This chapter provides an overview of the risk of infection associated with the use of the most important implanted medical devices (see Table 45.1), their clinical features, pathogenesis, epidemiology, diagnosis and treatment and, perhaps most importantly, strategies for their prevention.

GENERAL ASPECTS OF PATHOGENESIS

Implantation of prosthetic material evokes a host response, which intrinsically increases the risk of infection. Animal models have shown that the inoculum needed to establish infection is greatly reduced in the presence of a foreign body. The characteristics of the implanted device and the material from which it is manufactured, the likelihood that the device might be exposed to micro-organisms, the intrinsic virulence of the involving organisms and the capacity of the host to resist infection all contribute to the overall risk of device related infection.

'Biomaterial' is a generic term for the material from which a medical device, manufactured for the distinct purpose of implantation in the human body, is constructed. Most devices are constructed of hydrocarbon polymers, which can now be engineered with predictable mechanical properties. Biomaterial in contact with deep tissues can have one or more physiologic effects: the biomaterial releases chemicals toxic to contiguous tissue; the biomaterial is non-toxic, but unable to resist the inflammatory response its presence elicits, and the material is absorbed over time (e.g. chronic gut sutures); the biomaterial is non-toxic and unaffected by the inflammatory response, avoiding absorption by the body, but elicits chronic inflammation, resulting in encapsulation of the device (e.g. hip arthroplasty) or local thrombosis (e.g. vascular catheters); the biomaterial is both non-toxic and biocompatible, and well tolerated by tissue, resulting in adhesive bonds that stabilize the device and attenuate the inflammatory reaction (e.g. bioactive glass-ceramics and bioactive composites).

Almost all implanted medical devices in use today fall into the third category. Development of a biologically totally inert material that does not induce a host response and is non-thrombogenic remains the 'holy grail' of biomaterials research.

The ensuing host-foreign body reaction plays an integral role in promotion of implant infection by distorting the local immune response and coating ('processing') of the surface by matrix proteins. Animal models show striking derangement of the immune response in the peri-implant environment, most notably in phagocytosis. Neutrophils recovered from the surface of foreign bodies show greatly reduced levels of granule-associated bactericidal enzymes and oxidative burst-dependent bactericidal activity.

The presence of a foreign body not only perturbs local immune dysfunction but also provides an altered surface to which bacteria can more readily adhere and form a complex microenvironment, or biofilm. While non-specific physicochemical forces, such as surface tension, electrostatic forces, hydrophobic interactions and van der Waal's forces mediate the initial microbial adherence to a foreign body, durable adherence is also influenced by specific host-protein-microbial interactions.

After placement, vascular catheters are rapidly coated by host proteins, including albumin, fibrinogen, fibrin, fibronectin and platelets; a similar process probably occurs with other implanted devices. Studies with Staphylococcus aureus have identified specific microbial fibronectin- and fibrinogen-binding surface proteins, and other proteins with broader specificity that can bind fibronectin as well as fibrinogen, vitronectin, thrombospondin and bone sialoprotein. Direct support for the importance of these bacterial surface proteins comes from both in-vitro and animal models: knockout strains of Staph. aureus that are deficient in fibronectin-binding surface proteins show a markedly reduced capacity to bind to polymethylmethacrylate (PMMA) coated slides in vitro or to traumatized heart valves in a rat model. Moreover, strains of...
**Staph. aureus** deficient in the gene for production of the fibronogenc-binding surface protein lack the ability to adhere to PMMA-coated slides that are covered with fibrinogen. The capacity to adhere is regained when the gene is restored to the knockout strain.

Coagulase-negative staphylococci also have the ability to bind fibronectin, although with less avidity than *Staph. aureus*. In contrast, fibrinogen does not appear to be a major receptor for binding of coagulase-negative staphylococci to implant surfaces, although other surface binding proteins unique to this micro-organisms have been reported. A polysaccharide capsular adhesin that mediates the attachment to uncoated polyester catheters has been identified, and antibodies to this epitope have been shown to inhibit binding to silicone catheters and prevent catheter-related infection in a rabbit model.

Once bound to an implanted device, most micro-organisms that cause device-related infection are able to produce an extracellular polysaccharide matrix. The combination of host proteins in intimate association with microcolonies of the infecting organism, embedded in massive quantities of exoglucocylax, comprises a unique microecosystem, the biofilm. Biofilms can be found almost universally on infected implanted materials of all types, and have been best characterized with:

- Gram-positive bacteria, especially *Staph. aureus*, *Staphylococcus epidermidis*, and *Enterococcus faecalis*;
- Gram-negative bacilli, such as *Escherichia coli*, *Pseudomonas aeruginosa* and *Burkholderia cepacia*;
- Yeasts, such as *Candida albicans*.

Organisms within a biofilm are uniquely adapted to extreme environments and form a nidus of chronic infection on the surface of the implanted device from which planktonic phase organisms are released, producing signs and symptoms of infection.

Biofilms greatly facilitate surface adherence, protect the micro-organism and allow its survival, even under intense attack from the immune system and high concentrations of antimicrobial drugs. Several mechanisms appear to be responsible:

1. Micro-organisms encased in a biofilm are resistant to phagocytosis, and there is evidence that antimicrobial oxidants produced by phagocytic cells are inactivated in the superficial layers of a biofilm.
2. Antimicrobial drugs penetrate biofilms poorly and lose activity in the acidic and anaerobic environment of the deepest layers of a biofilm.
3. Micro-organisms in a biofilm are in a sessile, or slow-growing phase of growth that further enhances resistance to antimicrobials, most of which are most effective against rapidly multiplying organisms.
4. Micro-organisms in a biofilm exhibit unique phenotypic features, expressing genes that are not expressed in the planktonic, rapidly growing phase encountered in infections unrelated to implanted devices.

The extraordinary capacity of the biofilm to produce refractory infection can be seen in vitro experiments: studies have shown that concentrations of a bactericidal antibiotic 100 to 1000 times those effective against the planktonic phase of the organism (the minimal inhibitory concentration or MIC) do not kill the micro-organisms within a biofilm. Thus, while antimicrobial therapy is often effective in resolving the acute features of device-associated infection, such as local inflammation and fever, antimicrobial therapy alone rarely kills the indolent sessile organisms within the deepest layers of an implant-associated biofilm. For these reasons, the management of most implanted device-related infections requires removal of the infected device as well as appropriate antimicrobial therapy.

### INFECTIONS ASSOCIATED WITH ORTHOPEDIC DEVICES

#### EPIDEMIOLOGY

Over seven million orthopedic procedures were performed in the USA in 1996, including 500,000 total knee arthroplasties and total hip arthroplasties. The site of prosthetic joint implantation, characteristics of the implant, and events surrounding the operation have a profound impact on the risk of infection.

Rates of deep infection after total hip arthroplasty range from 0.5 to 1.5% at most centers; rates of infection with total knee arthroplasty appear to be somewhat higher, in the range of 0.8-2.5% (Table 45.1). The risk of infection appears to be highest in the first 2-3 years after surgery: combined rates of hip and knee prosthetic infection are 6.5 per 1000 joint years in the first year after surgery. Rates of infection during the second postoperative year and 1.4 per 1000 in the total years thereafter. Rates of infection with other prosthetic joint implants have been less well characterized but average 1% for shoulders, 2.4-6.0% for ankles and wrists and as high as 7-9% for elbows.

The characteristics of the artificial joint clearly influence the risk of infection. Use of metal-on-metal hinged knee prostheses has been shown to be associated with a risk of infection 20 times higher than encountered with the modular metal-on-polyethylene prosthetic joints most widely used today. Host factors associated with an increased risk of postoperative infection of the prosthesis include rheumatoid arthritis, diabetes mellitus, malignancy, concurrent corticosteroid use, hemophilia and revision arthroplasty. Other factors that may increase the risk of infection, such as obesity and active urinary tract infection at the time of surgery, have been less rigorously evaluated.
Table 45.1 Risk of infection with the implanted medical devices in widest clinical use

<table>
<thead>
<tr>
<th>Device</th>
<th>Approximate risk of infection over the lifetime of the device</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Orthopedic devices</strong></td>
<td></td>
</tr>
<tr>
<td>Total joint prostheses</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>0.5-1.5</td>
</tr>
<tr>
<td>Knee</td>
<td>0.8-2.5</td>
</tr>
<tr>
<td>Elbow, ankle, and wrist</td>
<td>1-9</td>
</tr>
<tr>
<td><strong>Cardiovascular devices</strong></td>
<td></td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td>-5</td>
</tr>
<tr>
<td>Bioprosthetic</td>
<td>-6</td>
</tr>
<tr>
<td>Coronary stents</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pacemakers and implantable cardiac defibrillators</td>
<td>1-7</td>
</tr>
<tr>
<td>Left ventricular assist devices</td>
<td>5-70</td>
</tr>
<tr>
<td>Implanted artificial heart</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Intravascular devices</strong></td>
<td></td>
</tr>
<tr>
<td>Short-term vascular catheters</td>
<td></td>
</tr>
<tr>
<td>Peripheral venous catheters and needles</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Arterial catheters</td>
<td>1-2</td>
</tr>
<tr>
<td>Central venous catheters</td>
<td>3-4</td>
</tr>
<tr>
<td>Temporary hemodialysis catheters</td>
<td>13-18</td>
</tr>
<tr>
<td><strong>Long-term devices</strong></td>
<td></td>
</tr>
<tr>
<td>Cuffed and tunneled central venous (Hickman and Broviac) catheters</td>
<td>18-22</td>
</tr>
<tr>
<td>Peripheral inserted central catheters</td>
<td>0.5-2</td>
</tr>
<tr>
<td>Subcutaneous central ports</td>
<td>4-6</td>
</tr>
<tr>
<td>Tunneled and cuffed hemodialysis catheters</td>
<td>4-9</td>
</tr>
<tr>
<td>Vascular Gore-tex and Dacron arterial grafts</td>
<td>1-5</td>
</tr>
<tr>
<td><strong>Neurosurgical devices</strong></td>
<td></td>
</tr>
<tr>
<td>Ventriculoperitoneal, ventriculatrial and lumboperitoneal shunts</td>
<td>2-9</td>
</tr>
<tr>
<td>Ventriloplasty catheters</td>
<td>-10</td>
</tr>
<tr>
<td>Intra-arterial coils</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Urologic/renal devices</strong></td>
<td></td>
</tr>
<tr>
<td>Urethral catheters</td>
<td>10-50</td>
</tr>
<tr>
<td>Ureteral stents</td>
<td>-7</td>
</tr>
<tr>
<td>Peritoneal dialysis catheters</td>
<td>20-50</td>
</tr>
<tr>
<td>Penile implants</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Breast implants</td>
<td>-3</td>
</tr>
<tr>
<td>Intra-abdominal mesh</td>
<td>2-8</td>
</tr>
</tbody>
</table>

**PATHOGENESIS**

Several staging systems have been proposed for prosthetic joint sepsis but consensus is lacking. The most widely accepted system is that formulated originally by Coventry 56 and modified by Gillespie. 57

Stage 1 infections are defined as those occurring within 1 month of surgery; patients with stage 1 infections typically present with signs of sepsis as well as local signs of infection, with local erythema and wound discharge. The organisms most commonly recovered from stage 1 infections derive from the patient's skin, bacteria in operating room air, or the skin of members of the surgical team. 58,19

Stage 2 infections are defined as those that occur after 1 month but within 2 years of surgery. These infections are also thought to derive from the introduction of organisms of low pathogenicity, such as coagulase-negative staphylococci and Propionibacterium sp., at the time of surgery. Patients typically exhibit gradual impairment of prosthetic function, (i.e. early loosening of the prosthesis and increasing joint pain).

Stage 3 infections are arbitrarily defined as infections that occur more than 2 years after surgery and are assumed to derive from hematogenous seeding of the joint.
There are limitations with the above classification. The Coventry system fails to take into account the possibility of hematogenous seeding of the newly placed joint that might occur from intravascular device-related bloodstream infections as well as from intercurrent urinary tract or other remote infections. Furthermore, the capacity of certain microorganisms, such as coagulase-negative staphylococci to be present in the joint for prolonged periods before manifesting signs of overt infection is well known, and an arbitrary cutoff of 2 years to define local versus hematogenous infection fails to take this into account. Nevertheless, most stage 3 infections behave differently than stage 2 infections in that patients typically have completely normal joint function then abruptly develop acute pain and inflammation of the joint, in contrast to the gradual decline in function seen with most stage 2 infections.

While definitively identifying the source of a prosthetic joint infection may be difficult, several lines of evidence suggest that the vast majority derive from contamination of the wound at the time of surgery.

1. The risk of prosthetic joint infection is highest in the perioperative period.
2. Most late infections are caused by Staph. aureus and coagulase-negative staphylococci, which are acquired from skin of the patient or members of the operating team at the time of surgery.
3. Operating theaters that provide ultrafiltered air, to reduce airborne microbial counts to <5 colony forming units (cfu)/m³, have 10-60% lower rates of infection than operating rooms that do not employ such systems.
4. Studies of perioperative antibiotic prophylaxis have shown a 64-85% reduction in rates of prosthetic joint infection, with the benefit of prophylaxis becoming ever greater the longer the period after surgery. Studies that have rigorously attempted to identify the source of prosthetic joint infections have found that hematogenous seeding appears to account for only 7-11% of all cases.

**MICROBIOLOGY**

Staph. aureus and coagulase-negative staphylococci predominate in prosthetic joint infections (Figure 45.1); infections with other Gram-positive organisms, such as streptococci and enterococci, are less common. Infections caused by aerobic Gram-negative bacilli usually occur in association with Gram-positive organisms (mixed infections), and in this situation probably reflect gross intraoperative contamination of the surgical wound or, perhaps, postoperative invasion of microorganisms through surgical drains. Hematogenous seeding is more likely when organisms are isolated in pure culture, although direct inoculation is still possible. The microbial profile of prosthetic joint infections has been remarkably stable over time, which suggests that the pathogenesis of infection in both early and late infection is similar (i.e. most originate in the operating theater, even most late-onset infections).

**DIAGNOSIS**

Patients with early postoperative prosthetic joint infection usually show impressive signs and symptoms of joint inflammation: severe pain and limited range of motion, usually in association with erythema of the surgical wound, with or without discharge. Signs of systemic sepsis, with fever, tachycardia and even shock, may be present, depending on the virulence of the infecting organism(s) (e.g. Staph. aureus or Gram-negative bacilli). Patients with late hematogenous infection often show a similarly fulminant course complicating recent skin or respiratory tract infection, or dental manipulation. This
pattern was highlighted in a recent report where 16 of 59 patients with orthopedic devices and documented nosocomial Staph. aureus bacteremia developed prosthetic device infection 0–65 days (median 3 days) after the onset of bacteremia. 70

Patients with stage 2 infections often follow an indolent course, characterized by increasing pain and slowly deteriorating joint function that may or may not be associated with loosening of the prosthesis radiographically. Most are afebrile. No single test or clinical finding is pathognomonic of infection, thus it is necessary to interpret the results of multiple tests and, especially, to obtain joint aspirates or deep operative cultures off antibiotics.

Routine laboratory studies usually, but not always, show leukocytosis. 71 The erythrocyte sedimentation rate (ESR) is elevated in most cases but is a non-specific finding, with a sensitivity ranging from 54 to 82% and specificity 65–85%. 72–75 C-reactive protein (CRP) appears to be a better diagnostic test, with reported sensitivities of 80–96% and specificities ranging from 93 to 100%, respectively. 73,74 CRP is particularly useful in the early postoperative period as the level should normalize within 2–3 weeks after surgery; 75 persistent elevation should prompt suspicion of indolent infection. Finally, the combined use of the ESR and CRP, when both are normal, virtually rules out prosthetic joint infection. 74

Plain radiographs are usually normal in early postoperative and hematogenously derived infections. Loosening of the joint prosthesis may be seen with chronic infection but this finding is not specific. 76 Periosteal reaction or scalloping of the bone is more specific for infection but is often absent in chronic infections, especially those caused by coagulase-negative staphylococci. Ultrasound may be useful for identifying hematomas in the early postoperative period as well as guiding needle aspiration of a joint suspicious for infection.

Numerous studies have evaluated nuclear imaging modalities for the diagnosis of prosthetic joint infection. Unfortunately, most studies were limited by bias introduced through patient selection, lack of randomization, the use of multiple sequential scans, 80 and, especially, lack of a rigorous definition infection. Published studies have reported sensitivities of 38–68% for technetium/gallium radionuclear scanning, 81–83 72–83% for technetium/indium 111-labelled granulocyte scanning, 81,84 and 64–100% for indium 111-labelled IgG scanning. 84–86 Specificity is not much better, ranging from 40 to 100% for the above three tests. 81–86

Microbiologic confirmation of infection remains the gold standard for the diagnosis of prosthetic joint infection and should always be sought. Blood cultures are positive in only 20% of prosthetic joint infections and are rarely positive in the absence of systemic signs of sepsis. Superficial swabs of surgical wounds or draining sinuses are unreliable for identifying the specific organism(s) infecting the prosthetic joint. 87 The failure of non-invasive tests to be able to reliably confirm the presence of infection requires imaging guided aspiration of the suspect joint or intraoperative sampling. The sensitivity of preoperative joint aspiration is >80%, (range 50–100%), 73,83,85,89 and recovery of an organism usually is indicative of infection (specificity, 92 to 100%). 83,88,89 Concurrent antimicrobial therapy clearly reduces the yield of joint aspiration culture and its use should be deferred until all appropriate microbiologic studies have been completed.

Intraoperative Gram stain has been advocated by some as a method for rapidly identifying or ruling out the presence of prosthetic joint infection. Unfortunately, the Gram stain is positive in less than one-third of prosthetic joint infections and is almost certainly less accurate with intercurrent antibiotic therapy. 73,83,90,91 Intraoperative cultures have the highest yield, provided that antibiotic therapy is withheld until immediately after obtaining specimens for culture. Tissue samples, rather than swabs, are preferable and obtaining multiple samples (three or more) improves the specificity. 90 Sampling from the sonicated removed implant may further increase yield by the release of biofilm organisms. 92 It is imperative that multiple samples be inoculated on solid media in the microbiology lab rather than cultured solely in liquid media: multiple colonies growing on solid media almost always represent true infection, whereas microbial growth only in broth is most often indicative of contamination.

TREATMENT

Management of a patient with confirmed prosthetic joint infection requires careful consideration of the stage of the infection (early postoperative, chronic or acute hematogenous infection), the characteristics of the infecting organism, the patient’s comorbidities and life expectancy.

Surgical management

Historically, infection of a prosthetic joint has been most effectively managed with two-stage exchange arthroplasty: 93–95 surgical debridement with removal of the infected prosthetic device and all cement, followed by a prolonged period of parenteral antimicrobial therapy-6–12 weeks or longer-during which time the joint is immobilized, increasingly with the use of an antibiotic-impregnated spacer; 96,97 when all clinical signs of infection have resolved and, ideally, the ESR and CRP have normalized, a new prosthetic device is implanted, often with the use of antibiotic-impregnated cement” or a cementless prosthesis.” Multiple intraoperative specimens are cultured and if persistent infection is found parenteral antibiotic therapy is continued postoperatively, guided by resolution of the clinical features of infection and laboratory measures of inflammation (ESR and CRP). With this approach, long-term eradication of a prosthetic joint infection can be achieved in 87–96% of infected total hip arthroplasties 100–103 and in 83–96% of infected total knee arthroplasties. 98,99,102,104

Obviously, this approach is costly, both for the healthcare system and the patient, who must endure prolonged immobilization, deconditioning and not one but two major operations. This has led to three alternative approaches to management: initial irrigation and debridement with retention of the pros-
thtic device, followed by prolonged antimicrobial therapy; one-stage exchange arthroplasty followed by antimicrobial therapy; and the use of indefinite antimicrobial suppression.

Irrigation and debridement with retention of the prosthetic device has been best evaluated with early postoperative infections and has shown encouraging results. 105,106 In contrast, attempts to salvage the prosthesis in patients who have late infections or evidence of ongoing infection for more than 5 days have shown failure rates ranging from 62% to 86%. 104,107-110 Debridement with retention of the prosthesis may achieve rates of success of about 70% in carefully selected patients who are in the early postoperative period (< one month); 107,111-113 (1) patients must have a hyperacute presentation (< 2-5 days), 105,108,110 as shown in one study where the failure with debridement and retention greatly increased if symptoms of infection had been present for more than two days (RR = 4.2, 95% confidence interval = 1.6-10.3); 108 (2) the prosthesis must be stable without radiologic evidence of loosening; (3) the patient must be willing to comply with prolonged antimicrobial therapy for 3-6 months or longer; and (4) most importantly, the infecting micro-organism must be highly susceptible to both parenteral and oral antibiotics, such as a-hemolytic or group A streptococci.

Published studies of one-step exchange arthroplasty have reported success rates that exceed 80%, 114-118 which approaches the rate seen with the traditional two-step exchange arthroplasty. However, almost all of the published experiences are case series of highly selected patients (i.e. prosthetic infections caused by Gram-negative bacilli or methicillin-resistant Staph. aureus (MRSA) were excluded). Notably, Hanssen et al found that only 11% of patients presenting with prosthetic joint infection at their institution met criteria for one-step exchange arthroplasty. 119 Moreover, a study of 118 unselected infected total knee arthroplasties found that one-step exchange arthroplasty was successful in only 63% of cases, 120 and a retrospective analysis from the UK revealed that the rate of recurrent infection after one-stage exchange was three times higher than two stage exchange arthroplasty. 121 The lack of randomized trials, the lack of proven benefit with resistant Gram-positive and Gram-negative infections, and concerns over the emergence of resistance with the use of antimicrobial-impregnated cement during refractory infection' 16 limit the utility of this surgical approach.

Despite its proven benefit in the treatment of late prosthetic joint infection, there are situations where exchange arthroplasty is not feasible and where the quality of life associated with prolonged immobilization is unacceptable to the patient. In these situations, debridement with retention of the infected prosthesis, followed by indefinite suppressive antimicrobial therapy, has been proposed. 122,123 In contrast to prosthesis retention in the early postoperative period, the goal of therapy in this situation is not cure but rather indefinite suppression of infection. Segreti et al reported the utility of this approach in 18 patients with both early and late prosthetic joint infections; 123 eight were infected with Staph. aureus, two with MRSA, and seven with coagulase-negative staphylococci. Eleven of the 18 patients (61%) remained successfully suppressed at the end of the study period (median 49 months); seven discontinued antibiotic therapy, three because of breakthrough infection and four chose voluntarily to stop relapse of infection occurred in only one of the four. Other studies have met with lesser rates of success, ranging from 23 to 63%. 122-124

Antimicrobial therapy

Staphylococci are the most common infecting organisms and treatment of these infections is often most challenging. For strains susceptible to methicillin, nafcillin (oxacillin or flucloxacillin) is the agent of choice; for patients with well-documented allergy to penicillin, vancomycin or clindamycin is recommended. For staphylococci resistant to methicillin vancomycin is always the drug of choice and should be combined with rifampicin (rifampin).

Animal models have demonstrated the beneficial impact of rifampicin-containing antimicrobial regimens in implant-associated infections. 125,126 Growing clinical data confirm these findings; 105,127 a randomized study conducted by Zimmerli et al found that administration of a rifampicin-containing regimen to patients with prosthetic joint infections, who underwent irrigation and debridement with retention of their prosthesis, resulted in long-term cure in all of the 12 patients who completed at least 3-6 months of therapy. 105 Unless the infecting organism demonstrates in-vitro resistance or the patient has known allergy to rifampicin, based on these data we believe rifampicin should be routinely included in the regimen for all staphylococcal prosthetic joint infections, especially if vancomycin is used.

Newer fluoroquinolones (other than ciprofloxacin), such as levofloxacin and gatifloxacin, exhibit excellent in-vitro activity against staphylococci (although they are often inactive against MRSA), are highly bioavailable orally, and attain high joint fluid concentrations in experimental animal models of staphylococcal prosthetic joint infection. 128 Moreover, clinical trials of oral therapy in chronic osteomyelitis have demonstrated their equivalency to parenteral regimens, 129,130 although the studies were underpowered. Fluoroquinolone-containing regimens for treatment of staphylococcal prosthetic joint infection have shown benefit in a limited number of clinical studies. 105,127 However, in our opinion the role of fluoroquinolones in the initial antimicrobial regimen for treatment of prosthetic joint infections caused by staphylococci remains undefined. Rather, their utility at this time appears to be in the consolidation phase of therapy, after a patient has completed a prescribed period of intravenous nafcillin (oxacillin or flucloxacillin) or vancomycin in conjunction with rifampicin; or for the patient where chronic suppression, rather than cure is the goal. In-vitro confirmation of susceptibility is necessary before their use can be considered, and any fluoroquinolone-containing regimen should also include another effective antimicrobial, usually rifampicin, as at least one prospective study has described the emergence of fluoroquinolone resistance during prolonged monotherapy. 105
tive study of 3490 patients with prosthetic joints found that only seven developed prosthetic joint infection temporally related to a dental procedure.~ Five of these seven had underlying co-morbidity that predisposed them to infection, such as diabetes mellitus or rheumatoid arthritis. Based on these data, recent recommendations for the use of antibiotic prophylaxis in patients with prosthetic joints undergoing invasive procedures include patients with rheumatoid arthritis with a prosthesis implanted within the past year, an overt oral infection, a prolonged dental procedure (>1 15 minutes) and, possibly, diabetes mellitus or chronic corticosteroid therapy.~

**INFECTIONS ASSOCIATED WITH PROSTHETIC HEART VALVES**

### EPIDEMIOLOGY

Of all complications seen with implanted devices used in modern medicine, infection of a prosthetic valve is perhaps the most feared. It is estimated that 60,000 prosthetic valve replacements are performed in the USA each year. 146 Prosthetic valve endocarditis (PVE) accounts for 10-20% of all cases of endocarditis,147-149 and the 5-year risk of developing infection of a prosthetic valve after surgery has remained in the range of 3-6% since the 1960s. 150-154 The risk of PVE is highest within the first 2-3 months after surgery then falls to approximately 0.1-0.7% per patient-year thereafter. 150,152,154,155

The risk of infection of mitral and aortic valves appears to be similar. 150-152,156 However, the risk of infection with mechanical and bioprosthetic valves differs with the proximity to surgery: mechanical prosthetic valves have a higher incidence of infection in the first 12 months after implantation150,151 whereas the incidence of infection after 12 months is higher with bioprosthetic valves. 150,151 This results in an overall 5-year risk of infection that is similar for the two types of valves - 5.0% for mechanical and 6.3% for bioprosthetic valves. 150,151,156,158

Outcome with PVE has improved greatly over the past two decades but mortality remains high and is estimated to range from 32 to 64%. 150,156,159-161 The highest mortality is seen with early PVE (<60 days): 92 deaths occurred in a pooled analysis of 180 cases of early PVE (51%). 156,160,162-165 Mortality in late PVE (>60 days) is lower: 97 deaths occurred in the pooled analysis of 298 cases of late PVE (32%). 156,160-163

### PATHOGENESIS AND MICROBIAL ETIOLOGY

Infection of newly implanted mechanical and bioprosthetic valves may begin at the annular sewing line or on the valve itself. Early studies showed that mechanical valves are relatively resistant to infection of the prosthetic valvular component and that most infections begin at the interface between the endocardium of the annulus and the cloth sewing ring. In contrast, infection of bioprosthetic valves is more likely to begin on the valve structure itself. These observations are supported by older studies showing a much higher rate of perivalvular abscess with infection of mechanical valves. 110,166 More recent studies have failed to show such a difference. 155,167,168

As with orthopedic devices, most prosthetic valve infections are thought to derive from contamination of the valve at the time of surgery or in the early postoperative period. Similar to the definitions for early and late infection with orthopedic devices, infection of a prosthetic valve is arbitrarily defined as early or late based on whether it manifests within 60 days or later or, as now promoted by Karchmer, within 12 months of surgery or later. 168 These arbitrary cutoffs are relevant pathophysiologically because the risk of infection and the organisms encountered in early and late PVE differ significantly (Table 45.2). Most infecting organisms within the first 12 months after surgery are common nosocomial pathogens, most notably Staph. aureus and coagulase-negative staphylococci (Table 45.2); the coagulase-negative staphylococci recovered from PVE during the first year after surgery are far more likely to be resistant to methicillin than those recovered more than one year after surgery (87% versus 22%), 168 strongly suggesting that the former were acquired intraoperatively or in the immediate postoperative period. Furthermore, infections classically associated with native-valve endocarditis, such as streptococci and the ‘HACEK’ organisms are rarely (if ever) encountered in PVE until 12 months or longer after valve implantation (Table 45.2).

Although intraoperative contamination of the valve during surgery almost certainly accounts for most early postoperative prosthetic valve infections, 161,170 the contribution of hemato-

### Table 45.2 Micro-organisms involved in early and late prosthetic valve endocarditis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Early PVE (12 months)</th>
<th>Late PVE (&gt;12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>98 (37.4)</td>
<td>23 (10.5)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>49 (18.7)</td>
<td>41 (18.7)</td>
</tr>
<tr>
<td>Fungi</td>
<td>25 (9.5)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>24 (9.1)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>23 (8.8)</td>
<td>25 (11.4)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>12 (4.6)</td>
<td>74 (33.3)</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>10 (3.8)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>HACEK</td>
<td>0 (0)</td>
<td>11 (5.0)</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>15 (5.7)</td>
<td>17 (7.8)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6 (2.3)</td>
<td>9 (4.1)</td>
</tr>
</tbody>
</table>

a Pooled data from eight studies of early and late prosthetic valve endocarditis. 156,165,172,547

b PVE = Prosthetic valve endocarditis.

c HACEK Haemophilus parainfluenzae, Haemophilus aphrophilus, Actinobacillus actinomyocetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.
genous seeding cannot be overlooked. Heavy use of invasive devices, especially intravascular and urinary catheters, in the early postoperative period and the risk of nosocomial bloodstream infection related to their use is very high (see below).171,172 Studies suggest that 31-92% of cases of early postoperative PVE stem from another nosocomial infection.166,168,172 A study by Fang et al further highlights the risk of PVE in the setting of nosocomial bacteremia: 24% and 10% of patients with a prosthetic valve exposed to nosocomial bloodstream infection with Staph. aureus or Gram-negative bacilli developed secondary PVE, respectively.171

The organisms causing PVE greatly influence the outcome. PVE with Staph. aureus and coagulase-negative staphylococci is associated with a mortality ranging from 28% to 100%156,159-161,163,174-178 and, although data are limited, infections with aerobic Gram-negative bacilli and fungi appear to be associated with worse outcomes.171,171 In contrast, mortality from PVE caused by streptococci appears to be much lower, ranging from 5% to 35%.161,163,165

PVE is not only associated with a higher mortality than that seen with native valve endocarditis but is also associated with a higher rate of complications.111,166-168,180 Infection involving the suture line results in invasive infection of the annulus and underlying myocardium, with development of ring abscess, conduction abnormalities, and dehiscence of the prosthesis (with valvular incompetence). Moreover, the vegetations on a mechanical valve can interfere with normal closure, producing regurgitation or, alternatively, functional stenosis. Both complications are associated with a worse outcome and help define `complicated PVE':

- a new or worsening murmur due to valve dysfunction;
- new or worsening congestive heart failure due to valvular dysfunction or abscess;
- new electrocardiographic conduction abnormalities; or
- an intracardiac abscess detected by echocardiogram, surgery, or autopsy.119,168,178,181

Each of these complications is regarded as a clear-cut indication for surgical replacement of the infected prosthetic valve.

**DIAGNOSIS**

The clinical presentation of PVE does not differ greatly from that seen with native valve endocarditis. Signs and symptoms include fever (>90%),182 a new or changing murmur (40-70%),182 congestive heart failure (30-100%),182 petechiae (30-60%),182 splenomegaly (15-40%),182 embolic phenomena, including strokes or transient ischemic attacks (5-40%),182 shock (0-30%),182 and conduction abnormalities (5-20%).182 Osler’s nodes, Janeway lesions and Roth’s spots are relatively infrequent (5-15%).182 The likelihood that a patient will present with one or more clinical signs or symptoms is influenced in greatest measure by the virulence of the infecting organism. For example, in recent studies, PVE caused by Staph. aureus was associated with a necrologic event in 25-67% of cases, septic shock in 30% of cases and an overall mortality of 33-75%.161,163,178

Leukocytosis, anemia and elevations in the ESR and CRP are common in PVE but are non specific, especially in the early postoperative period.182 Isolation of a micro-organism from blood cultures is usually the first and best clue to PVE, and obtaining at least two - preferably three - blood cultures before beginning empiric antimicrobial therapy, is mandatory when evaluating unexplained fever in a patient with a prosthetic heart valve. If at least 20-30 ml of blood is obtained from each of three separate venepuncture sites, 99% of detectable bacteremias should be identified if the patient has not received recent antimicrobial therapy.183,184 In rare situations where blood cultures remain negative despite strong clinical suspicion of PVE, the use of special cultures or serologic tests to detect fastidious organisms, such as the `HACEK' species, Legionella spp., rapid growing mycobacteria, Coxiella burnetii, Mycoplasma hominis and fungi other than Candida, should be employed.185 The presence of a sustained, high-grade bacteremia or fungemia strongly suggests PVE and must prompt further evaluation of the prosthetic valve.186,187

The availability of transesophageal echocardiography (TEE) has greatly improved the capacity of clinicians to make a definitive diagnosis of PVE. For a variety of reasons, but most importantly because of the distance between the transducer and the heart, transthoracic echocardiography (TTE) can detect only the largest vegetations on a prosthetic valve in any location (>10 mm);188 compared with sensitivity of 17-40% for TTE189-191 the sensitivity of TEE for the diagnosis of PVE ranges from 77 to 100%.165,189,191 Moreover, TEE is greatly superior to TTE for detection of perivalvular abscess (up to 100% for TEE, 0-40% for TTE)192,193 and valvular dysfunction (86% for TEE, 43% for TTE). TEE visualizes the mitral valve extremely well but may have difficulty visualizing the entire aortic valve as well as portions of the left ventricular outflow track, and thus an approach that utilizes both TEE and TTE is recommended.194

The combination of clinical signs and symptoms, the results of blood cultures and echocardiography has been used to formulate criteria for the diagnosis of native valve endocarditis.185 Application of the Duke criteria to PVE has been evaluated in several studies;161,165,178 in confirmed cases of PVE, Duke criteria for definite PVE were met in 76-79% and criteria for possible PVE in an additional 20-24% cases.161,161 Perez-Vasquez et al have recommended amending these criteria for the diagnosis of PVE, adding heart failure and conduction disturbances to the minor criteria; 165 adding these two additional criteria increased the percentage of definite cases of PVE from 79 to 90%, although the effect on specificity was not addressed.

**TREATMENT**

The best management of patients with PVE often requires a combined medical and surgical approach. A careful analysis of
the nature of the infection and the infecting micro-organism is imperative to determine the best approach. Unfortunately, even when armed with this information, many aspects of the care of the patient with PVE remain unclear. For example, the findings that mandate surgical intervention and the timing of that intervention are still areas of dispute. Moreover, whether to continue or discontinue anticoagulation in a patient with an infected mechanical PVE is also unclear.

**Antimicrobial therapy**

Antimicrobial therapy must always be withheld until appropriate cultures can be obtained. The decision to then begin empiric antimicrobial therapy, before the results of cultures are available, is influenced by the perceived clinical urgency. With patients who are hemodynamically stable and without signs of complicated PVE, antimicrobial therapy can generally be safely withheld until bloodstream infection is confirmed.

With the patient who warrants immediate therapy because of fulminant sepsis or signs of dehiscence or other complications, therapy should be based on whether he or she has early PVE (< 12 months after surgery) or late PVE (> 12 months after surgery) and whether there is infection at a distant focus, such as urosepsis, surgical site infection, or an infected intravascular device, that points to a specific organism. Empiric therapy of patients with PVE should include vancomycin and gentamicin to cover resistant staphylococci, especially MRSA, enterococci and enteric Gram-negative bacilli. Antipseudomonal drugs may be indicated for early PVE in certain clinical settings, such as ventilator-associated pneumonia with suspected PVE. It is important to recognize that whereas the use of either vancomycin or gentamicin alone has a low risk of nephrotoxicity or ototoxicity (1-2%), when these drugs are used in combination for longer than 3-5 days, especially in elderly patients, the risk of toxicity rises sharply, to 25% or higher. In most importantly, the definitive regimen must be based on the identification and susceptibilities of the infecting organism.

Guidelines for antimicrobial therapy of native and prosthetic valve endocarditis caused by various organisms are summarized in Table 45.3. In general a bactericidal agent to which the micro-organism is susceptible should be used; for staphylococci, streptococci and enterococci in combination with gentamicin for at least 2 weeks to enhance the bactericidal activity of the regimen. The duration of therapy for PVE is longer than for native valve endocarditis, and antibiotic therapy should generally be continued for a minimum of 6 weeks, often longer, regardless of whether surgical intervention has occurred or is planned. Rifampicin may be added to the regimen with staphylococcal infections, based on its adjunctive value in osteomyelitis and prosthetic joint infections. Resistance to rifampicin develops rapidly when it is used as a single agent or when the microbial burden is high, and it may be desirable to delay adding rifampicin to the regimen until after 3-5 days of therapy with other agents. In the presence of high-level aminoglycoside resistance, therapy for enterococcal PVE should be prolonged to 8-12 weeks. The best

**Surgical therapy**

The onset of PVE within 2 months of valve replacement, new or worsening congestive heart failure due to valve dysfunction, new high-grade electrocardiographic conduction abnormalities, an intracardiac abscess detected echocardiographically, infection with staphylococci, *Ps. aeruginosa* or fungi, uncontrollably infection with persistent bloodstream infection despite appropriate antimicrobial therapy, relapse of endocarditis after a full course of appropriate antimicrobial therapy, and fever that persists beyond 10 days despite appropriate antimicrobial therapy are all associated with a poor outcome, and are regarded as indications for surgical intervention, with removal of the infected prosthetic valve, debridement of the annulus (and any abscesses found), and implantation of a new prosthetic valve. The decision to intervene surgically must take into account all of these factors as well as host factors predictive of poor surgical outcome such as stage IV heart failure, acute renal failure or, especially, multiorgan failure.

PVE presenting with severe heart failure, while associated with high operative mortality, is almost universally fatal within 6 months without surgery. Studies have shown that patients with paravalvular abscesses, which occur in 45-60% of patients with PVE, have survival rates approaching 80% when a combined medical-surgical approach is employed. In a recent study, *Staph. aureus* PVE treated medically was associated with a mortality of 83% whereas treatment with a combined medical-surgical approach was associated with a 20% mortality. It's a difference that remained highly significant, even after correcting for age, severity of illness and medical comorbidities.

Ideally, patients with clear indications for surgery but risk factors for a poor outcome should be taken immediately to the operating room before their heart failure worsens or their renal function is compromised - but, understandably, surgeons may be hesitant to perform valve replacement, which is associated with a mortality of 10-30% in experienced hands, when patients appear to be clinically stable and seem to be responding to antimicrobial therapy. Moreover, there is obviously theoretical concern about reimplanting a new prosthetic valve in an infected surgical site; however, the data indicate that the rate of recurrent PVE is low, 6-15%. Finally, delaying surgery to provide a longer duration of antimicrobial therapy

**Fungal PVE**

Fungal PVE has been associated with a very poor outcome and current management mandates surgical replacement of the infected valve followed by prolonged antifungal therapy. Amphotericin B, with or without 5-fluorocytosine, is recommended for *Candida* PVE, and some have recommended follow-up long-term suppressive therapy with an azole, based on reports of recurrent infection after parenteral therapy has been completed.

**Conclusion**

The management of PVE remains uncertain at this point, although there have been reports of successful outcomes, both with linezolid and with quinupristin-dalfopristin. Fungal PVE remains uncertain at this point, although there have been reports of successful outcomes, both with linezolid and with quinupristin-dalfopristin.
in the hopes of sterilizing the surgical bed has not been shown to improve outcome.\textsuperscript{1,2} Thus, the data indicate that a patient presenting with one or more indications listed in Table 45.6 will benefit from early cardiac surgery.

### Anticoagulation

A final controversial aspect of the care of patients with PVE is the decision whether to continue anticoagulation. Currently, most patients with bioprosthetic heart valves are anticoagulated for the first 3 months after valve replacement;\textsuperscript{2,5} however, in the setting of bioprosthetic valve endocarditis, the risk of anticoagulation outweighs the benefit and oral anticoagulants should be discontinued.

In contrast, patients with mechanical prosthetic heart valves have an annual risk of embolic stroke that approaches 4% without anticoagulation,\textsuperscript{2,5} and discontinuing anticoagulation in these patients is more problematic. Anticoagulation of patients with infected mechanical valves appears to offer protection against embolic stroke: in a large cohort study, patients with mechanical PVE who were anticoagulated had a much lower risk of stroke than patients who were not receiving anticoagulants (12% versus 42%).\textsuperscript{2,5}

Unfortunately, when stroke occurs in anticoagulated patients there is a higher risk of hemorrhagic extension,\textsuperscript{161,178,207} especially if Staph. aureus is the infecting pathogen. Studies suggest that the risk of neurologic deterioration is increased when patients with an embolic stroke undergo cardiac surgery within 2-3 weeks of the event, presumably because of the need for heparinization during cardiopulmonary bypass.\textsuperscript{2,5} Thus, it is generally considered desirable to continue anticoagulants in patients with mechanical valves and PVE, but every effort must be made to avert excessive anticoagulation; using intravenous heparin may provide a safer alternative during the early phase of therapy. Finally, if cerebral embolism does occur, anticoagulation should be withheld for several days to reduce the risk of hemorrhagic complications, and surgical intervention should be delayed, if possible, for at least 2-3 weeks to allow stabilization of the cerebral vasculature.\textsuperscript{2,5}

### PREVENTION

Prosthetic heart valves, whether bioprosthetic or mechanical, are considered at high risk for endocarditis in the latest American Heart Association guideline,\textsuperscript{2,5} and the use of prophylactic antibiotics before procedures that are likely to produce bacteremia is recommended to prevent late PVE.\textsuperscript{2,5} Interventions that reduce the risk of intraoperative contamination at the time of surgery will have the greatest impact on prevention of early PVE.\textsuperscript{2,5} Therefore, scrupulous asepsis and meticulous surgical technique combined with perioperative antimicrobial prophylaxis with drugs exhibiting antistaphylococcal activity - cefazolin, cefuroxime or cefamandole - forms the cornerstone of prevention of PVE. Vancomycin should not be routinely used for prophylaxis unless the hospital has a high rate of MRSA infection or the patient is a known MRSA carrier.\textsuperscript{2,5}

A novel silver-coated St. Jude valve (Silzone\textsuperscript{®}, St. Jude Medical Inc.) has been advocated to prevent recurrent PVE, with anecdotal success. The large, multicenter, Artificial Valve Endocarditis Reduction Trial (AVERT) trial was undertaken in 1999\textsuperscript{2} with the goal of assessing the efficacy of the novel medicated valve; however, there have been reports of recurrent PVE despite its use.\textsuperscript{2} Most importantly, enrollment in the AVERT trial was suspended in January 2001 because of evidence of increased paravalvular incompetence in patients who received the silver-coated valve.

### PACEMAKER INFECTIONS

#### EPIDEMIOLOGY

Approximately 370 000 pacemakers were implanted in the USA in 1996.\textsuperscript{3} Pacemaker infection manifests clinically in one of three ways depending on the type of pacing leads used:

- Localized infection of the pulse generator pocket
- Pericarditis and/or mediastinitis due to infection of epicardial pacing leads; or
- Primary bloodstream infection in association with rightsided endocarditis due to infection of transvenous endocardial pacing leads.

Overall rates of infection following implantation of a permanent pacemaker range from 1 to 7%.\textsuperscript{215-219}

Pacemaker endocarditis, a complication seen almost exclusively with endocardial pacing leads and caused mainly by Staph. aureus, occurs least commonly (0.5-1% of implantations).\textsuperscript{2,22} However, mortality is high, approaching 40% without removal of the infected leads.\textsuperscript{2,20}

Infection of the pulse-generator pocket is far more common in the early post-implant period, but can occur years later when the pacemaker battery is replaced.\textsuperscript{216} Invasive infection of the pacing leads typically manifests late, although infection may develop early if the leads become contaminated at the time of implantation.

The risk of pacemaker infection is increased in patients with diabetes mellitus or underlying malignancy,\textsuperscript{2,21} with operator inexperience,\textsuperscript{22} with manipulation of the pacemaker such as replacement of the battery,\textsuperscript{216} and if the patient requires a temporary transvenous pacemaker before implantation of the permanent pacemaker.\textsuperscript{22}

#### PATHOGENESIS

Infection occurs early (< 2 weeks), intermediate (2 weeks to 6 months), or late in the post-implantation period (> 6 months). Infections of the pulse-generator pocket constitute the majority of early and intermediate pacemaker infections, deriving
from contamination of the pulse generator pocket by cutaneous organisms at the time of implantation. Seeding of epicardial leads also occurs most frequently at the time of implantation, less often later, by migration of infection from the pulse-generator pocket, and thus also tends to present in the early and intermediate post-implantation period. Infection of transvenous pacemaker leads may occur at implantation, with migration of micro-organisms from an infected pulse-generator pocket, or derive from hematogenous seeding during a late bloodstream infection, and these infections tend to present in the intermediate or late post-implantation period, few presenting early.

**MICROBIOLOGY**

Predictably, most pacemaker infections are caused by Gram-positive organisms, especially Staph. aureus or coagulase negative staphylococci. Propionibacterium acnes, Gram-negative bacilli and Candida albicans account for most of the rest. Rare cases of late pacemaker endocarditis caused by viridans streptococci or enterococci have been reported.

Finally, rare organisms implicated in pacemaker infection have included Brucella melitensis, non-tuberculosis mycobacteria, Aspergillus Spp. and Petriellidium boydii.

**DIAGNOSIS**

The clinical presentation of pacemaker infection depends on whether it involves the pulse-generator pocket or the pacing leads. Infection of the pulse-generator pocket typically occurs shortly following implantation or battery exchange, and manifests with localized erythema, pain, and fluctuance, occasionally with erosion of the overlying skin. Rarely, migration of infection from the pocket produces pericardial involvement (when epicardial leads are used) or bloodstream infection, with endocardial leads. Infection of endocardial pacing leads typically presents as a primary bloodstream infection that varies in severity, depending on the causative organism: indolent febrile illness with coagulase-negative streptococci as contrasted with fulminant sepsis with Staph. aureus. In either case, signs and symptoms of right-sided endocarditis are often present, including fever and chills (> 80%), septic pulmonary emboli (20-45%), tricuspid regurgitation (25%).

A presumptive diagnosis of a pulse-generator pocket infection can usually be made on clinical grounds alone and is confirmed by a percutaneous aspirate from the pocket that shows micro-organisms on Gram stain or in culture. Diagnosing infection of an epicardial pacing lead can be more challenging unless bloodstream infection is present. Cryptogenic pericarditis or mediastinitis are usually identifiable by computed tomography (CT) or magnetic resonance imaging (MRI) of the chest but microbiologic confirmation is mandatory if blood cultures are non-diagnostic. As seen with PVE, foreign body-related endovascular infections are associated with high-grade bloodstream infection that typically does not quickly clear after starting antimicrobial therapy. Therefore, patients with endocardial pacing lead infection, in addition to manifesting signs of right-sided endocarditis, usually show high-grade bloodstream infection, despite days of appropriate antimicrobial therapy. Echocardiography shows vegetations on the endocardial leads and/or the tricuspid valve, and is valuable for confirming infection. TEE, with a sensitivity that ranges from 91 to 96% (compared with a 22-43%. sensitivity seen with TTE) is preferred.

**TREATMENT**

Successful treatment of pacemaker-related infection usually requires a combined medical and surgical approach. While isolated reports have claimed successful eradication of pacemaker infections with limited debridement followed by prolonged antimicrobial therapy, most of the published series report an unacceptably high failure rate unless the entire pacing system, including the battery pack and pacing wires, is removed. Lewis et al found that 31 of 32 patients with pacemaker infection treated at their center with medical therapy alone recurred and ultimately required removal of the entire pacing system to achieve cure. Similar experiences were reported by Molina et al, who found that 12 of 12 patients treated medically suffered recurrence. Most importantly, the mortality with infected endocardial leads is greatly increased in patients treated medically, as shown in an analysis of 182 cases by Cacoub et al, who found a 41% mortality in medically treated patients, compared with 18% in patients whose entire pacemaker was removed.

Traditional management mandates removal of the entire infected pacing system, placement of a temporary pacemaker, if indicated (not indicated in 13-52% of patients), followed by several weeks of parenteral antibiotic therapy, after which a new battery and endocardial pacing system are implanted. Recent studies have shown low recurrence rates with removal of the entire infected pacemaker followed by immediate placement of a new permanent epicardial pacing system, obviating the need for temporary pacing.

Transcutaneous extraction of infected endocardial leads that have been in place for prolonged periods is often difficult, as the lead is incorporated into a fibrous sheath in the right atrium and traction fails to dislodge the infected lead in 14-36% of cases. In this situation, open-heart surgical extraction is usually necessary. Recently, a transvenous excimer laser sheath has permitted successful lead extraction in 94% of cases, as contrasted with only 64% in a group where simple traction and a telescoping sheath were utilized.

Removal of an infected lead with large vegetations by transcutaneous extraction engenders concern over potential embolization. A study by Klug et al demonstrated that 30% of patients with endocardial lead vegetations had scintigraphic evidence of pulmonary emboli following removal of the lead, although none of these patients developed clinical symptoms.
Several series have reported successful transcutaneous extraction of infected leads with vegetations > 10 mm in size; however, concerns remain with vegetations this size and some authorities recommend proceeding directly to surgical removal. "

### PREVENTION

Strict aseptic technique and well-trained, experienced operators are be associated with reduced rates of pacemaker-related infection. Antibiotic prophylaxis has traditionally been discouraged, except in high-risk patients, however, a recent meta-analysis that encompassed 2023 patients found that routine antibiotic prophylaxis with anti-staphylococcal drugs was associated with a 75% reduction in pacemaker-related infections (CI 0.10-0.66, p = 0.005). Unfortunately, heterogeneity of the studies and inclusion of only a single, double-blinded, randomized trial limits application of this analysis. If prophylaxis is to be used, an antistaphylococcal drug, such as cefuroxime or cefazolin, is recommended (vancomycin if the patient has been colonized by or has had previous infection with MRSA).

### INFECTIONS RELATED TO INTRAVASCULAR DEVICES

#### EPIDEMIOLOGY

Reliable vascular access for administration of fluids and electrolytes, blood products, drugs, nutritional support and for hemodynamic monitoring has become one of the most essential features of modern medical care. Unfortunately, vascular access is associated with substantial and generally under-appreciated potential for producing iatrogenic disease, particularly bloodstream infection originating from infection of the percutaneous device used for vascular access or from contamination of the infusate administered through the device. More than one-half of all epidemics of nosocomial bacteremia or candidemia derive from vascular access in some form. More than 250 000 intravascular device (IVD) related bloodstream infections occur in the USA each year, each associated with 12-25% attributable mortality, prolonged hospital stay, and an added cost to healthcare of $33 000-$35 000.

Prospective studies in which every IVD was cultured at the time of removal show that every device carries some risk of causing bloodstream infection, but the magnitude of risk varies greatly (Table 45.4)."
Contamination of device prior to insertion
Extrinsic >> manufacturer

*HCW: health care worker

![Fig. 45.2 Routes of microbial colonization in the pathogenesis of intravascular device-related bloodstream infection (adapted from Maki and Mermel, 1998)](image)

- Coagulase-negative staphylococci (39%)
- *Staph. aureus* (26%)
- *Candida* species (11%)

MICROBIOLOGY

Micro-organisms found on patients' skin and which gain access to the IVD extraluminally, occasionally intraluminally - coagulase-negative staphylococci (39%), *Staph. aureus* (26%), and *Candida* species (11%) - account for 76% of IVD-related infections with short-term, non-cuffed devices of all types; only 14% are caused by Gram-negative bacilli (Figure 45.3). In contrast, with long-term surgically implanted devices such as cuffed and tunneled catheters, peripherally inserted central catheters, Hickman- and Broviac-type catheters, cuffed hemodialysis central venous catheters (CVCs), subcutaneous central ports and peripherally inserted central catheters, 260-262
catheters and subcutaneous central venous ports, coagulase-
negative staphylococci (25%) and Gram-negative bacilli (45%) 
(which most commonly gain access intraluminally and contam-
inate infusate in the device) account for 76% of IVD-related 
bloodstream infections; only 2% are caused by Candida species 
(Figure 45.3). 213

**DIAGNOSIS**

Despite the challenge in identifying the source of a patient’s 
signs of sepsis, 264 several clinical, epidemiological, and micro-
biologic findings point strongly towards an IVD as the source of 
a septic episode. 246 Patients with the abrupt onset of signs 
and symptoms of sepsis without any other identifiable source 
should prompt suspicion of infection of an IVD. 246 The presence 
of inflammation, with or without purulence, at the IVD 
insertion site, while present in the minority of cases, when com-
bined with signs and symptoms of sepsis has been shown to be 
predictive of IVD-related bacteremia and should prompt 
removal of the IVD. 246 Finally, recovery of certain micro-
organisms in multiple blood cultures, such as staphylococci, 
Corynebacterium or Bacillus spp., or Candida or Malassezia spp., 
strongly suggests infection of the IVD.

Removal and culture of the IVD has historically been the 
gold standard for the diagnosis of IVD-related infections, par-
icularly with short-term catheters. Numerous studies have 
deemonstrated the superiority of semiquantitative or quantita-
tive culture methods over qualitative broth culture for the diag-
nosis of such infections. 265,266 Growth of >15 cfu from an IVD 
segment by semiquantitative culture or growth of >103 cfu 
from a catheter segment cultured after sonication, when 
ampanied by local signs of infection or the systemic inflam-
atory response syndrome (SIRS) usually indicates infection of 
the IVD. The diagnosis of IVD-related bloodstream infection 
is completed when a heavily colonized IVD is associated with 
concurrent infection, with no other plausible source (i.e. 
primary bloodstream infection); the linkage becomes virtually 
certain when the strains recovered from the colonized IVD and 
from blood cultures are shown to be identical by phenotypic 
or, better, genotypic subtyping. 267-269

Semiquantitative and quantitative cultures of IVDs obvi-
ously require their removal. As noted, this can be a major 
problem in patients with long-term, surgically implanted IVDs 
such as Hickman and Broviac catheters, cuffed and tunneled 
hemodialysis catheters and subcutaneous central venous ports. 
Prospective studies of patients with long-term IVDs have 
shown that only 25-45% of episodes of sepsis represent true 
IVD-related bloodstream infection. 270,271 Thus, it would seem 
that development of in-situ methods of detecting such infec-
tions that do not require removal of the IVD would be of great 
utility to clinicians and patients, and in research studies.

If a laboratory is prepared to do pour-plate blood cultures 
or has available an automated quantitative system for cultur-
ing blood, such as the Isolator® lysis centrifugation system 
(Wampole Laboratories, Cranbury, NJ), quantitative blood 
cultures drawn through the IVD and concomitantly by 
venepuncture from a peripheral vein (or another IVD) can 
permit the diagnosis of IVD-related bacteremia or fungemia 
to be made with sensitivity and specificity in the range of 
80-95%. 266 without removal of the catheter, if empiric anti-
microbial therapy has not yet been initiated. With infected 
IVDs, the blood culture drawn through the device usually 
shows a five- to ten-fold rise in the concentration of organisms 
compared to the quantitative blood culture drawn percuta-
neously from a peripheral site. High grade peripheral can-
idemia (25 cfu/ml) reflects an infected IVD 90% of the 
time. 266 Quantitative IVD-drawn blood cultures are most 
useful for the diagnosis of infection with long-term devices but, 
because of their expense, have had limited utility for the diag-
nosis of infections associated with short-term devices. 22 There 
is evidence that a single quantitative culture drawn from a long-
term device, even without an accompanying quantitative 
culture drawn from the periphery, can accurately identify IVD-
related infection if there is >100 cfu/ml of growth. 266

Quantitative blood cultures are labor intensive and cost 
almost twice as much as standard blood cultures. 266 The wide 
availability of radiometric blood culture systems (e.g. 
BACTEC system®, Becton Dickenson), in which blood cul-
tures are continuously monitored for microbial growth 
(approximately every 20 min), has led to a clever application 
of this system for the detection of IVD-related bloodstream 
infeciton. The differential-time-to-positivity of blood cultures 
drawn through the IVD and concomitantly from a peripheral 
site has been evaluated as a surrogate for paired quantitative 
blood cultures. Detection of positivity in a blood culture drawn 
from the IVD more than 2 h before positivity of the culture 
drawn from a peripheral site has been shown to be highly pre-
dictive of IVD-related infection, in one study correctly identi-
fying 16 of 17 such infections with long-term catheters, yielding 
an overall sensitivity of 94% and specificity of 91%. 273 
Subsequent studies with short-term catheters, used mainly in 
the intensive care unit (ICU), have generally found lower pre-
dictive values, 274 probably related to the extraluminal patho-
genesis of infection with most of these devices.

Another simple but rapid and potentially cost-effective 
method of detecting IVD-related infection is acridine-orange 
leukocyte cytopsin (AOLC) staining, combined with Gram 
staining, of a sample of lysed and centrifuged blood drawn 
from the suspected IVD. In a recent prospective study of 124 
adult surgical patients, this method was found to be 96% sen-
sitive and 92% specific. 25 In contrast, AOLC with Gram stain-
ing was found in a recent prospective study to be of limited 
utility in diagnosing infection with short-term IVDs (mean 
duration of catheterization 6 days): AOLC failed to diagnose 
all 12 confirmed IVD-related infections. Therefore, AOLC 
with Gram stain will probably remain useful primarily for diag-
nosing infections associated with long-term IVDs. 277

In-situ testing using a novel culture-brush, which can be 
passed down the lumen and out the end of a long-term IVD 
to pick up luminal biofilm and colonized fibrin and thrombus 
around the tip, has also been proposed as an alternative to
removal and culture of the IVD. A prospective study that compared use of the endoluminal brush with semiquantitative culture of removed IVDs found the brush to be 95% sensitive and 84% specific. 276 However, a subsequent study failed to demonstrate this level of efficacy: van Heerdan et al found that use of the endoluminal brush was associated with a sensitivity of 21% although the specificity was 100%. 2" The predominance of organisms on the extraluminal surface of infected short-term catheters may limit the utility of the brush-culture in the ICU.

TREATMENT

If a short-term vascular catheter is suspected of being infected because the patient has no obvious other source of infection to explain fever, there is inflammation at the insertion site, or cryptogenic staphylococcal bacteremia or candidiasis has been documented, blood cultures should be obtained and the catheter should be removed and cultured. Failure to remove an infected catheter puts the patient at risk of developing septic thrombophlebitis with peripheral intravenous catheters, septic thrombosis of a great central vein with central venous catheters,278 or even endocarditis. Continued access, if necessary, can be established with a new catheter inserted in a new site. A new catheter should never be placed in an old site over a guidewire if the first catheter is suspected of being infected, especially if there is purulence at the site.

Bloodstream infection that might have originated from a cuffed and tunneled central venous catheter does not automatically mandate removal of the device, unless:

- There has been persistent exit site infection, the tunnel is obviously infected, there is evidence of complicating endocarditis, septic thrombosis, or septic pulmonary emboli, the infecting pathogen is Staph. aureus, 219 Corynebacterium jeikeium, 28 a Bacillus species, 291 Stenotrophomonas spp., Burkholdena cepacia, and all pseudomonas species, 282 a filamentous fungus or Malassezia species, 283 or a mycrobacterial species; 284 bactereemia or candidemia persists for more than 3 days despite adequate therapy.

Studies of 7-21 days of antibiotics infused through the infected line have shown success rates of 60-91% without catheter removal, 285-287 although there was significant variability in the response rates depending on the infecting microorganism; with infections due to coagulase-negative staphylococci, the risk of recurrent bacteremia has been approximately 20%. 288 Several studies have reported successful treatment of IVD-related infections due to Candida spp. without removing the device by administering prolonged courses of amphotericin B administered through the catheter; 289,290 however, this is in contrast to the results of other prospective studies that found an increased duration of candidemia and mortality in patients who retained their infected IVD. 291,292

In addition to infusion of systemic antibiotics through the infected line, which is mandatory for any patient with documented IVD-related infection, instillation of a highly concentrated solution of the antibiotic or antibiotic combination, ‘locked’ into the infected tunneled catheter, may be of adjunctive value to ‘cure’ an infected long-term IVD. In-vitro testing has proven the long-term stability of solutions of most antimicrobial agents over periods of time as long as 10 days. 293

In small, uncontrolled clinical trials, ‘antibiotic lock therapy’, usually in conjunction with systemic antibiotic therapy, has shown ‘cure’ rates with infected IVDs in excess of 90%, 294,295 but the vast majority of IVDs reported in these studies were infected with Gram-positive organisms other than Staph. aureus or Bacillus spp. (primarily coagulase-negative staphylococci or Gram-negative bacilli other than Ps. aeruginosa). Data are lacking on the value of lock therapy for IVD-related fungemia, and therefore at this time it cannot be recommended for the management of long term IVDs infected by Staph. aureus, Bacillus spp., Corynebacterium jeikeium, Stenotrophomonas spp., Burk. cepacia, all pseudomonas species, fungi or mycobacterial species.

Historically, central ports are rarely curable with medical therapy alone if the device is clearly infected (e.g. an aspirate from the port shows heavy growth), 296,297 In-vitro studies of antibiotic lock solutions in simulated models of infected central ports raise the possibility of using antibiotic lock therapy to preserve these long-term devices when they become infected. A recent study of patients with AIDS with central ports who developed IVD-related bloodstream infection found that lock therapy combined with systemic antibiotic therapy resulted in 70% of the ports being salvaged (although long-term follow-up was not reported). A recent larger clinical trial of antibiotic lock therapy for central port infections achieved salvage rates less than 50%. 298 Based on the marginal efficacy of the technique in these two studies and the historically poor cure rate achieved with systemic antibiotics alone, we believe that definitive treatment of infected central ports mandates their removal.

The decision to treat a suspected IVD-related infection before microbiologic confirmation (i.e. empirically) comes down to clinical judgment, weighing the evidence suggesting bloodstream infection and the risks of delaying treatment. In general, fever or other signs of sepsis in a granulocytopenic patient must be regarded as infection until proven otherwise.

If IVD-related bloodstream infection is suspected after cultures have been obtained, the combination of intravenous vancomycin (for staphylococci resistant to methicillin) with a fluoroquinolone (preferably ciprofloxacin) or with cefepime or a carbapenem (for aerobic Gram-negative bacilli) should prove effective against the bacterial pathogens most likely to be encountered. Initial therapy can then be modified based on the microbiologic identity and susceptibility of the infecting organisms.

While there are no prospective data to guide the duration of antimicrobial therapy for IVD-related infections, most coagulase-negative staphylococci infections can be cured with 5-7 days of therapy 246,288,299,300 whereas most infections caused by
other micro-organisms can be adequately treated with 10-14 days of antimicrobial therapy. These recommendations hold only as long as there are no complications related to the infection - endocarditis, septic thrombophlebitis, septic thrombosis, or metastatic infection such as osteomyelitis - and the infection clears within 72h of initiating therapy. Nosocomial enterococcal bacteremia deriving from an IVD is rarely associated with persistent endovascular infection, and unless there is clinical or echocardiographic evidence of endocarditis, treatment with intravenous ampicillin or vancomycin alone for 7-14 days should suffice.

The management of Staph. aureus device-related infection deserves special mention, as there have been no prospective studies to evaluate the optimal duration of therapy for such infection. Historically, high rates of associated infectious endocarditis and late complications led to a universal policy of 4-6 weeks of antimicrobial therapy for all patients with Staph. aureus bacteremia. Earlier diagnosis and initiation of bactericidal therapy of nosocomial Staph. aureus bacteremias in recent years have been associated with lower rates of infectious endocarditis and metastatic complications, prompting suggestions that short-course therapy (14 days) is effective and safe for most cases of IVD-related Staph. aureus bacteremia if the patient defervesces within 72h and there is no evidence of metastatic infection. In a study where TEE was routinely performed in 103 hospital patients with Staph. aureus bacteremia, 69 related to an IVD, Fowler et al found a surprisingly high rate of late complications, 2.3% with IVD-related Staph. aureus bacteremia. More recently, these authors reported that TEE is a cost-effective way to stratify patients with IVD-related Staph. aureus infection into short-course or long-course regimens. However, at this time there are no prospective studies to confirm this approach. Until more data are available, short-course antimicrobial therapy for IVD-related Staph. aureus bacteremia therapy should be used only when TEE is unequivocally negative, the patient has defervesced within 72h of starting therapy, and there is no evidence of distant metastatic infection.

All patients with IVD-related candidemia should be treated, even if the patient becomes afebrile and blood cultures spontaneously revert to negative following removal of the IVD without antifungal therapy. IVD-related candidemia that responds rapidly to removal of the catheter and institution of intravenous amphotericin B can be reliably treated with a daily dose of 0.3-0.5 mg/kg and a total dose of 3-5 mg/kg. Fluconazole (400 mg/day) has been shown to be as effective as amphotericin B in randomized trials in non-neutropenic patients, and has further been shown to be comparable to amphotericin B in observational studies of neutropenic patients with Candida IVD-related infection but should not be used with infections associated with septic thrombosis and high-grade candidemia or, obviously, with infections caused by fluconazole-resistant organisms such as Candida krusei or Candida glabrata.

All patients with an IVD-related bloodstream infection must be monitored closely, for at least 6 weeks after completing therapy, especially if they have had high-grade bacteremia or candidemia, to detect late-appearing endocarditis, retinitis or other metastatic infections, such as vertebral osteomyelitis.

**PREVENTION**

Over the past decade many investigators have evaluated strategies for the prevention of IVD-related infections, with greater success than with any other form of nosocomial infection. Guidelines for the prevention of such infections were last issued by the Hospital Infection Control Practices Advisory Committee in 1996 and have recently been revised. Wide adoption of these measures has resulted in a substantial decline in hospital-acquired primary bloodstream infections in the USA. More consistent adoption of control measures and wider acceptance of novel technologies shown to be effective (and cost-effective) will be needed to reduce this rate further.

**Aseptic technique**

Although there has been considerable controversy as to the level of barrier precautions necessary during insertion of a CVC, recent studies have shown that the use of maximal barriers - a long-sleeved, sterile surgical gown, mask, cap and large sterile drape, sterile gloves - significantly reduces the risk of CVC-related infection. The use of maximal barriers has further been shown to be highly cost-effective. Such measures are not necessary, however, for peripheral venous or arterial catheters used for hemodynamic monitoring, where sterile gloves and a small sterile fenestrated drape will suffice.

Given the evidence for the importance of cutaneous microorganisms in the genesis of IVD-related infection, the choice of the chemical antiseptic for disinfection of the insertion site would seem of high priority. In the USA, iodophors such as 10% povidone-iodine are widely used. Eight randomized, prospective trials have compared a chlorhexidine-containing antiseptic with povidone-iodine for disinfection of the skin before insertion of IVDs: both agents were well tolerated in every trial, seven of eight found lower rates of catheter colonization, and three showed a significant reduction in CVC-related infections in the chlorhexidine-containing antiseptic group. These studies indicate that chlorhexidine is superior to iodophors and should be the antiseptic of first choice for vascular access.

**Novel dressings**

IVDRs can be dressed with sterile gauze and tape or with a sterile transparent, semipermeable, polyurethane film dressing. The available data suggest that the two types of dressings are equivalent in terms of their impact on IVD-related infections.

Based on the superiority of chlorhexidine for cutaneous dis-
infection of vascular access sites, a novel chlorhexidine-impregnated sponge dressing has been developed (Biopatch®, Johnson and Johnson Medical Inc.) and evaluated in three trials to date.322-324 A large prospective, randomized trial comparing the use of the chlorhexidine dressing to a standard polyurethane dressing with short-term central venous and arterial catheters in adults admitted to two teaching hospital ICUs showed a 60% reduction in catheter-related bloodstream infections with use of the chlorhexidine sponge dressing (adjusted RR 0.38, p = 0.01), with no adverse reactions associated with its use.324 Moreover, testing of the in-vitro susceptibility of isolates from infected catheters in both groups showed no evidence that the antiseptic dressing promoted resistance to chlorhexidine.

**Innovative IVD design**

Hickman and Broviac catheters incorporate a subcutaneous Dacron® cuff which becomes ingrown by host tissue, creating a mechanical barrier against invasion of the tract by skin organisms. Rates of bloodstream infection per 1000 days with these catheters are far lower than with short-term percutaneously inserted, non-cuffed CVCs inserted in the ICU (Table 45.4).246,252 and can be considered a quantum advance for safer long-term vascular access.

Surgically implanted subcutaneous central venous ports, which can be accessed intermittently with a steel needle, have been associated with the lowest rates of bloodstream infection (Table 45.4; p. 588). A prospective observational study of Hickman catheters and central ports in oncology patients showed that for patients needing intermittent central access, ports appear to carry lower risk of IVD-related infection.290

Studies also suggest that peripherally inserted central catheters pose substantially lower risks of infection than standard non-tunneled, non-cuffed CVCs (Table 45.4),252 perhaps because bacterial colonization on the arm is lower than the neck or upper chest.202

A novel CVC made of polyurethane that is impregnated with minute quantities of silver sulfadiazine and chlorhexidine (ArrowGard®, Arrow International) became available approximately 10 years ago. There have now been 15 randomized trials of this catheter for prevention of related infection. Most have demonstrated a reduction in colonization of the catheter but only two studies were able to show a significant reduction in CVC related bloodstream infections.263,325 In the most rigorous study to date 268 which used molecular subtyping to conclusively identify CVC-related infections, the antiseptic catheter was associated with a two-fold reduction in catheter colonization and a five-fold reduction in catheter-related bloodstream infection (RR 0.21, p = 0.03). In-vitro analysis of 58 isolates from infected catheters in the two groups showed no evidence that use of the antiseptic catheter induced resistance to chlorhexidine and silver sulfadiazine. Use of the antiseptic catheter was shown to be highly cost effective if baseline rates of catheter-related blood infection exceeded 2% (3.3 per 1000 IVD-days).

Recent meta-analyses by Veenstra et al.326 and Mermei311 have shown that chlorhexidine-silver sulfadiazine-impregnated CVCs reduce rates of catheter related infection by at least 40% (OR 0.40-0.56). Veenstra et al have also published analyses suggesting that use of the antiseptic catheter is cost-effective if the baseline incidence of CVC-related infection is greater than 0.4 per 1000 IVD-days.327,328 They project that $59 000 will be saved, seven cases of bloodstream infection avoided and one death prevented for every 300 antiseptic catheters used.

Raad et al proposed the use of a minocycline-rifampin-coated catheter, based on in-vitro and animal data demonstrating potent activity of this novel combination against Gram-positive, and Gram-negative organisms and *Candida albicans*.329,330 A randomized clinical trial with nearly 300 short-term CVCs found that the coated catheters were associated with greatly reduced catheter colonization (8% versus 26%; p = < 0.001) and CVC-related infection (0% versus 5%; p = <0.01).269 N0 resistance to the minocycline-rifampicin combination was detected.

A multicenter trial comparing minocycline-rifampin-coated and chlorhexidine-silver sulfadiazine-impregnated CVCs found that antibiotic-coated catheters were far less likely to be colonized at removal (RR 0.34, p < 0.001).331 While Kaplan-Meier analysis showed the two catheters to be equivalent with regard to the risk of catheter-related blood infection until day 7, overall rates of such infection were much lower among patients with the minocycline-rifampin-coated catheter (0.3 versus 4.1 per 1000 IVD-days p = <0.001).

The major theoretical deterrents to using antibiotics for coating percutaneous intravascular catheters are the inefficacy of antibiotics against antibiotic-resistant nosocomial bacteria and yeasts, the risk of promoting bacterial resistance with long-term topical use332,333 and potential for hypersensitization.344 Although no induction of resistance to minocycline-rifampin has been identified in the three clinical trials to date,269,331,335 an in-vitro study has shown that resistance can develop.336 It would seem of high priority that future studies carefully evaluate the long-term impact of anti-infective-coated catheters on nosocomial microbial resistance.

Two second-generation silver-impregnated catheters have been studied clinically. The Erlanger™ catheter uses a micro-dispersed silver technology to greatly increase the quantity of available ionized silver and has been evaluated in two trials.337,338 Adult patients randomized to the Erlanger™ catheter had lower rates of catheter colonization and rates of ‘catheter-associated sepsis’ than those in the control catheter arm (5.3 versus 18.3 per 1000 IVD-days, p = <0.05).

A novel silver-impregnated CVC utilizing oligodynamic iontophoretic technology has also been developed and evaluated in two clinical trials. This novel catheter incorporates both silver and platinum in the polyurethane, putatively increasing the surface release of silver ions. A single randomized clinical trial, while underpowered, found a trend towards reduced catheter-related bloodstream infection with the use of this catheter (4% versus 12%; p = 0.09).339 A larger trial that used historical controls, demonstrated rates of CVC-related infec-
Anti-infective hubs

A novel hub developed by Segura et al (Segur-Lock®, Inibsa laboratories) contains a connecting chamber filled with iodinated alcohol and was shown in a randomized clinical trial to be associated with greatly reduced rates of catheter colonization and CVC-related bloodstream infection (4% versus 16%; \( p = <0.01 \)).347 Although a subsequent trial failed to show benefit with the use of this hub, 342 Another model, using a povidone-iodine saturated sponge to encase the hub, also showed significant reductions in CVC-related infection, compared to a control hub (0% versus 24%, \( p = <0.05 \)).343

Antibiotic lock therapy

Prophylactic use of systemic antibiotics at the time of IVD implantation has not proven effective in reducing the incidence of IVD-related bloodstream infections and is strongly discouraged.313 However, studies of continuous infusion of vancomycin, incorporated into total parenteral nutrition admixtures, have shown reduced rates of coagulase-negative staphylococcal bacteremia in low-birth-weight infants.344 Unfortunately, this form of prophylaxis results in prolonged low blood levels of vancomycin, which may be conducive to promoting resistance.

The ‘antibiotic lock’ is a novel technique of local prophylaxis: an antibiotic solution is instilled into the catheter lumen and allowed to dwell for a defined period of time, usually 6-12 hours, after which it is removed. There have been six prospective randomized trials of antibiotic lock solutions for the prevention of bloodstream infections with long-term IVDs. The largest trial and most recent trial by Henrickson et al345 randomized 126 pediatric oncology patients (36,944 “-days) who had recently had a tunneled CVC implanted to three prophylactic lock regimens: heparin (10 U/ml) (control); heparin, vancomycin (25 gg/ml); and heparin, vancomycin and ciprofloxacin (2 gg/ml). Use of the vancomycin-ciprofloxacin containing lock solution was associated with a markedly lower rate of IVD-related infection, than with heparin alone (0.55 versus 1.72 per 1000 IVD-days; \( p = 0.005 \)). Similarly, the rate of infection with vancomycin-containing lock solution was significantly reduced (0.37 per 1000 IVD-days; \( p = 0.004 \)). The two antimicrobial lock solutions showed comparable protection against Gram-positive and Gram-negative IVD-related infection. Unfortunately, failure to separate local infections from bloodstream infections in the final data limits analysis of the results of this study. While rates of nosocomial colonization or infection with vancomycin-resistant enterococci, as detected by clinical cultures ordered by patients’ physicians, were comparable in the three groups, no effort was made to proactively assess the impact of antibiotic-containing lock solutions on nosocomial colonization by vancomycin-resistant enterococci, MRSA and fluoroquinolone-resistant Gram-negative bacilli.

Most studies used a lock solution containing vancomycin. It seems unlikely that micro-organisms in the exposed patient’s flora could develop resistance to vancomycin from the minute quantities of drug in a catheter lumen (< 15 gg), yet there is just concern over the possible effect of wide prophylactic use of vancomycin lock solutions, and more data are needed before their routine use can be recommended, specifically, randomized studies that prospectively assess the impact on nosocomial colonization by resistant micro-organisms. However, because antibiotic lock solutions clearly reduce the risk of implant-related infections with long-term IVDs, the new HICPAC Guideline considers their use acceptable in individual cases in which a patient who requires indefinite vascular access continues to experience such infections despite maximal compliance with infection control guidelines.313

Infection of Cerebrospinal Fluid Shunts

Epidemiology

Cerebrospinal fluid (CSF) shunts are widely used for surgical decompression and diversion of excess CSF in the management of hydrocephalus. Approximately 25,000 shunt procedures are performed in the USA annually, making it the most commonly performed neurosurgical operation.346 While considerable success in the treatment of hydrocephalus has been achieved, the most serious complication remains infection. Early studies reported rates of CSF shunt infection ranging from 1.5 to 39% (mean 10-15%);347,348 however, during the past two decades infection rates have dropped to 2-9%.349-352 Most reported series are from infant and pediatric populations, as most shunts are placed for treatment of congenital hydrocephalus. Ventricular shunt infection rates range from 3.9 to 5.2%353 in the most recent US national nosocomial infection surveillance report, with the highest risk in children, particularly premature infants,354 and elderly people.349 CSF shunt infections are associated with a mortality of 20-50%,355,356 prolonged stay in hospital, and an increased risk of seizure disorder357 and decreased intellectual performance in survivors.358

A CSF shunt system consists of a catheter placed either in the ventricle or the lumbar subarachnoid space which is connected to a subcutaneous silastic tube through which CSF drains into the central great veins, the pleural space or, most commonly, the peritoneum. A reservoir to allow percutaneous access for CSF sampling and intraventricular administration of antibiotics or chemotherapy may be incorporated (e.g., Hakim system) or may be independent (Rickham or Ommaya reservoir). Pressure-regulating valves are also usually integrated into the system.

A variety of different shunt systems have been evaluated but...
ventriculoatrial (VA) and ventriculoperitoneal (VP) shunts have been employed most widely in clinical practice (Figure 45.4). VP shunting has become the diversion procedure of choice because of its shorter operative time and the need for fewer revisions than VA shunts. The rate of infection does not appear to differ greatly between VA and VP shunts.

A number of studies have identified risk factors that predispose to the occurrence of shunt-related ventriculitis or meningitis. One large, recent prospective study of 299 patients using multivariable techniques of data analysis found the presence of a CSF leak (odds ratio 19.2), infant prematurity (odds ratio 4.7) and a breach in surgical asepsis (odds ratio 1.07) to be the most important risk factors for shunt infection. Other risk factors include younger age (10-20% rates of infection in infants <6 months of age) and high cutaneous floral density.

**PATHOGENESIS**

Micro-organisms gain access to the shunt by three routes: (1) intraoperative colonization; (2) hematogenous seeding of the shunt; or (3) retrograde spread of infection from the distal portion of the catheter, such as the peritoneal cavity or bloodstream. Intraoperative contamination of the shunt is widely considered to be most important, since 80% of infections occur within 6 months of surgery. Bayston et al compared organisms cultured from the surgical wound at the time of shunt insertion or revision with those cultured from the patient’s nose, ear or skin before operation: 58% of wounds were colonized, and in one-half the colonizing organism originated from the patient’s own flora. The level of contamination of the wound was directly proportional to the duration of the surgical procedure. More recently, airborne bacteria in the operating room have been identified as an important source of shunt infection.

Three factors play a central role in the development of shunt infection: the microbial inoculum; microbial virulence, and the patient’s host defenses. CSF shunt implantation is a clean-nonsurgical procedure; hence, the inoculum should be small. Coagulase-negative staphylococci cause most infections and are of low intrinsic virulence. Host defenses are severely impaired, however, because of the foreign body nature of the shunt. The pressure valves have been found to be the most heavily colonized portion of an infected shunt.

Bacteremia from a remote source can also cause secondary infection of CSF shunts. The frequency of VP shunt infection by this route is unclear but is thought to be low. VA shunts, however, are continuously and directly exposed to potential infection by silent transient bacteremias. Reports of late Haemophilus influenzae with VA shunts infections in children affirm the potential for hematogenous infection of these devices.

Infection of the distal portion of a VP shunt may derive from perforation of an intra-abdominal viscus or pelvic inflammatory disease in women, with retrograde extension of infection throughout the drainage tubing and valve apparatus. Although lumbo-ureteral shunts are now rarely used, retrograde infection by Gram-negative bacilli derive from silent bacteriuria.

**MICROBIOLOGY**

Staphylococcus epidermidis and other coagulase-negative staphylococci are responsible for the vast majority of CSF shunt infections, and Staph. aureus causes about 25% of cases (Table 45.5). Gram-negative enteric bacteria and Pseudomonas spp. account for about 5-10% of infections and are associated with greater morbidity and mortality.

Anaerobic organisms, particularly Propionibacterium species, account for 3-20% of infections in various series. Polymicrobial infection must prompt suspicion of bowel perforation as the source. Fungal infections, fortunately, are rare, accounting for less than 1% of infections; C. albicans is the leading pathogen, although infections with Coccidioides immitis, Cryptococcus neoformans and Histoplasma capsulatum have been reported.

**Table 45.5 Microbiologic profile of CSF shunt infections**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis</td>
<td>60-70</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2-25</td>
</tr>
<tr>
<td>Streptococcal species</td>
<td>8-10</td>
</tr>
<tr>
<td>Enteric Gram-negative bacilli</td>
<td>6-20</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>6</td>
</tr>
<tr>
<td>Diphtheroids</td>
<td>1-14</td>
</tr>
<tr>
<td>Organisms of traditional meningitis</td>
<td>2-8</td>
</tr>
</tbody>
</table>

* Pooled data.  
* H. influenzae, Str. pneumoniae and N. meningitidis
DIAGNOSIS

The clinical manifestations and diagnostic approach to shunt infections vary, depending in part on the type and location of the shunt. Fever is the most common manifestation of infection with all types of shunts but is not universally present, especially if the infecting organism is CNS. With proximal infection (ventriculitis), headache may be absent and non-specific symptoms such as lethargy and malaise may be the only clinical clues to infection; meningismus is present in less than one-third of cases. Complications of VA shunt infections include septic pulmonary emboli, perforation of the interatrial septum, superior or inferior vena caval obstruction, atrial thrombus and right-sided endocarditis. A rare manifestation of chronic VA shunt infection is shunt nephritis caused by deposition of antigen-antibody complexes onto the glomerular basement membrane, similar to the immune complex nephritis of bacterial endocarditis. The nephritis characteristically resolves when the underlying shunt infection is eradicated.

Up to one-third of patients with VP shunts present with abdominal symptoms. A loculated CSF collection often develops; however, if encystation by the peritoneum is unsuccessful, frank peritonitis may occur. The presence of a peritoneal pseudocyst in a patient with a VP shunt almost always indicates shunt infection. VP shunts are also well known to spontaneously perforate the bowel. In the early postoperative period, local signs of inflammation with wound infection or infection of the subcutaneous course of the drainage tubing may be present. The first indication of occult infection is often shunt malfunction. Occult infection must be ruled out in every case of shunt malfunction.

The diagnosis of shunt infection requires a high index of suspicion because of its insidious and frequently nonspecific presentation. Fever in a shunted patient should always prompt suspicion of shunt infection. Blood cultures reliably identify the causative organism in 95% of VA shunt infections. In contrast only 20% of VP infected shunts produce bacteremia.

The peripheral white blood cell count (WBC) is of limited value in diagnosing shunt infection; up to 25% of patients have a normal WBC count. CSF leukocytosis is also usually modest: one study reported a median CSF WBC count of 79 cells/mm3. Gram-stained smears of CSF were positive in the majority of cases of infection with Staph. aureus and Gram-negative bacilli (82% and 91% respectively) but in only a minute fraction of cases (4%) caused by coagulase-negative staphylococci. Other CSF changes are rarely helpful in the diagnosis; hypoglycorrhachia is infrequent and slight, when present; protein elevation is often present but is non-specific.

Cultures of CSF obtained from the shunt are essential to establish the diagnosis and are positive in 90% of patients when pleocytosis is > 100 white cells/mm3, but only 50% of patients when pleocytosis is < 20 white cells/mm3. The highest yield is when the CSF is aspirated directly from the shunt (92%). Radiologic imaging is useful if the patient has abdominal symptoms or a palpable mass, to evaluate for the presence of a peritoneal pseudocyst, which almost always signifies infection. If the shunt is malfunctioning, brain imaging may show hydrocephalus.

TREATMENT

Management of the shunt

Once CSF shunt infection is diagnosed, usually by a positive CSF culture, options for treatment include:

- complete removal of the shunt apparatus, delaying replacement until the infection has been eradicated with parenteral antibiotics;
- surgical removal of the shunt, temporary external CSF drainage, parenteral antimicrobial therapy, with shunt replacement after the infection has been eradicated;
- externalization of distal portion of shunt (for VP shunts), followed by delayed replacement, in conjunction with systemic antimicrobial therapy;
- retention of shunt, attempting to eradicate the infection with antibiotic therapy alone.

All of these approaches, except the last, subject the patient to one or more surgical procedures, with attendant risks. The most widely accepted approach has been complete removal of the entire shunt apparatus, followed by prolonged antimicrobial therapy, with later implantation of a new shunt on the contralateral side. If CSF drainage is necessary during the interim period temporary external CSF drainage can be provided with a ventriculostomy catheter.

In a prospective randomized study, James et al compared three groups of patients with VP shunt infections who were treated by three different approaches: one group underwent shunt removal, systemic antibiotic therapy and external ventricular drainage; the second, shunt removal with immediate shunt replacement, followed by intrashunt antibiotic therapy; and the third, systemic and intraventricular antibiotic therapy alone without shunt removal. The cure rates were 100%, 90% and 30%, respectively. The group that received antimicrobial therapy alone had a much longer hospital course and two of the ten patients died. Larger retrospective series have corroborated these results (Table 45.6), and removal of an infected shunt is considered mandatory to achieve reliable cure of shunt infections. McLaurin et al have suggested that some VP shunt infections may be cured without removing the ventricular portion of the apparatus, by externalizing the peritoneal catheter and closed system drainage, combined with intraventricular and systemic antimicrobial therapy; of 11 patients with VP shunts (age range three weeks to 14 years), 10 were reportedly cured of infection with this approach. Follow-up periods ranged from 4 months to 5 years. However, in a more recent study, externalization of distal tubing with retention of the
shunt and systemic antimicrobial therapy in patients with VP shunt infections showed persistently positive CSF cultures in 10 of 21 patients. The most common infecting organisms were coagulase-negative staphylococci.

Meningitis due to fastidious, highly sensitive organisms that reach the CSF from the primary bloodstream infections (e.g. *H. influenzae*, *Str. pneumoniae* and *Neisseria meningitidis*) has been treated successfully without shunt removal.

### Antimicrobial therapy

Several factors must be taken into consideration when choosing systemic antimicrobial therapy, including: CSF penetration of the agent; susceptibility of the infecting organism; and the potential for neurotoxicity. Nearly 90% of coagulase-negative staphylococcal infections acquired in the hospital implicated in shunt infections are now resistant to methicillin, and vancomycin is thus the drug of choice for most Gram-positive infections. Although its CSF penetration is modest, with meningeal inflammation it is usually possible to achieve therapeutic CSF concentrations. Rifampicin is often added for enhanced bactericidal activity, high CSF penetration, in-vitro synergism with vancomycin and β-lactams, and its adjunctive value in other device-related infections.

For Gram-negative infections, group 4 cephalosporins or carbapenems, such as imipenem, provide effective treatment if the infecting organism is susceptible, however, with imipenem use in the setting of meningitis or ventriculitis, the risk of seizures is considerable (33% in some series); meropenem appears to pose a lower risk.

Intraventricular antimicrobial therapy has been extensively used in the past, with or without systematically administered antibiotics for treatment of CSF shunt infections, although the indications for intraventricular therapy are uncertain. The most commonly used intraventricular antimicrobials have been the aminoglycosides and vancomycin.

Intrathecal aminoglycosides have been widely used for the treatment of shunt infections, however, ototoxicity has been encountered, and no randomized trials have confirmed their benefit. The only prospective randomized trial to compare systemic to intrathecal administration of gentamicin, a study of neonates with Gram-negative meningitis, showed that mortality was higher in infants given intrathecal gentamicin (43%) than in those given systemic gentamicin (13%). Some authors have recommended routine measurement of CSF aminoglycoside levels to reduce the risk of toxicity; however, accurate measurement of CSF drug levels is fraught with difficulty and studies have failed to show a correlation between toxicity and CSF aminoglycoside levels, even with peak levels as high as 450 mg/l and trough levels as high as 76 mg/l.

No prospective studies have compared the efficacy of intrathecal vancomycin with systemic vancomycin, although anecdotal reports suggest that intrathecal vancomycin therapy is beneficial. Vancomycin penetrates the CSF poorly in the absence of inflammation, and even in the presence of inflammation attains CSF levels only one-fifth of those it reaches in serum. Vancomycin typically is administered intrathecally in doses of 5-20 mg per 24 h. There have been no reports of neurotoxicity, even with CSF levels as high as 100 mg/1.

Intraventricular β-lactams and cephalosporins cause seizures and neurological deficits and their use is strongly discouraged.

Antimicrobials given intrathecally should be constituted in a preservative-free medium to reduce the risk of arachnoiditis. In general, removal of the infected shunt and intravenous antibiotic therapy will prove effective in the vast majority of cases, and intraventricular antibiotic therapy should be used only if there is reason to believe that therapeutic CSF concentrations cannot be achieved with systemically administered antibiotics, such as in patients with severe scarring of the choroid plexus or if the antimicrobial of choice is known to have poor CSF penetration, such as an aminoglycoside.

There is a paucity of clinical data regarding the duration of therapy for CSF shunt infections; a minimum of 7 days has been suggested, with the final duration influenced by the rapidity of clinical improvement and results of serial CSF cultures.

### PREVENTION

As it appears that intraoperative contamination by skin flora or airborne skin organisms is the most important mechanism of infection of CSF shunts, efforts have been directed at improving intraoperative asepsis and reducing contamination of the operative field. Novel measures that have been evaluated include adhesive plastic drapes, use of ultraviolet lights in the operating room, soaking shunts in an antimicrobial solution and irrigating the wound with an antibiotic solution. None has been evaluated in a randomized trial, and thus most cannot be routinely recommended.

Faillace et al reported a meticulous ‘no-touch’ protocol for CSF shunt implantation, which involved minimal handling...
of shunt components during implantation through use of special instruments, placing the shunt on a separate table away from skin dissection instruments, limiting the number of personnel in the operating room, and intensive education of surgical assistants and nurses: a threefold decrease in the rate of shunt infection was observed, from 9.1% before implementation of the new protocol to 2.9% (odds ratio 0.30; P = 0.05).

Choux et al employed an even more intensive perioperative protocol, including not shaving the operative site, using chlorhexidine or povidone-iodine for site disinfection, implantation early in the morning before other operations, single-dose perioperative prophylaxis, meticulous surgical technique and limiting the implantation procedure to 40 minutes. With adoption of these measures, the authors observed a decreased infection rate from 7% to 0.2%. However, because so many modifications of the surgical procedure were made, it is difficult to draw conclusions about the independent role of each measure. While most neurosurgeons shave their patients preoperatively, randomized trials have shown that shaving may increase the risk of CSF shunt infection.

The use of perioperative prophylactic antibiotics for shunt implantation procedures has been controversial. Most studies have suffered from methodologic problems: most were uncontrolled, retrospective comparisons. Few of the randomized trials done were adequately powered to detect a clear-cut benefit from use of preoperative prophylactic antibiotic therapy. In one prospective trial of 243 patients undergoing 300 CSF shunt implantations, oral trimethoprim and rifampicin were administered 2 h before surgery and for 48 h postoperatively. A lower infection rate (12%) was found in the treatment group than the placebo group (19%); however, the results did not achieve statistical significance. In another randomized trial, Blomstedt reported significantly fewer infections among patients receiving perioperative trimethoprim-sulfamethoxazole than those receiving placebo; however, children less than 12 years of age were excluded from the study, and the 29% baseline rate of infection is very high.

Bayston et al determined that a randomized trial with power to detect a statistically significant difference, if one exists, would require 712 patients. Their multicenter trial was not able to achieve this goal and was terminated after 2.5 years. Several meta-analyses have attempted to resolve this issue. Two suggest benefit: one early and smaller meta-analysis did not: the same authors also showed that catheters impregnated with clindamycin and rifampicin resisted three successive challenge doses of Staph. epidermidis over a 28-day period as well as biweekly challenges with strains of Staph. aureus and Staph. epidermidis over periods as long as 56 days.

While these in-vitro studies are promising, the efficacy, thrombogenic and epileptogenic potential of medicated shunts must be evaluated by randomized clinical trials before they can be recommended.

An ineffective immune response against infection in infants is thought to contribute to the higher infections rates of CSF shunts in patients less than one year of age. A prospective randomized trial of administering a single dose of intravenous immunoglobulin prior to shunt implantation in infants showed a lower rate of infection in the group given immunoglobulin (0 versus 5.1%), however, the study was underpowered (60 patients), and the results did not achieve statistical significance.

**VENTRICULOSTOMY-RELATED INFECTIONS**

**EPIDEMIOLOGY**

Intracranial pressure monitoring has become essential for the management of patients with closed head injuries or who have undergone major neurosurgical operations. Techniques used to measure intracranial pressure include use of ventriculostomy catheters (72%), intraparenchymal catheters (47%), subarachnoid bolts (25%), epidural catheters (15%) and subdural catheters (5%). The most accurate and widely used method to continuously measure intracranial pressure is by placement of an intraventricular catheter through a burr hole into the lateral ventricle. Unfortunately, ventriculostomy catheters are associated with a substantial risk of ventriculitis and meningitis, which has significant morbidity.

Infection is the primary complication associated with the use of ventriculostomies, ranging from 0 to 40%. Most studies average 10% and a large meta-analysis, which included more than 6000 patients, found an overall rate of infection of 5.8%. Prospective studies indicate that the greatest risk factor for development of ventriculostomy-related infection is the duration of ventricular catheterization.

In a large prospective study, found that the risk of infection rose to 9% after 5 days of catheterization (RR, 7.0). Paramore et al found that the rate of infection rose to 10.3% by the sixth day. Irrigation of the system, intracerebral or intraventricular hemorrhage (RR 3.5) and high intracranial pressures have also been found to increase the risk of nosocomial ventriculitis.
**PATHOGENESIS AND MICROBIOLOGY**

The pathogenesis of ventriculostomy-related infection is poorly understood: infecting organisms can be introduced at the time of catheter insertion, but probably more often gain access during later manipulation of the system for CSF drainage or calibration.440

Ventriculostomy-related infection is very similar to postoperative neurosurgical wound infection. The most common infecting micro-organisms have been coagulase-negative staphylococci and *Staph. aureus*, which cause 60-80% of all cases.433,442 However, a significant number of cases of nosocomial meningitis are caused by Gram-negative bacilli, ranging from 16 to 33%.443,444

**TREATMENT**

Similar to the treatment of CSF shunt infections, the treatment of ventriculostomy-related infection should be guided by the results of the CSF Gram-stain and culture. If feasible, the catheter should be removed unless intrathecal therapy is considered essential (e.g. for *P. aeruginosa* ventriculitis). For most nosocomial staphylococcal infections, intravenous vancomycin and oral rifampicin are required, unless in-vitro susceptibility testing shows susceptibility to (3-lactams.

For ventriculitis caused by Gram-negative bacilli, a cephalosporin such as cefepime or cefotaxime or a carbapenem (meropenem, rather than imipenem, given the higher risk of seizures with the latter440), with or without ciprofloxacin, should prove effective in most cases.

As noted, the role of intraventricular antimicrobial therapy in the treatment of CSF infections related to neurosurgery is undefined, but its use should be considered in patients who fail to improve despite the use of appropriate systemic antimicrobial therapy.

**PREVENTION**

Prevention of catheter-related ventriculitis begins with limiting the duration of catheterization to the fewest days necessary and maintaining a stringently closed system. Mayhall et al have recommended relocating the ventricular catheter to a new site if monitoring exceeds 5 days;433 however, the risks associated with placement of a new ventriculostomy catheter, especially intracranial hemorrhage, have been estimated to be as high as 6%.430

Data on the prophylactic use of antibiotics at the time of catheter insertion and/or throughout the duration of ventricular catheterization are also conflicting. Of five retrospective431,434-436,438 and two prospective trials4,433,437 only two retrospective studies found the use of antimicrobial prophylaxis to be beneficial.434,435

One randomized trial in 228 patients receiving ventriculostomy catheters compared brief perioperative administration of prophylactic antibiotics with prolonged prophylaxis, in which the patients received therapy for the entire period of catheterization, and showed a lower infection rate in patients receiving prolonged prophylaxis with ampicillin-sulbactam and aztreonam (3% versus 11%, P = 0.01).445 However, the pathogens causing infection in patients receiving prolonged prophylaxis showed greater antimicrobial resistance. Two other randomized trials, one in 52 patients and the other in 95 patients, did not demonstrate any benefit from prophylactic antibiotic use, but the studies were severely underpowered.422,446 Prophylactic antibiotics to prevent monitoring-related ventriculitis with ventriculostomy catheters are probably not effective, are likely to promote infection by multiresistant pathogens, and based on current data, are not recommended.

**CATHETER-ASSOCIATED URINARY TRACT INFECTIONS**

**EPIDEMIOLOGY**

Catheter-associated urinary tract infections (CAUTIs) account for 40% of all nosocomial infections in the USA, affecting an estimated 800 000 patients per year.441 In the 25% of patients that have a urinary catheter inserted at some time during their hospital stay the incidence of nosocomial UTI is approximately 5% per day, with virtually all patients developing bacteriuria by 30 days of catheterization.448 Even though the vast majority of these infections are asymptomatic,449 silent CAUTIs comprise the largest pool of antibiotic-resistant pathogens in the hospital435 and drive a great deal of generally unnecessary antibiotic therapy.

Large, prospective studies in which catheterized patients were cultured daily and which used multivariable techniques of statistical analysis have identified risk factors independently predictive of an increased risk for CAUTI: 450-453 females have a higher risk than males (RR, 2.5-3.7), and patients with other active sites of infection (RR, 2.3-2.4) or a major pre-existing chronic condition such as diabetes (RR, 2.2-2.3), malnutrition (RR, 2.4), or renal insufficiency (RR, 2.1-2.6), are also at higher risk; inserting the catheter outside the operating room (RR, 2.0-5.3) or late in hospitalization (RR, 2.6-8.6), the presence of a ureteral stent (RR, 2.5) or using the catheter to measure urine output (RR, 2.0) further increase risk. The most important modifiable risk factor, identified in every study, is prolonged catheterization - beyond six days. Antimicrobial therapy is protective against CAUTI for short-term catheterizations (RR, 0.1-0.4) but clearly selects for infection caused by multiresistant micro-organisms such as *P. aeruginosa* and other resistant Gram-negative bacilli, enterococci and yeasts.

A recent large, prospective study monitored compliance on a daily basis with seven recommended precepts for catheter care, including closed drainage, proper position of the drainage tubing and collection bag, and protection of the drainage...
port. The only violation predictive of an increased risk of CAUTI was improper position of the drainage tube, above the level of the bladder or sagging below the level of the collection bag. This study suggests we may be at the point of diminishing returns in terms of behavioral modification for further reduction in CAUTI, and that technologic innovations will be needed to further reduce risk.

**PATHOGENESIS**

Excluding rare hematogenous pyelonephritis, most CAUTIs derive from micro-organisms in the patient’s own colonic and perineal flora or transmitted from the hands of healthcare personnel during catheter insertion or manipulation of the collection system. Organisms gain access extraluminally - by direct inoculation when the catheter is inserted or later, by organisms ascending from the perineum by capillary action in the thin mucous film contiguous to the external catheter surface - or intraluminally, by reflux of micro-organisms gaining access to the catheter lumen from failure of closed drainage or contamination of collection bag urine (Figure 45.5). Recent studies suggest that CAUTIs most frequently are extraluminally-acquired, but both routes are important.

Infected urinary catheters are covered by a thick biofilm, which forms intraluminally, extraluminally or both, usually advancing in a retrograde fashion. Anti-infectioe-impregnated and silver-hydrogel catheters, which inhibit adherence of micro-organisms to the catheter surface, significantly reduce the risk of CAUTI, particularly infections caused by Gram-positive organisms or yeasts, which are most likely to be acquired extraluminally from the periurethral flora. These data suggest that microbial adherence to the catheter surface is important in the pathogenesis of many, but not all, CAUTIs.

Infections in which the biofilm does not play a pathogenic role are probably caused by mass transport of intraluminal contaminants into the bladder by reflux of microbe-laden urine when a catheter or collection system is moved or manipulated.

**MICROBIOLOGY**

As noted, CAUTIs comprise the largest institutional reservoir of nosocomial antibiotic-resistant pathogens, the most important of which are multidrug-resistant Enterobacteriaceae other than *Escherichia coli* (such as *Klebsiella, Enterobacter, Proteus, and Citrobacter* spp.), *Ps. aeruginosa, enterococci* and *Candida* spp. (Figure 45.6).

**DIAGNOSIS**

**Clinical presentation**

Classically, urinary tract infections (UTIs) in non-catheterized patients present with dysuria and frequency, often associated with lower abdominal pain or even flank pain. The irritating effects of a urinary catheter can mimic some of these symptoms in the absence of infection, and thus corroborating evidence of CAUTI is needed before initiation of antimicrobial therapy.

Although there have been recommendations to treat CAUTIs only when they are symptomatic, until recently the symptoms associated with CAUTI had not been clearly defined. In a recent prospective study of 1497 newly catheterized patients, over half of whom were in an ICU, undertaken to determine the prevalence of signs and symptoms attributable to CAUTI and the relative contribution of CAUTI to nosocomial bloodstream infections, quantitative urine cultures and urine leukocyte counts were taken daily and each patient was questioned by a research nurse regarding symptoms. In this study, there were no significant differences between patients with and without CAUTI in subjective symptoms commonly associated with urinary tract infection; most were afebrile. There were also no significant differences between the two groups in mean peripheral leukocyte counts, although the urine WBCs in patients with CALM were significantly higher than in uninfected catheterized patients. Of 79 nosocomial bloodstream infections identified in the study population, there was only one that appeared unequivocally to have derived from a CAUTI; interestingly, this patient had no symptoms referable to the urinary tract.

This study shows that, although a large proportion of patients with indwelling urinary catheters develop bacteriuria, fewer than 10% with microbiologically documented CAUTI (most with active infection and pyuria for many days) report any symptoms commonly associated with community-acquired UTI unrelated to a urinary catheter, such as dysuria, urgency, fever or chills. Symptoms referable to the urinary tract not only are infrequent in patients with UTI but also have little pre-
Laboratory tests

Pyuria has become universally regarded as an essential criterion for the diagnosis and management of urinary tract infection in the non-catheterized patient. However, studies that have examined the utility of quantitative pyuria in catheterized patients have found conflicting results on its prognostic value. In a study of 761 hospital patients with newly inserted indwelling urinary catheters, Tambyah et al found that 82 (10.8%) patients studied developed CAUTI while catheterized, and the mean urine WBC in patients with CAUTM was significantly higher than in patients without infection (71 vs. 4 per mm³; P = 0.006). However, using a urine WBC count greater than 10 per mm³ (>5 per high-powered field in a conventional urinalysis) as the cutoff for defining its presence, pyuria had a specificity of 90% for predicting CAUTI with >10⁵ cfu/ml but a sensitivity of only 37%.

The clinical relevance of this study seems clear: pyuria cannot and should not be used as the sole criterion for obtaining a urine culture in the catheterized patient. This is especially true in the case of infections caused by yeasts or Gram-positive cocci, which account for nearly one-half of nosocomial CAUTs in the ICU. It is clear that most patients with CAUTI are asymptomatic and do not have fever. If a catheterized patient develops fever or signs of sepsis that cannot be linked to another source such as nosocomial pneumonia, surgical site infection or vascular catheter-related infection, urine cultures should be obtained even if the patient does not have demonstrable pyuria.

In the outpatient setting, particularly in clinics that may not have rapid access to laboratory testing, non-cultural rapid diagnostic tests are widely used, most commonly the leukocyte esterase and bacterial nitrite rapid dipstick tests. These tests have shown excellent sensitivity in non-catheterized patients with a high pre-test probability of UTI because of characteristic symptoms; however, in a non-selected patient population sensitivity of the tests has been poor, in the range of 50%. In a recent prospective study of the leukocyte esterase and nitrite urinary dipstick in catheterized ICU patients, the sensitivity (50 and 79%), specificity (48 and 55%), and predictive value (60 and 81%) of both tests were poor.

Gram stains of urine, of either unspun or centrifuged specimens, have high sensitivity and specificity for detection of high-level quantitative bacteriuria (>10⁵ CFU/ml), with specificity and positive and negative predictive values all greater than 90%. However, inexplicably, clinicians encountering patients with symptomatic UTI or even frank urosepsis rarely use Gram stains. A Gram stain of urine is simple, can be done rapidly, and is highly reliable (90%) for detecting bacteriuria or candiduria; moreover, it permits immediate determination of whether the infection is caused by Gram-negative bacilli,
Gram-positive cocci such as enterococci or staphylococci, or yeasts, such as *Candida Spp.*

**Microbiologic studies**

In clinical practice, a quantitative culture of a spontaneously voided, clean-catch urine specimen showing >10^1 cfu/ml is widely considered to represent infection. Studies have shown that a count > 10^2 cfu/ml of enteric Gram-negative bacilli recovered in culture of a clean catch specimen from a woman with pyuria and symptoms of UTI correlates highly with recovery of the same organism from bladder urine obtained by urethral catheterization or suprapubic aspiration, and can reliably be considered to represent true lower urinary tract infection, i.e., cystourethritis.

Because urine cultures obtained by aspiration from an indwelling urethral catheter bypass potentially contaminating periurethral flora, it seemed likely that microbiologic concentrations considerably below 10^5 cfu/ml in a culture of urine taken from a catheterized patient might well be relevant pathogenetically, epidemiologically, and clinically. In a prospective study of 110 newly catheterized patients, low-level bacteriuria or candiduria (<10^5 cfu/ml), which developed in 41 patients, progressed to concentrations >10^5 cfu/ml of the time (P<0.001), usually within 3 days of the first culture showing growth, unless the patient received intercurrent, suppressive antimicrobial therapy. Even with very low-level bacteriuria or candiduria (1-99 organisms per ml), 90% of the cases progressed to high-level bacteria within 48-72 h, demonstrating that in the catheterized patient a considerably lower level of bacteriuria than 10^5 cfu/ml, (probably > 10^2 cfu/ml) is valid as an index of infection; 10^2 cfu/ml is a concentration that can be easily and reproducibly detected in a clinical laboratory.

In sum, a quantitative urine culture showing growth but less than 10^5 cfu/ml should not reflexly be disregarded, especially if the patient is immunologically compromised or has clinical signs of UTI. In this circumstance, the culture result may reasonably form the basis for antimicrobial therapy if symptomatic CAUTI or, especially, urosepsis is suspected clinically.

**TREATMENT**

Only patients with symptomatic CAUTI should receive antimicrobial therapy; however, two clinical exceptions to this dictum exist: asymptomatic CAUTI in patients who are profoundly granulocytopenic and patients who have silent CAUTI in association with urinary tract obstruction. Urosepsis in the presence of obstruction rapidly converts silent bacteriuria to symptomatic urosepsis, which if unrelieved, culminates in bacteremia and septic shock. Harding et al reported that of 27 catheterized patients with asymptomatic catheter-associated bacteriuria seven (26%) developed symptoms referable to the urinary tract, but only after the catheter had been removed.

In the absence of the above exceptions, empiric therapy may be initiated, in the symptomatic patient, based on the results of Gram stain and culture and then modified based on the results of in-vitro sensitivity testing. The optimal duration of therapy in patients with symptomatic CAUTI remains undefined, but in general, antimicrobials should be continued for 7-14 days.

**PREVENTION**

Catheter-care practices universally recommended to prevent or at least delay the onset of CAUTI include.Catheter-care practices universally recommended to prevent or at least delay the onset of CAUTI include: avoiding unnecessary catheterizations, using a condom or suprapubic catheter, having trained professionals insert catheters aseptically, removing the catheter as soon as it is no longer needed, maintaining uncompromising closed drainage, ensuring dependent drainage, minimizing manipulations of the system and geographically separating catheterized patients. While entirely defensible, few of these practices have been proven to be effective by randomized controlled trials.

Systemic antimicrobial prophylaxis with trimethoprim-sulfamethoxazole, methenamine mandelate, or especially, a fluoroquinolone can reduce the risk of CAUTI for short-term catheterizations. Although use of antimicrobials in this way may reduce the rate of CAUTI, infections that do occur are far more likely to be caused by antibiotic-resistant bacteria and yeasts. Since most CAUTs are asymptomatic and do not result in urosepsis, it is difficult to justify antimicrobial prophylaxis to prevent asymptomatic bacteriuria.

**Novel technology**

Many technologic innovations proposed and evaluated during the past 25 years have not proven beneficial, including the use of anti-infective lubricants when inserting the catheter, soaking the catheter in an antimicrobial solution before insertion, regular meatal cleansing or periodically applying anti-infective creams or ointments to the meatus, continuously irrigating the catheterized bladder with an anti-infective solution through a triple-lumen catheter or periodically instilling an anti-infective solution into the collection bag. Bladder irrigation with antimicrobial solution has not only shown no benefit for prevention but has also been associated with a strikingly increased proportion of CAUTIs caused by microorganisms resistant to the drugs in the irrigating solution.

Given the widely accepted importance of closed catheter drainage, efforts have been made to seal the connection between the catheter and collection tubing. An initial trial with a sealed junction showed modest benefit and suggested a reduction in hospital deaths; however, follow up studies have not demonstrated a reduction in CAUTI with a sealed catheter-collecting tube junction.

Medicated catheters, which reduce adherence of microorganisms to the catheter surface, may confer the greatest benefit for preventing CAUTI. Two catheters impregnated
with anti-infections have been evaluated clinically, one with the urinary antiseptic nitrofurazone and the other with minocycline and rifampicin. Both catheters showed a significant reduction in bacterial CAUTIs; however the studies were small and the impact of the coating on selection of antimicrobial-resistant uropathogens was not satisfactorily resolved. Coating the catheter surface with an antiseptic, such as a silver compound, offers another alternative to reduce the risk of CAUTI. Silver oxide-coated catheters, however, did not show efficacy in large, well-controlled trials. In one trial, male patients receiving a coated catheter had a paradoxical and inexplicably increased risk of CAUTI.

A silver-hydrogel catheter has been developed that inhibits adherence of micro-organisms to the catheter surface in vitro and has also been evaluated clinically. In a recent, large, double-blind trial in 850 patients, the silver-hydrogel catheter reduced the incidence of CAUTI by 26%, and was most effective in preventing infections caused by Gram-positive organisms, enterococci, staphylococci and Candida, micro-organisms that appeared to gain access to the bladder extraluminally; the catheter conferred no protection against CAUTIs with Gram-negative bacilli, which most often gain access intraluminally. Use of the silver-hydrogel catheter was not associated with an increased incidence of infections caused by antibiotic-resistant organisms or Candida, and in-vitro susceptibility testing of isolates from both treatment groups showed no infections caused by silver-resistant micro-organisms. Cost-utility analysis indicates that use of this catheter could bring substantial cost savings to healthcare institutions. In a large crossover trial of a silver-hydrogel catheter in 27,878 patients, Karchmer et al also found a lower risk of CAUTI with the novel catheter (RR 0.70; p = 0.04).

### MICROBIOLOGY

Table 45.7 summarizes the range and frequencies of pathogens causing PD-related peritonitis. Gram-positive organisms account for 60-80% of culture-proven cases. Unusual organisms include Alcaligenes xylosoxidans, Stenotrophomonas maltophilia, Burkholderia cepacia, Agrobacterium spp., Mycobacterium spp., and Fusarium spp.

In approximately 20% of cases, cultures of the peritoneal fluid fail to grow any organisms despite the presence of a large number of inflammatory cells. These patients usually respond to empiric antimicrobial therapy.

Staph. aureus accounts for approximately 50% of PD catheter exit site and tunnel infections, and coagulase-negative staphylococci are implicated in 30-40% of cases. In contrast to surgical peritonitis, Gram-negative bacilli are less commonly involved with PD catheter exit site and tunnel infections, with Ps. aeruginosa being the most common.
remain sterile in up to 30% of cases. Negative cultures are usually negative and in the absence of signs of sepsis their value empiric antimicrobial therapy. Peripheral blood cultures are 9-28% of cases but when positive is useful for guiding intraperitoneal antibiotics. described with fungal infections and hypersensitivity to anomalous mycobacteria. Peritoneal eosinophilia has been associated with M. tuberculosis or fungi, especially if monocyotosis or eosinophilia is present, or a non-infectious cause, such as renal cell carcinoma, leukemia or peritoneal lymphoma.

Plain films and CT scans of the abdomen are generally not useful or recommended, and often reveal a small volume of pneumoperitoneum that does not represent bowel perforation. However, if the patient presents with signs of sepsis or multiple organisms are seen on the Gram stain or recovered in culture, or if a large volume of free air is seen radiographically, a perforated viscus must be suspected, and appropriate combination antibiotic therapy and surgical consultation are indicated.

DIAGNOSIS

Patients with PD-related peritonitis present clinically with cloudy dialysate (98%), abdominal pain (79%) and abdominal tenderness (70%), although frank rebound tenderness is infrequent (50%). In contrast to surgical peritonitis, PD-related peritonitis is associated with fever only 53% of the time. Nausea and vomiting are common (25% of cases); however, septic shock is unusual unless the infecting organism is Staph. aureus.

Exit-site infection usually manifests with erythema and crusting around the exit site. Frank purulence with fluctuance over the subcutaneous portion of the catheter suggests tunnel infection and is often associated with extrusion of the cuff.

The normal WBC in returned dialysate from uninfected patients is <8 white cells/mm³; in contrast, 90% of patients with PD-related peritonitis will show a dialysate WBC >100/mm³, associated with a neutrophilic predominance. However, up to 15% present with monocyotosis. Delay in the rise of the dialysate WBC has been reported and therefore abdominal pain in a patient with a PD catheter should be assessed with serial dialysate cell counts and cultures to rule out PD-related peritonitis. Lymphocytic pleocytosis may be the first clue to the presence of an unusual organism, such as Mycobacterium tuberculosis or anomalous mycobacteria. Peritoneal eosinophilia has been described with fungal infections and hypersensitivity to intraperitoneal antibiotics.

Gram-stain of centrifuged dialysate is positive in only 9-28% of cases but when positive is useful for guiding empiric antimicrobial therapy. Peripheral blood cultures are usually negative and in the absence of signs of sepsis their value is dubious. Whereas dialysate cultures are usually positive they remain sterile in up to 30% of cases. Negative cultures are thought to most often represent a failure of culture methods rather than infection with an unusual organism. The most common mistakes are obtaining cultures too early in the course of peritonitis, before microbial counts rise to detectable levels; culturing inappropriately small volumes of dialysate (<10 ml); and administration of antibiotics before obtaining cultures. Persistently elevated cell counts despite appropriate empiric antibiotic therapy should raise suspicion of an unusual pathogen, such as M. tuberculosis or fungi, especially if monocyotosis or eosinophilia is present, or a non-infectious cause, such as renal cell carcinoma, leukemia or peritoneal lymphoma.

Plain films and CT scans of the abdomen are generally not useful or recommended, and often reveal a small volume of pneumoperitoneum that does not represent bowel perforation. However, if the patient presents with signs of sepsis or multiple organisms are seen on the Gram stain or recovered in culture, or if a large volume of free air is seen radiographically, a perforated viscus must be suspected, and appropriate combination antibiotic therapy and surgical consultation are indicated.

TREATMENT

Initial anti-infective therapy of PD-related peritonitis is based on the most likely infecting organisms, namely Gram-positive bacteria, unless the initial Gram-stain indicates to the contrary. Since PD-related peritonitis is a local infection, treatment with intraperitoneal antibiotics is preferred as very high levels are achieved quickly, as are therapeutic blood levels, with most antimicrobials.

Historically, concerns over infection caused by methicillin-resistant organisms led to the use of vancomycin in empiric regimens; however, the appearance of vancomycin resistance among enterococci (and, even more alarmingly, among Staph. aureus) has prompted recommendations to limit the empiric use of this critical antibiotic. Empiric regimens that include a group 1 cephalosporin, either cefotaxime or cefazolin, or cefepime combined with an aminoglycoside have been shown to be equivalent to vancomycin containing regimens, and vancomycin can be withheld unless a patient has infection caused by MRSA or has life-threatening allergy to R-lactam drugs (Table 45.8). Studies of once-daily intraperitoneal cephalosporin regimens have shown blood and intraperitoneal drug levels far above the MIC of most infecting Gram-positive organisms for the entire 24-h period, with therapeutic success rates comparable to continuous administration of intraperitoneal cephalosporins.

Combined use of an aminoglycoside must take into account the patient's residual renal function; patients with a urine output >100 nil/day should not receive an aminoglycoside, based on studies showing accelerated decline in renal function, but should receive a higher dose of the R-lactam in monotherapy; in contrast, patients with a urine output <100 ml/day may safely receive a combined R-lactam/aminoglycoside.

Table 45.7 Distribution of micro-organisms causing peritoneal dialysis-related peritonitis

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>30-40</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0-20</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>0-15</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3-6</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5-10</td>
</tr>
<tr>
<td>Pseudomonas spp.</td>
<td>5-10</td>
</tr>
<tr>
<td>Other Gram-negative bacilli</td>
<td>7-16</td>
</tr>
<tr>
<td>Anaerobic organisms</td>
<td>2-5</td>
</tr>
<tr>
<td>Fungi</td>
<td>2-10</td>
</tr>
<tr>
<td>Other</td>
<td>3-7</td>
</tr>
<tr>
<td>Culture negative</td>
<td>0-30</td>
</tr>
</tbody>
</table>

* Adapted from Vas, 1994.
glycoside regimen (Table 45.8). Clindamycin, vancomycin, and ciprofloxacin are acceptable alternatives in patients with R-lactam allergies.508

When the Gram stain or culture confirms the presence of a specific organism, therapy should be adapted to reflect the sensitivities of that organism (Table 45.9). *Staph. aureus* usually responds to 21 days of therapy with an intraperitoneal group 1 cephalosporin; however, in 20-51% of cases this results in catheter loss,479,513 especially when there is a concurrent exit site or tunnel infection (which results in loss of the catheter in 70-80% of episodes514,515). If symptoms of infection persist for more than 72 h or a patient has experienced a recurrent bout of peritonitis, rifampicin should be added.508

*Ps. aeruginosa* infections are very difficult to treat and even with combination antimicrobial therapy have been associated with failure rates and catheter loss ranging from 20% to 80%.516,517 Initial therapy requires two drugs, such as cefazidime, cefepime, or an antipseudomonal penicillin, in combination with an aminoglycoside or ciprofloxacin (Table 45.9). If peritonitis fails to clear or recurs within 4 weeks of discontinuing therapy, removal of the PD catheter is usually necessary.

Management of fungal peritonitis also represents a formidable challenge to the clinician, and is associated with failure rates approaching 35%.518,519 despite therapy that includes early removal of the PD catheter and prolonged antifungal therapy. Fungal peritonitis has been associated with a mortality ranging from 17% to 32%.50,521 A single retrospective study reported a catheter salvage rate of 64% with the use of prolonged antifungal therapy,515 although the number of cases was small. Other, larger, case series have reported high rates of catheter loss, in the range of 66-86%.518,519,521 Fluconazole combined with flucytosine is the anti-infective combination of choice for peritonitis caused by *C. albicans*,479 which has been implicated in >75% of cases of fungal peritonitis,520 and is generally continued for 4-6 weeks. Amphotericin B exhibits broader antifungal activity than the currently available azoles, but does not penetrate the peritoneum well when given intravenously522 and is irritating when given by intraperitoneal route.523 However, its use is recommended in critically ill patients, when definitive identification of the fungus is pending, and in known infections with filamentous fungi, such as *Aspergillus*, which are intrinsically resistant to fluconazole.508

Patients with PD-related peritonitis should be instructed to increase their dialysate dwell times as this is associated with increased peritoneal levels of IgG and activated macrophages.524 Some authors have recommended discontinuing PD altogether for at least 48 h in an attempt to allow recovery of a local inflammatory response to help control the infection.525 Anecdotally, the use of thrombolytics has been reported to be beneficial526 but at this time neither intervention can be routinely recommended.

The decision to remove the PD catheter must take into account the patient’s dialysis requirements, the availability of vascular access if transitioning to hemodialysis, the type of infection and, obviously, the patient’s wishes. Fungal peritonitis, as noted, is associated with high mortality,520,521 as is peritonitis caused by *Staph. aureus*.527 In seriously ill patients with peritonitis caused by these two organisms, a low threshold for early PD catheter removal is advisable. Additional indications for PD catheter removal include *Ps. aeruginosa* peritonitis not responding to therapy, obvious tunnel or refractory exit site infection, fecal peritonitis, relapsing bouts of peritonitis with the same organism or recurrent bouts of culture-negative peritonitis.479 Several studies have demonstrated the utility of one-stage removal of the infected catheter with simultaneous placement of a new PD catheter,128,529 with success rates as high as 83%.529

### PREVENTION

Given the dominance of catheter contamination in the pathogenesis of PD-related peritonitis, interventions aimed at reducing microbial colonization of the extraluminal and intraluminal surfaces of the PD catheter would seem most likely to impact favorably on the risk of infection. The first effective technology was the Y-set connector system, which reduces the number of times that patients must access their vascular access if transitioning to hemodialysis, the type of access, the availability of delivery systems,487-489,531 with success rates as high as 83%.529

Anecdotally, the use of thrombolytics has been reported to be beneficial526 but at this time neither intervention can be routinely recommended.

The decision to remove the PD catheter must take into account the patient’s dialysis requirements, the availability of vascular access if transitioning to hemodialysis, the type of infection and, obviously, the patient’s wishes. Fungal peritonitis, as noted, is associated with high mortality,520,521 as is peritonitis caused by *Staph. aureus*.527 In seriously ill patients with peritonitis caused by these two organisms, a low threshold for early PD catheter removal is advisable. Additional indications for PD catheter removal include *Ps. aeruginosa* peritonitis not responding to therapy, obvious tunnel or refractory exit site infection, fecal peritonitis, relapsing bouts of peritonitis with the same organism or recurrent bouts of culture-negative peritonitis.479 Several studies have demonstrated the utility of one-stage removal of the infected catheter with simultaneous placement of a new PD catheter,128,529 with success rates as high as 83%.529

### PREVENTION

Given the dominance of catheter contamination in the pathogenesis of PD-related peritonitis, interventions aimed at reducing microbial colonization of the extraluminal and intraluminal surfaces of the PD catheter would seem most likely to impact favorably on the risk of infection. The first effective technology was the Y-set connector system, which reduces the number of times that patients must access their vascular access if transitioning to hemodialysis, the type of access, the availability of delivery systems,487-489,531 with success rates as high as 83%.529

Anecdotally, the use of thrombolytics has been reported to be beneficial526 but at this time neither intervention can be routinely recommended.

The decision to remove the PD catheter must take into account the patient’s dialysis requirements, the availability of vascular access if transitioning to hemodialysis, the type of infection and, obviously, the patient’s wishes. Fungal peritonitis, as noted, is associated with high mortality,520,521 as is peritonitis caused by *Staph. aureus*.527 In seriously ill patients with peritonitis caused by these two organisms, a low threshold for early PD catheter removal is advisable. Additional indications for PD catheter removal include *Ps. aeruginosa* peritonitis not responding to therapy, obvious tunnel or refractory exit site infection, fecal peritonitis, relapsing bouts of peritonitis with the same organism or recurrent bouts of culture-negative peritonitis.479 Several studies have demonstrated the utility of one-stage removal of the infected catheter with simultaneous placement of a new PD catheter,128,529 with success rates as high as 83%.529

### PREVENTION

Given the dominance of catheter contamination in the pathogenesis of PD-related peritonitis, interventions aimed at reducing microbial colonization of the extraluminal and intraluminal surfaces of the PD catheter would seem most likely to impact favorably on the risk of infection. The first effective technology was the Y-set connector system, which reduces the number of times that patients must access their vascular access if transitioning to hemodialysis, the type of access, the availability of delivery systems,487-489,531 with success rates as high as 83%.529

Anecdotally, the use of thrombolytics has been reported to be beneficial526 but at this time neither intervention can be routinely recommended.

The decision to remove the PD catheter must take into account the patient’s dialysis requirements, the availability of vascular access if transitioning to hemodialysis, the type of infection and, obviously, the patient’s wishes. Fungal peritonitis, as noted, is associated with high mortality,520,521 as is peritonitis caused by *Staph. aureus*.527 In seriously ill patients with peritonitis caused by these two organisms, a low threshold for early PD catheter removal is advisable. Additional indications for PD catheter removal include *Ps. aeruginosa* peritonitis not responding to therapy, obvious tunnel or refractory exit site infection, fecal peritonitis, relapsing bouts of peritonitis with the same organism or recurrent bouts of culture-negative peritonitis.479 Several studies have demonstrated the utility of one-stage removal of the infected catheter with simultaneous placement of a new PD catheter,128,529 with success rates as high as 83%.529

### PREVENTION

Given the dominance of catheter contamination in the pathogenesis of PD-related peritonitis, interventions aimed at reducing microbial colonization of the extraluminal and intraluminal surfaces of the PD catheter would seem most likely to impact favorably on the risk of infection. The first effective technology was the Y-set connector system, which reduces the number of times that patients must access their vascular access if transitioning to hemodialysis, the type of access, the availability of delivery systems,487-489,531 with success rates as high as 83%.529

Anecdotally, the use of thrombolytics has been reported to be beneficial526 but at this time neither intervention can be routinely recommended.
<table>
<thead>
<tr>
<th>Infecting organism</th>
<th>Initial antibiotics</th>
<th>At 48-96 h</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococci</td>
<td>Ampicillin 125 mg/I/bag combined with an aminoglycosideb or Vancomycin 15-30 mg/kg i.v. every 5-7d</td>
<td>If no improvement, reculture and evaluate for a concurrent exit site or tunnel infection</td>
<td>14 days</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Group 1 cephalosporin or Vancomycin 15-30 mg/kg i.v. every 5-7d</td>
<td>Start rifampicin 600 mg/day orally. If no improvement, reculture and evaluate for a concurrent exit site or tunnel infection</td>
<td>21 days</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>Continue cephalosporin</td>
<td>Consider vancomycin if methicillin resistance documented. If no improvement, reculture and evaluate for a concurrent exit site or tunnel infection</td>
<td>14 days</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>Ceftazidime or cefepime 1 g/bag daily plus an aminoglycosideb if U0&lt;100 ml/day or Piperacillin 4 g i.v. every 12 h plus an aminoglycosideb if U0&lt;100 ml/day. Ciprofloxacin 500 mg p.o. twice daily if U0&gt;100 ml/day or Aztreonam 1 g I load followed by 250 mg/I/bag plus an aminoglycosideb if UO&lt;100 ml/day. Ciprofloxacin 500 mg p.o. twice daily if UO&gt;100 ml/day</td>
<td>If no improvement, reculture and evaluate for a concurrent exit site or tunnel infection. Consider removal of peritoneal dialysis catheter</td>
<td>21 days</td>
</tr>
<tr>
<td>Stenotrophomonas spp.</td>
<td>Trimethroprim-sulfamethoxasole 1-2 IDS tabs/day ± ciprofloxacin 500 mg p.o. twice daily (confirm sensitivities)</td>
<td>Consider removal of dialysis catheter</td>
<td>21 days</td>
</tr>
<tr>
<td>Other Gram-negative bacilli</td>
<td>Aminoglycosideb if U0&lt;100 ml/day</td>
<td>If no improvement, reculture and evaluate for a concurrent exit site or tunnel infection</td>
<td>14 days</td>
</tr>
<tr>
<td>Fungi</td>
<td>Remove PD catheter and start fluconazole 200 mg p.o. or i.p. qd plus flucytosine 1 g p.o. qd Amphotericin 8 if resistant yeast or filamentous, fungi are present or the patient is severely ill</td>
<td>If dialysis catheter retained it should be removed at 48 hours if infection not clearing</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>Continue cephalosporin and stop aminoglycoside, if given with empiric regimen</td>
<td>Reculture fluid if patient not improving and adjust based on results. Consider infection with fungi and mycobacteria</td>
<td>14 days</td>
</tr>
</tbody>
</table>

UO, urine output; i.p., intraperitoneally; p.o., by mouth; DS, double strength.

* Adapted from Keane et al, 2000.

b Refer to Table 45.13 for dosing.

Use only with confirmed ampicillin or methicillin resistance or in patients with major penicillin allergy.

A drainage and new infusion bag have demonstrated even lower rates of infection than single bag systems, with rates of PD-related peritonitis ranging from one episode per 12-14 patient-months for the single bag system to one episode per 25-46 patient-months for the dual bag system. Use of these systems has resulted in a reduction in cases of Coagulase-negative staphylococcal peritonitis but has had little impact on rates of Staph. aureus infection. Given the predominance of Coagulase-negative staphylococci in PD-related peritonitis, wider use of Y-systems should result in significant declines in rates of PD-related infection.

The use of CCPD, which requires only a single night-time connection, also reduces the number of times a PD catheter must be handled, and several studies have reported lower rates of infection than in CAPD, which requires the PD catheter to be accessed 3-4 times a day (one episode per 8-14 patient-months in CAPD patients; one per 20-25 patient-months in patients using CCPD). Reducing rates of PD catheter exit site infections should, in theory, also reduce the rate of PD-related peritonitis. Patients with nasal colonization by Staph. aureus are much more likely to develop PD catheter exit site infections and at least two studies have demonstrated that these patients are also at increased risk of peritonitis. A randomized clinical trial of oral rifampicin, 600 mg/day for 5 days every 3 months, regardless of Staph. aureus colonization, demonstrated a significant reduction in the rate of Staph. aureus exit-site infection. Studies of the application of 2% nasal mupirocin
ointment to the anterior nares, 2-3 times daily for 5 days each month, have also shown reduced rates of PD catheter exit site infection but no effect on rates of peritonitis; 538-140 moreover, re-colonization by Staph. aureus occurred in the majority of patients after 1 year. 540 Direct application of 2% mupirocin ointment to intravascular catheter access sites has been shown to reduce rates of IVD-related bloodstream infections in patients undergoing hemodialysis, 541 and studies of direct application to PD catheter exit-sites has similarly shown a reduction in CAPD exit-site infections. 142 However, these studies did not show any favorable cost-benefit with mupirocin use, 543 and sharply rising mupirocin resistance in Staph. epidermidis 533 and Staph. aureus 544 clinical isolates have been seen with routine use. We believe further studies are needed before prophylactic mupirocin can be routinely recommended in PD or hemodialysis.

Use of perioperative antibiotics for placement of permanent PD catheters has recently been studied. 541,146 Rates of peritonitis occurring within 10 days of catheter placement were lower in patients given perioperative cefuroxime compared to placebo in one randomized trial; 545 another study demonstrated a reduced rate of PD-related peritonitis within 2 weeks of the procedure with prophylactic use of either vancomycin or cefazolin. 546

References

24. Kojima Y, Tojo M, Goldmann DA, Tosteson TD, Pier GB 1990 Antibody to the capsular polysaccharide/adhesin protects rabbits against catheter-related bacteremia due to coagulase-negative staphylococci. Journal of Infectious Diseases 162:435-441
34. Shiu AL, Wu CL 1998 The inhibitory effect of Staphylococcus epidermidis slime on the phagocytosis of murine peritoneal macrophages is interferon-independent. Microbiology and Immunology 43: 33-40
Anderl JN, Franklin MJ, Stewart PS 2000 Role of antibiotic penetration limitation in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. Antimicrobial Agents and chemotherapy 44:1818-1824

Xu KID, McFeters GA, Stewart PS 2000 Biofilm resistance to antimicrobial agents. Microbiology 146:547-549


Friedman RJ 1988 Infection in total joint arthroplasty from distal intravascular lines. A case report. Journal of Arthroplasty(3(Suppl)):S69-71


Spangfeld MJ, Masi BA, O'Connell JX, Duncan CP 1999 Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. Journal of Bone and Joint Surgery - American Volume 81:672-683


Shih LY, Wu JI, Yang DJ 1987 Erythrocyte sedimentation rate and C-reactive protein values in patients with total hip arthroplasty. Clinical Orthopaedics and Related Research 225:238-246

Bilgen 0, Atici T, Durak K, Karaemogullari, Bilgen MS 2001 C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty. Journal of Orthopaedic Practice Medical Research 29:7-12


prosthetic valve endocarditis: prospective study of six cases and review of the literature. Clinical Infectious Diseases 22: 262-267


Weinstein MP, Murphy JR, Relier LB, Lichtenstein KA 1983 The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. Reviews of Infectious Diseases 5: 54-70


Berbari EF, Cockerill FR, 3rd, Steckelberg JM 1997 Infective endocarditis due to unusual or fastidious microorganisms. Mayo Clinic Proceedings 72: 532-542


Ryan EW, Bolger AF 2000 Transesophageal echocardiography (TEE) in the evaluation of infective endocarditis. Cardiology Clinics 18: 773-787


Furlong WB, Rakowski TA 1997 Therapy with RP 59500 (quinupristin/dalfopristin) for prosthetic valve endocarditis due to enterococci with VanA/VanB resistance patterns. Clinical Infectious Diseases 25: 163-164


Kjaergaard HK, Tingleff J, Aabildgaard UI, Pettersen G 1999 Recurrent endocarditis in silver-coated heart valve prosthesis. Journal of Heart Valve Disease 8: 140-142


Harcombe AA, Newall SA, Ludman PF et al 1998 Late complications following permanent pacemaker implantation or elective unit replacement. Heart 82: 240-244


Lewis AB, Hayes DL, Holmes DR, Vlietstra RE, Pluth JR, Osborn MJ 1985 Update
273. Blot F, Nitenge G, Chachaty E et al 1999 Diagnosis of catheter-related bac-
teraemia: a prospective comparison of the time to positivity of hub-blood
versus peripheral-blood cultures. Lancet 354: 1071-1077

274. Rijnders BJ, Verwaest C, Peertmans WE et al 2001 Difference in time to posi-
tivity of hub-blood versus nonhub-blood cultures is not useful for the diag-
nosis of catheter-related bloodstream infection in critically ill patients. Critical
Care Medicine 29:1399-1403

275. Kite P, Dobbins BM, Wilcox MH, McMahon MJ 1999 Rapid diagnosis of cen-
tral-venous-catheter-related bloodstream infection without catheter
removal. Lancet354: 1504-1507

brush method for in situ diagnosis of catheter-related sepsis. Journal of
Clinical Pathology 50: 278-282

277. van Heerden PV, Webb SA, Fong S, Golledge CL, Roberts BL, Thompson WR
1996 Central venous catheters revisited - infection rates and an assessment
of the new Fibrin Analysing System brush. Anaesthesia and Intensive Care 24:
330-333

278. Verghese A, Wicricht WC, Arbeid RD 1985 Central venous septic throm-
bophlebitis-the role of medical therapy. Medicine64: 294-400

279. Dugdale DC, Ramsey PG 1990 Staphylococcus aureus bacteremia in patients with
Hickman catheters. American Journal of Medicine 89:137-141

a cause of nosocomial device-related infection. Reviews ooffiscine Diseases
8:42-49

281. Banerjee C, Bustamante CI, Wharton R, Taylor E, Wade JC 1988 Bacillus infec-

282. Elling LS, Bodey GP 1990 Septicemia due to Xanthomonas species and non-
aerogena pneumonia: increasing incidence of catheter-related infections.
Journal ofClinical Microbiology 28: 396-396

Medical Science 275:265-269


285. Elting LS, Bodey GP 1990 Septicemia due to Xanthomonas species and non-
aerogena pneumonia: increasing incidence of catheter-related infections.
Journal ofClinical Microbiology 28: 396-396

286. Champault G 1986 Totally implantable catheters for cancer chemotherapy:
French experience on 325 cases. Cancer Drug Delivery 3:131-137

287. Dato VM, Dajani AS 1990 Candidemia in children with central venous
catheters: role of catheter removal and amphotericin B therapy. Pediatric
Infectious Diseases Journal9: 309-314

288. Dato VM, Dajani AS 1990 Candidemia in children with central venous
catheters: role of catheter removal and amphotericin B therapy. Pediatric
Infectious Diseases Journal9: 309-314

289. Dato VM, Dajani AS 1990 Candidemia in children with central venous
catheters: role of catheter removal and amphotericin B therapy. Pediatric
Infectious Diseases Journal9: 309-314

a cause of nosocomial device-related infection. Reviews ooffiscine Diseases
8:42-49


a cause of nosocomial device-related infection. Reviews ooffiscine Diseases
8:42-49

293. Blot F, Nitenge G, Chachaty E et al 1999 Diagnosis of catheter-related bac-
teraemia: a prospective comparison of the time to positivity of hub-blood
versus peripheral-blood cultures. Lancet 354: 1071-1077

a cause of nosocomial device-related infection. Reviews ooffiscine Diseases
8:42-49

295. Krzywda EA, Andris DA, Edmiston CE Jr, Quebbeman EJ 1995 Treatment ofne-
ous disinfection with vascular catheters (Abstract). Paper presented at:
Conference on Antimicrobial Agents and Chemotherapy, 1992; Anaheim, CA

296. Champault G 1986 Totally implantable catheters for cancer chemotherapy:
French experience on 325 cases. Cancer Drug Delivery 3:131-137

297. Kite P, Dobbins BM, Wilcox MH, McMahon MJ 1999 Rapid diagnosis of cen-
tral-venous-catheter-related bloodstream infection without catheter
removal. Lancet354: 1504-1507

298. van Heerden PV, Webb SA, Fong S, Golledge CL, Roberts BL, Thompson WR
1996 Central venous catheters revisited - infection rates and an assessment
of the new Fibrin Analysing System brush. Anaesthesia and Intensive Care 24:
330-333

299. Verghese A, Wicricht WC, Arbeid RD 1985 Central venous septic throm-
bophlebitis-the role of medical therapy. Medicine64: 294-400

300. Mermel LA, Farr BM, Sherritz RJ et al 2001 Guidelines for the management of
infectious device-related infections. Critical Infectious Diseases 32:
249-1272

301. Riebel W, Frantz N, Adelstein D, Spagnuolo PJ 1986 Corynebacterium JK
a cause of nosocomial device-related infection. Reviews ooffiscine Diseases
8:42-49

302. Maki DG, Agger WA 1988 Enterococcal bacteremia: clinical features, the risk
of endocarditis, and management. Medicine 67:248-269

303. Bowler I, Conlon C, Crook D, Peto K 1992 Optimum duration of therapy for
catheter related Staphylococcus aureus bacteremia: A cohort study of 75
patients (Abstract). Programs and Abstracts of the Thirty-Second Interscience
Conference on Antimicrobial Agents and Chemotherapy, 1992; Anaheim, CA

304. Raad, II, Luna M, Khalil SA, Costerton JW, Lam C, Bodey GP 1994 The relation-
ship between the thrombotic and infectious complications of central venous
 catheters. Journal of the American Medical Association 271: 1014-1016

305. Rose HD 1978 Venous catheter-associated candidemia. American Journal of
Medical Science 275:265-269

Medical Science 275:265-269

fungemia in patients with cancer: analysis of 155 episodes. Critical Infectious
Diseases 14:875-883

308. Phillips P, Shafran S, Gargar B et al 1997 Multicenter randomized trial of
fluconazole versus amphotericin B for treatment of candidemia in non-
neutropenic patients. Canadian Candidemia Study Group. European Journal
ofClinical Microbiology and Infectious Diseases 16:337-345

309. Nguyen MH, Peacock JE Jr, Tanner DC et al 1995 Therapeutic approaches in
patients with candidemia. Evaluation in a multicenter, prospective, observa-
tional study. Archives ooffiscine Medicine 155: 2429-2435

310. Lee YH, Kerstein MD 1971 Osteomyelitis and septic arthritis. A complication of
subdavian venous catheterization. New England Journal of Medicine 285:
1179-1180

Annals ooffiscine Medicine 132: 391-402

312. Mermel LA, Maki DG 2001 The promise of novel technology for prevention of
intravascular device-related bloodstream infection, part I: short-term devices.
Critical Infectious Diseases in press

313. O'Grady NP, Alexander M, Dellinger EP et al 2001 HICPAC Guideline (Draft) for
the prevention of intravascular catheter-related infection. Federal Registerin
Press

314. CDC 2000 Monitoring hospital-acquired infections to promote patient safety
49:149-153

catheter-related infections by using maximal sterile barrier precautions dur-
ing insertion. Infection Control and Hospital Epidemiology 15: 231-238

316. Maki DG, Ringer M, Alvarado CJ 1991 Prospective randomized trial of povi-
done-iodine, alcohol, and chlorhexidine for prevention of infection associ-
ated with central venous and arterial catheters. Lancet 338: 339-343

317. Muzo O, Pieroni L, Lawrence G et al 1996 Prospective, randomized trial of
two antiseptic solutions for prevention of central venous or arterial catheter
colonization and infection in intensive care unit patients. Critical Care
Medicine 24:1818-1823

1% chlorhexidine-756 alcohol tincture versus 10% povidone-iodine for cuta-
neous disinfection with vascular catheters (Abstract). Paper presented at:
31 st Annual Society for Hospital Epidemiology of America Meeting, Toronto

319. Conly JM, Grieses P 1989 A prospective, randomized study compar-
ting transparent and dry gauze dressings for central venous catheters. Journal
ofInfectious Diseases 159: 310-319


334. Sampath L, Tambe S, Modak S 1999 Comparison of the efficacy of antiseptic and antibiotic catheters impregnated on both their luminal and outer surfaces (Abstract). Programs and Abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, San Francisco, CA


361. Kulkarni AV, Drake JIM, Lomberti-Pasculli M 2001 Cerebrospinal fluid shunt...
patients with indwelling urethral catheters. Archives of Physical Medicine and Rehabilitation 70:839-841.


