] and patients with the clinical features of tamponade at presentation are at increased risk.[519] The addition of steroids to reduce inflammation and possibly avoid late constriction is favored by many, including the authors.[f] The use of corticosteroids, in addition to antituberculous therapy, is supported by the results of two large, controlled trials in Transkei reported by Strang and associates.[448,455] In a third large randomized trial in which two-thirds of the participants were HIV infected, the use of prednisolone did not have a significant effect on the combined end point of death from all causes, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis, but it did reduce the incidence of pericardial constriction and hospitalization.[522] In patients with tuberculous pericardial effusions the addition of prednisolone to a four-drug antituberculosis regimen reduced the risk of death, the need for repeat pericardiocentesis, and the need for open surgical drainage because of rapid reaccumulation of pericardial fluid; constrictive pericarditis developed in 8% of steroid recipients and 12% of controls.[455] Prednisolone was given in a dose of 60 mg daily for 4 weeks, followed by 30 mg daily for 4 weeks, 15 mg daily for 2 weeks, and 5 mg daily for 1 week in patients ≥15 years of age. In a similar trial in patients with active tuberculous constrictive pericarditis, the addition of prednisolone increased the rate of clinical improvement.[448] In 10 patients treated initially with 120 mg of prednisone daily, dramatic improvement occurred over a 1-week period, and the author suggested that higher initial doses might allow a shorter duration of treatment. Early surgical intervention is advocated in patients with hemodynamic compromise from recurrent effusion or progressive pericardial thickening.[456,491]

In a retrospective study of children with tuberculous pericarditis reported from Africa, 5 (40%) of 12 patients with evidence of constriction at presentation required pericardiectomy.[523] These authors recommended observation for a period of 6 weeks to 3 months after the initiation of treatment, with pericardiectomy reserved for those who fail to improve or who deteriorate. Pericardiectomy frequently results in striking hemodynamic improvement, but if diagnosis and therapy have been delayed, myocardial function may be affected, leading to less satisfactory results.[524,525] In some patients resolution of venous congestion requires several months.[523] Patients with calcific tuberculous pericarditis have a poorer prognosis than those who undergo operation earlier in the course of their disease.[523,525] Early pericardial drainage and intrapericardial fibrinolysis by means of the instillation of streptokinase have been advocated to facilitate drainage, prevent loculation, and reduce the risk of constrictive pericarditis.[526] However, this approach has not yet been evaluated with appropriate clinical trials.

[e]References 378, 445, 482, 484, 496, 505.

[f]References 442, 448, 455, 456, 520, 521.

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