Catheter-Related and Infusion-Related Sepsis

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KEYWORDS

• Intravascular cannulation • Fluid infusion • Colonization • Infection • Bacteremia • Central venous catheter

KEY POINTS

- Although continuous vascular access is one of the most pervasive modalities in modern medicine, there is a substantial potential for producing iatrogenic complications, the most important of which is blood-borne infection.
- Clinicians often fail to consider the diagnosis of infusion-related sepsis because clinical signs and symptoms are indistinguishable from bloodstream infections arising from other sites.
- Understanding and consideration of the risk factors predisposing patients to infusion-related infections may guide the development and implementation of control measures for prevention.
- The importance of meticulously following sepsis prophylaxis in all aspects of patient care cannot be overstated.

The proliferation of increasingly complex medical and surgical therapies for the management of critically ill patients over the last 30 years is associated with tremendous technological advances during this time. Among the most important advances have been improvements in vascular access for continuous hemodynamic monitoring as well as infusion therapy for the administration of fluids, drugs, total parenteral nutrition (TPN), and blood products. Although continuous vascular access is one of the most pervasive and essential modalities in modern-day medicine, there is a substantial and generally underappreciated potential for producing iatrogenic complications, the most important of which is blood-borne infection.

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This review focuses on the pathogenesis, diagnosis, prevention, and management of infectious complications of intravascular cannulation and fluid infusion. In this article, the term colonization refers to the presence and growth of viable microorganisms on the mucosa, skin, or in situ catheter in the absence of infection. Colonization may or may not be a precursor of infection. Infection represents a microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by microorganisms. Bacteremia is the presence of viable bacteria in the blood (usually demonstrated by positive blood culture). The term catheter colonization refers to the growth of significant numbers of organisms from the catheter surface in the absence of accompanying clinical symptoms. Catheter infection implies catheter colonization with accompanying clinical manifestations suggestive of infection. Health care–associated infection is any infection acquired in the hospital or health care environment. Sepsis represents the systemic response to infection (usually including various combinations of fever, tachycardia, tachypnea, and leukocytosis), typically associated with the presence of bacterial toxins and/or endogenous inflammatory mediators in the circulation. Central line–associated infection is the specific term for infection of central venous catheters whether or not it is associated with bacteremia. The general term catheter-related sepsis (CRS) relates to sepsis and septic complications, specifically attributable to the presence of intravascular catheters. Catheter-related bloodstream infection (CR-BSI) is a related term that indicates the isolation of identical infectious organisms from a catheter segment and from blood in a patient with CRS. Another related formal term, infusate-related bloodstream infection (IR-BSI), is more specific, indicating isolation of the same organism from infusate and percutaneous blood cultures. By contrast, infusion device–related sepsis (IRS) is a highly inclusive general term that relates to all sepsis and septic complications secondary to invasive monitoring and therapeutic devices including vascular catheters, fluid delivery systems, and infused solutions. Several of these terms are more precisely defined in the section on standardized microbiologic definitions of intravascular device-related infections.

EPIDEMIOLOGY

More than one-half of the 40 million patients hospitalized in the United States each year receive some form of infusion therapy.[1] Earlier estimates have suggested that nearly a million vascular device–related infections occur annually.[2] Although the prevalence of device–related infections has not been determined in the United States, in 1992 the European Prevalence of Infection in Intensive Care Study reported that 12% of patients in the intensive care unit (ICU) during a point prevalence study had a bloodstream infection.[3] The 2007 follow-up of this same study found in the 13,000 ICU patients observed, 15% had a bloodstream infection.[4] Mermel[5] estimated 80,000 to 200,000 cases of central line–associated bloodstream infections (CLA-BSIs) occur in United States ICUs annually. CLA-BSIs are an important and deadly cause of hospital-acquired infection, with a reported mortality of 12% to 25%.[6] Encouragingly, recent national initiatives have resulted in a decrease in the incidence of CLA-BSIs.

Analyzing data from several national registries, the Centers for Disease Control and Prevention (CDC) recently reported a 58% reduction (from 3.64 infections per 1000 central-line days to 1.65 infections per 1000 central-line days) in the incidence of ICU-related CLA-BSIs from 2001 to 2009, representing nearly 6000 lives saved.[6] The total cost of CLA-BSIs in the United States has been estimated at between $500 million and over $2 billion annually.[7–9] Although there has been improvement

in recent years, a substantial number of CLA-BSIs continue to occur among hemodialysis patients both in the inpatient and outpatient setting.

The CDC has published guidelines for the prevention of intravascular device–related infections.[10] These guidelines also provide standardized microbiological definitions for catheter-related infections. Definitions are not necessarily mutually exclusive. Infusion device–related infections are classified according to the following criteria and correlate with 4 main clinical syndromes.

Contamination

Contamination is the presence of microorganisms on the catheter taken for culture, inadvertently introduced while collecting the sample. Although a colony-forming unit (CFU) count of fewer than 15 colonies on semiquantitative culture suggests contamination, there is no definitive means of differentiating a contaminated specimen from a colonized or infected specimen.

Catheter Colonization

A positive semiquantitative (>15 CFU) or quantitative (>1000 CFU) culture of either the proximal or distal catheter segment in the absence of accompanying signs of inflammation at the catheter site is considered to be synonymous with colonization of the catheter.[10–18] Some investigators have suggested that a quantitative culture of more than 100 CFU is sufficient to define colonization rather than contamination.[9,10] Colonization may occur in the complete absence of notable clinical signs or symptoms. Positive semiquantitative cultures have a 15% to 40% concordance with concomitant bacteremia and are usually, but not invariably, associated with inflammation at the insertion site.

In hospitalized patients, between 5% and 25% of intravascular catheters cultured after removal demonstrate evidence of colonization. This clinical condition is also occasionally referred to as asymptomatic catheter infection. Although this condition itself is intrinsically benign, it provides the biological substrate necessary for bacteremia.

Catheter Infection

The term catheter infection indicates a positive semiquantitative or quantitative culture of the catheter in association with accompanying signs of local inflammation (eg, erythema, warmth, swelling, or tenderness) at the device site.[10] In the absence of positive quantitative or semiquantitative cultures of a catheter segment, catheter infection can still be diagnosed when there is purulent drainage from the skin-catheter junction.

Exit-Site Infection

Erythema, tenderness, induration, and/or purulence within 2 cm of the catheter exit site that may be associated with other signs of infection, including fever, indicates an exit-site infection (infection at the catheter-insertion site).[10] This infection is usually associated with catheter colonization and may be associated with CR-BSI.

Tunnel Infection

Erythema, tenderness, and induration in the tissues overlying the catheter tract and greater than 2 cm from the catheter exit site indicate a tunnel infection. Associated signs of infection, including fever, may be present.[10]

The clinical syndrome of symptomatic local infection occurs when the colonized microorganisms have invaded and infected the tissue. An inflammatory response may be evident as local redness, pain, swelling, heat, and/or purulence at the vascular access site. However, in severely debilitated or immune-compromised patients, these

classic clinical findings may be minimal or absent. The infection may primarily involve the skin and surface soft tissue (exit-site infection) or may involve the catheter tract (tunnel infection) with expressible purulence. Catheter cultures are positive, although infusate cultures may be negative. Local infection may resolve, or may become bloodborne and progress to systemic infection.

Catheter-Related Bloodstream Infection

CR-BSI is formally defined as isolation of the same organism (ie, identical species, antibiogram) from a semiquantitative or quantitative catheter-segment culture and from blood culture (preferably drawn from a peripheral vein) of a patient with clinical manifestations of bloodstream infection. Direct culture of the infusate should be negative. Clinical or autopsy microbiological data should disclose no other apparent source of bacteremia. In the absence of laboratory confirmation, defervescence after catheter removal may serve as indirect evidence of CR-BSI.[10,11,13–15,19]

Infusate-Related Bloodstream Infection

IR-BSI is formally defined as isolation of the same organism from infusate and from separate percutaneous blood cultures, with no other identifiable source of infection.[10–12,19] Typically the patient has clinical and laboratory evidence of sepsis. Culture of the catheter is negative or isolates an unrelated organism. This term is much more specific than the term IRS as used in this article.

Sepsis from an infected catheter or contaminated infusate is a clinical condition whereby the signs of local inflammation may or may not be present. Symptoms and/or signs of systemic infection are invariably present. Low-grade fever is a common presenting symptom of patients with systemic infusion-related infection involving *Staphylococcus epidermidis*. Other organisms may produce marked hyperthermia (pyrexia/fever) or hypothermia, depending on the organism and the patient's overall health, and nutritional and immune status. Blood cultures may be positive and, if so, should match the catheter or infusate culture. Septic shock is rare; contaminated infusate is more likely to be associated with shock than is catheter infection or CR-BSI.

Septic thrombophlebitis or endarteritis is a severe complication of an infected catheter. Each produces high-grade and unremitting bacteremia or fungemia with fulminant signs of overwhelming infection, which persist even after the catheter has been removed.[20–22] These forms of catheter-related infection are the most serious, and usually originate from central venous catheters that have been used for prolonged periods in patients at high risk of health care–associated infection.[20,21] The cannulated segment of the vessel becomes filled by an infected thrombus. The clinical course is predictable: unremitting bloodstream infection that often proves fatal. Of interest, patients with suppuration of the infected thrombus (suppurative phlebitis) may develop signs and symptoms of systemic infection only after the catheter has been removed.[20] Culture of the catheter is positive. Organisms isolated from the blood, thrombus, or adjacent resected parts of the vessel should match those isolated from the catheter.

PATHOGENESIS OF INFUSION-RELATED SEPSIS

When a catheter is placed in a blood vessel, a fibrin sheath quickly develops around the catheter. The clot generally produces no circulatory problem, but serves as a nidus for bacterial or fungal colonization.[20] Bacterial or fungal colonization of the intravascular device may occur via several mechanisms.

Migration of Cutaneous Flora Down the Skin Tract to the Intravascular Catheter

Aerobic microorganisms of cutaneous origin, such as coagulase-negative *Staphylococcus* (usually *S epidermidis*), *Staphylococcus aureus*, enterococci, or *Candida*, gain intravascular access through the insertion wound. The insertion site is commonly colonized heavily by the patient's endogenous cutaneous flora or becomes colonized by microorganisms from the hands of the medical personnel inserting or manipulating the catheter.[11,12,20,21,23–25] Maki and colleagues,[12] in a prospective study of 234 central venous catheters, found that the majority of early infections of percutaneously inserted central venous catheters originated from the skin at the insertion site rather than contamination of the hub. Overall, in venous catheters there is a strong correlation between skin microorganisms present on the catheter-insertion site and microorganisms implicated in CRS based on molecular typing.[11,12,24,25] The most common organism found in catheter-related infection is *S epidermidis*, the predominant aerobic species on the human skin. The risk of other, more pathogenic organisms rises with the presence and duration of severe illness.

Bloodstream Dissemination and Catheter Colonization from a Distant Septic Focus

The vascular catheter may become colonized by hematogenous seeding from remote sites of infection. For example, if patients have *Escherichia coli* bacteremia from an intra-abdominal source, vascular catheters may become seeded and colonized with *E coli*. The infected catheter may then, in turn, reseed the blood, thus propagating systemic infection even if the original septic focus has been eliminated. It has been suggested that CRS from certain organisms (yeast, enterococci, and enteric gram negatives) may often result from hematogenous spread.[26,27]

Manipulation and Contamination of the Catheter Hub

The hub of the catheter also may be a potential source of CRS. Sitges-Serra and colleagues[28] have suggested that the hub of the central venous catheter, rather than the intracutaneous tract, is the most important source of microorganisms that infect the catheter and bloodstream. These investigators reported little correlation between organisms found on the patient's skin and organisms found on the hub and on the catheter, but frequent contamination of catheter hubs and correlation with bacteremia. It was suggested that hubs became colonized during manipulation by clinicians. Maki and colleagues[12] have confirmed the occurrence of hub contamination, but were unable to demonstrate a major role in early CRS. Through the use of electron microscopy, Raad and colleagues[29] were able to demonstrate that hub contamination was the more likely mechanism of infection for long-term catheters (>30 days). Skin contamination was more likely in catheters in place for fewer than 10 days.

Contamination of the Delivery System

The catheter and hub are not the only elements of a vascular infusion that can produce infection. The delivery system, consisting of the fluid (infusate), stopcock, pressure transducer, and tubing, also can be a source of contamination, particularly epidemic nosocomial bacteremia (especially gram-negative bacteremia).[1,22,30,31]

Ostensibly closed delivery systems are frequently disrupted for the addition of medications and electrolytes, as well as withdrawal of blood for specific hemodynamic studies by members of the ICU staff. Accidental disconnection or leaks in the closed system may also occur. Overall, any disruption of the closed system and manipulation of infusion fluids may introduce microorganisms into the system.

Arterial lines are particularly vulnerable to contamination because they are so heavily manipulated. In all monitoring systems, meticulous care of stopcocks, replacing the sterile caps (deadheads) after withdrawal of blood, and flushing the sampling port of remaining blood are essential in the prevention of delivery-system contamination.

Infusate Contamination

Infusate contamination may also be a source of bacteremia or fungemia, but infusate-related infection can be identified only if the solution is cultured. This action is rarely taken in clinical practice because despite occasional epidemics, endemic bacteremia caused by extrinsically contaminated fluid during administration seems to be rare.[11,12,21] Based on anecdotal data, risk of infusate contamination may be higher with TPN and intravenous lipid emulsion–based medications such as propofol.[32–34]

DIAGNOSIS OF INFUSION-RELATED SEPSIS

Clinicians too often fail to consider the diagnosis of infusion-related sepsis, because clinical signs and symptoms are generally indistinguishable from bloodstream infections arising from other sites, such as the urinary tract or lung. Inflammation at the insertion site is not predictive of CR-BSI with short-term uncuffed catheters.[35] Sepsis from infected catheters and contaminated infusate also produce similar clinical features.[20] In general, the diagnosis of catheter-related or infusate-related infection should be considered whenever the patient has systemic or catheter-insertion site signs or symptoms of infection, particularly if the patient has no other identifiable septic focus. Maki[21,36] has listed 6 clinical and 3 microbiological findings that should alert the clinician to the possibility of infusion-related sepsis and prompt appropriate cultures and, in most cases, discontinuation of the infusion and removal of the catheter (**Box 1**).

Box 1
Findings suggestive of infusion-related sepsis

Clinical

1. Intravascular device in place at time of onset of sepsis, bacteremia, or candidemia (especially central venous catheter)
2. Patient is an unlikely candidate for sepsis, being young or without underlying predisposing diseases
3. Inflammation or expressible purulence at the catheter insertion site
4. Primary bacteremia or candidemia without apparent source of local infection
5. Precipitous onset of overwhelming sepsis with shock (often indicating massively contaminated infusate or intravascular suppuration)
6. Sepsis refractory to appropriate antimicrobial therapy or substantial improvement following removal of catheter or discontinuation of infusion

Microbiological

1. Bacteremia caused by staphylococci (especially coagulase-negative staphylococci), *Bacillus* species, *Corynebacterium* species, *Candida* species, and certain fungi or mycobacteria
2. Clusters of institutional outbreaks of sepsis due to *Enterobacter* species, *Serratia marcescens,* or *Pseudomonas* species other than *P aeruginosa*
3. High-grade candidemia (greater than 25 CFU/mL peripheral blood)

When CRS or IRS is suspected, ideally several cultures should be obtained, which should include a blood culture drawn from the suspected catheter, one or more peripheral blood cultures (from separate venipuncture sites) and, if the clinical presentation warrants, culture of the infusate in broth. If the suspected catheter is removed, semiquantitative tip culture should be performed. Blood cultures should be drawn before antibiotic administration whenever possible.

A firm diagnosis of IRS can be made only by demonstrating a colonized intravascular catheter or contamination of infusion solution, associated with culture-determined bacteremia or fungemia caused by the same microbial strain.[21] Negative catheter tip and infusion solution culture findings in the presence of bacteremia or fungemia strongly suggest that the intravenous device and solution are not the septic source.

When IRS is suspected, the catheter should be removed if possible (exceptions include limited situations involving surgically tunneled catheters or catheters that are unquestionably necessary and would be extremely risky to replace; in such situations, treatment of the catheter in situ may be attempted). The intravascular segment of the catheter is severed aseptically and then cultured.[20,21] Catheter segments may be cultured semiquantitatively rather than using broth cultures (qualitative culture). The clinical interpretation of a positive catheter culture in liquid media is uncertain because a single contaminating organism acquired from the skin as the catheter is being removed can produce a positive culture.[13] Positive broth-culture findings have not correlated well with signs of catheter-site inflammation either. The percentage of catheters showing positive cultures in broth is often many times higher than the true rate of CRS.[13]

The semiquantitative culture technique described by Maki and colleagues is now widely used to diagnose catheter-related infection. The proper method in obtaining the relevant catheter segments is crucial in ensuring reliable results.[14,15,24,31] For short catheters (arterial, peripheral venous): following catheter removal, aseptically cut the portion of the catheter that was within the vessel and transport it to the laboratory in a sterile container. For long catheters (central venous or pulmonary artery), obtain 2 segments for culture: a proximal segment that began several millimeters inside the former skin-catheter interface and the tip of the catheter. In the laboratory, the catheter segment is rolled or smeared (if unable to be rolled) back and forth across the plate. The plate is then incubated. Detecting 15 or more colonies growing on a semiquantitative plate is regarded as a positive culture. Positive semiquantitative cultures have a 15% to 40% concordance with concomitant bacteremia and are strongly associated with inflammation at the insertion site.[12–15,21,24,31]

The more arduous quantitative culture techniques using broth culture of catheter segments (>100–1000 CFU defines true colonization) have proponents.[16–18] However, studies suggest that culture of the external surface of the catheter segment, which reflects the microbiological status of the percutaneous wound and intravascular environment, distinguishes true catheter-related infection from contamination more reliably than the quantitative broth culture method.[13] Culturing catheters semiquantitatively also allows for more rapid identification of clinically significant isolates, because microbial growth usually occurs within 12 to 18 hours, whereas quantitative (broth) culture growth may take 24 to 48 hours. As a practical matter, most centers offer semiquantitative catheter culture rather than quantitative.

For those catheters that cannot be removed and safely replaced, comparison of quantitative peripheral and catheter-drawn blood cultures can make the diagnosis of catheter-associated bacteremia or fungemia (without catheter removal) with sensitivity and specificity of approximately 90%.[36–40] Quantitative cultures of blood drawn

from infected central venous catheters are usually 5 to 10 times higher than those from peripheral blood. Similarly, intraluminal brushes[41] and specialized staining of cytospin of lysed blood[42] drawn from infected central lines shows potential in the diagnosis of CRS without removal of the catheter. Another approach currently in development involves using polymerase chain reaction (PCR) to look for bacterial 16S ribosomal DNA in blood samples drawn from the catheter. Concentrations of such DNA above a certain threshold have been shown to have a very high predictive value for CR-BSI in febrile patients.[43]

An intriguing and potentially immediately useful new approach to the noninvasive diagnosis of CRS involves comparison of time to positivity of blood cultures drawn simultaneously from the catheter and peripheral sites.[44,45] Greater than 120 minutes' difference in time to detection of growth from the catheter versus peripheral site appears to be highly suggestive of catheter infection. However, all these techniques make medical and economic sense only in assessment of long-term indwelling catheters in cases where intraluminal colonization is likely, and where the patient's condition makes removal and replacement of the intravascular catheter unacceptably risky.

Safdar and colleagues[46] have recently performed a meta-analysis on the utility of a variety of currently available diagnostic tests for infusion-related sepsis. Overall, paired quantitative peripheral and catheter blood cultures were found to be superior to other techniques for diagnosis when such samples could be obtained, while quantitative segmental cultures appeared to be the most useful catheter culture technique.

A sudden onset of septic symptoms shortly after the start of infusion is suggestive of contamination of the intravenous fluid. If infusate contamination is suspected, the infusion must be immediately terminated. The entire infusate apparatus and infusate bag should be transported to the microbiology laboratory, where the infusate can be aseptically removed and cultured in broth.

A recommended approach to assessment of fever/sepsis in a patient with a central venous catheter is outlined in **Fig. 1**.

MICROORGANISMS ASSOCIATED WITH INFUSION-RELATED SEPSIS

CRS is associated with 2 major groups of organisms, those that are part of the normal skin flora (coagulase-negative staphylococci [CNS], *S aureus*, *Bacillus* species, *Corynebacterium* species) and those organisms that are transferred from the hands of medical staff and equipment (*Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophila*, and *Candida* species). Certain microorganisms are so prevalent in catheter-related infection that their recovery from blood should substantially raise the suspicion that an intravascular catheter is the source. These organisms include *S aureus, S epidermidis*, and *Candida*, the most common microorganisms in sepsis from infected catheters. For example, high-grade candidemia (>25 CFU/mL of peripheral blood) indicates CR-BSI in more than 90% of cases.[47]

Contaminated infusate solutions are strongly suggested by isolation of *Enterobacter cloacae, Enterobacter agglomerans*, or *Pseudomonas cepacia*, because these are major pathogens in sepsis from contaminated fluid.[20–22,30,31] The latter gram-negative organisms are able to multiply rapidly in 5% dextrose in water solution.[20–22,30] For this reason, the use of dextrose-containing solutions as irrigants for intravascular monitoring catheters should be discouraged.

S epidermidis is a normal skin inhabitant. For this reason, in the past blood-culture reports of *S epidermidis* were considered to be the result of skin contamination. Studies of central venous and peripheral venous catheter–related infections indicate that CNS such as *S epidermidis* are now the most common pathogens in intravenous

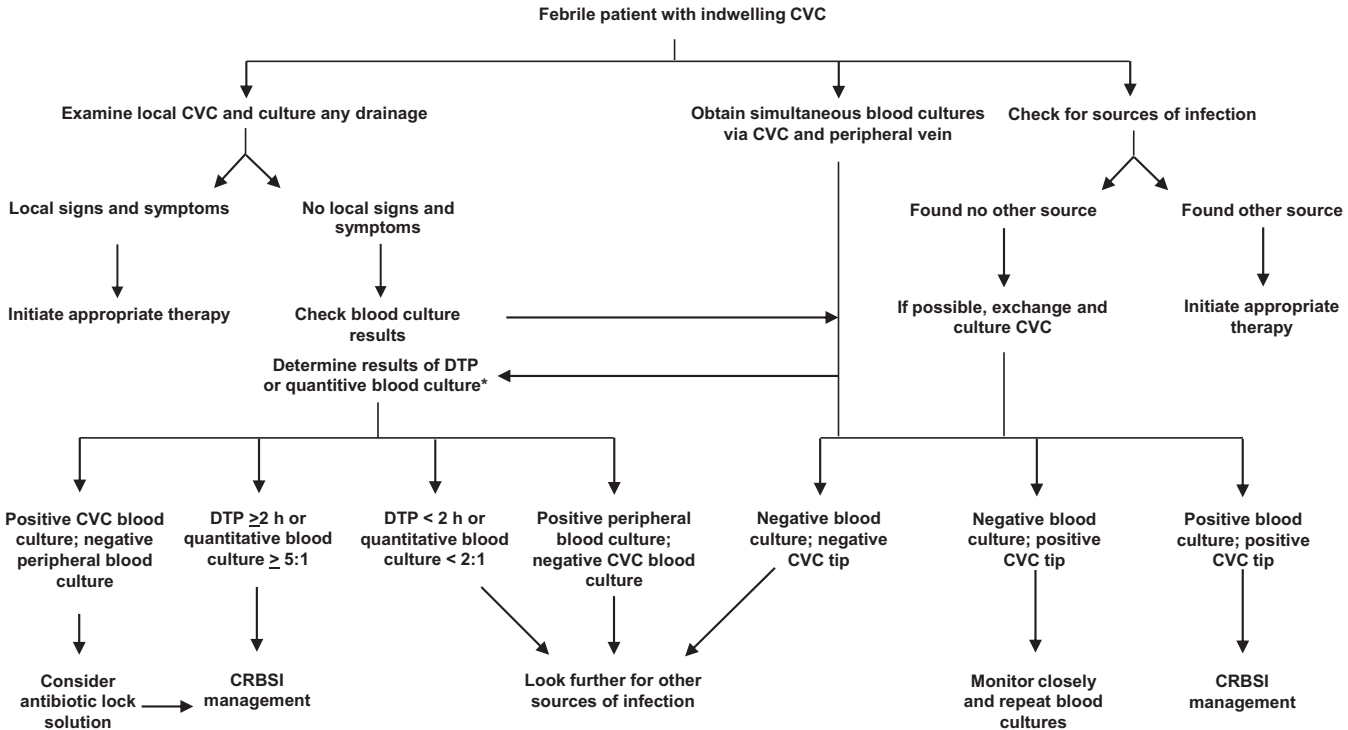

Fig. 1. Diagnosis of acute febrile episode in a patient with a central venous catheter. CVC, central venous catheter; DTP, differential time to positivity. Asterisk indicates that a blood culture is considered positive if the ratio of colony forming units growing from simultaneously drawn central and peripheral blood is at least 5:1 or the DTP is at least 2 hours (central blood culture turns positive before simultaneously drawn peripheral blood culture). (*From* Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis 2007;7:646; with permission.)

catheter–related sepsis and one of the most important pathogens in infection of all types of percutaneous and implantable devices.[11,12,20–25] CNS are important nosocomial pathogens because of their increasing resistance to many commonly used antibiotic agents, and their ability to adhere to and colonize vascular catheters. Many strains can withstand the application of topical antiseptics, and can grow well on foreign bodies and disrupted epithelium.[20–22]

The approach to therapy with specific pathogens and catheters is described in **Fig. 2**.

RISK FACTORS FOR INFUSION-RELATED SEPSIS

Understanding and consideration of the risk factors and sources of microorganisms predisposing patients to infusion-related infections may guide the development and implementation of control measures for prevention of these potentially lethal complications. The risk factors that predispose the patient to infusion-related sepsis include (1) patient factors, (2) concomitant therapies, and (3) catheter-specific factors (**Box 2**).

Patient Factors

Many patient and therapeutic factors predict an increased risk of health care–associated infection. Prospective studies[22,48–50] have shown that the following factors are associated with an increased risk of infection: age older than 65 years; severe and numerous underlying diseases; sepsis; major trauma, surgery, or burns; invasive devices; underlying immune system dysfunction and/or immunosuppressive drugs; breakdown of anatomic barriers; and confinement in a critical care environment.

Therapy-Related Factors

Overall, patients in ICUs have the highest risk profile for complicating infection. Most of these patients endure prolonged hospitalization and have serious underlying conditions associated with disease-related impairment of the immune system. Virtually all critically ill patients are exposed to multiple invasive procedures and monitoring equipment, and many receive TPN or acute hemodialysis, both of which are associated with an increased risk of IRS.[51] Increased nurse workload also appears to be a substantial risk factor for catheter-related infections.[52]

Catheter-Related Factors

Poor aseptic technique (such as during traumatic vascular catheter insertion) is unquestionably associated with a risk of catheter or infusate infection. This risk is related to not only the technique (Seldinger technique vs surgical cutdown) in catheter insertion, but also the quality of aseptic technique during vascular line maintenance. Catheter introduction using the Seldinger technique (catheter over a guide wire) for percutaneous catheter placement has almost completely replaced the cutdown technique for vascular access. In addition, studies have shown that the use of a trained team for catheter insertion and maintenance can significantly reduce central venous catheter infection rates.[53–55]

The longer the vascular catheter is left in situ, the greater the risk for local and systemic infection. An indwelling time longer than 5 days significantly increases the risk of catheter-related infection.[36,56] The necessity of breaking the closed fluid-filled delivery system and the requirements for catheter manipulation compound any risk factors inherent to the specific type of catheter.

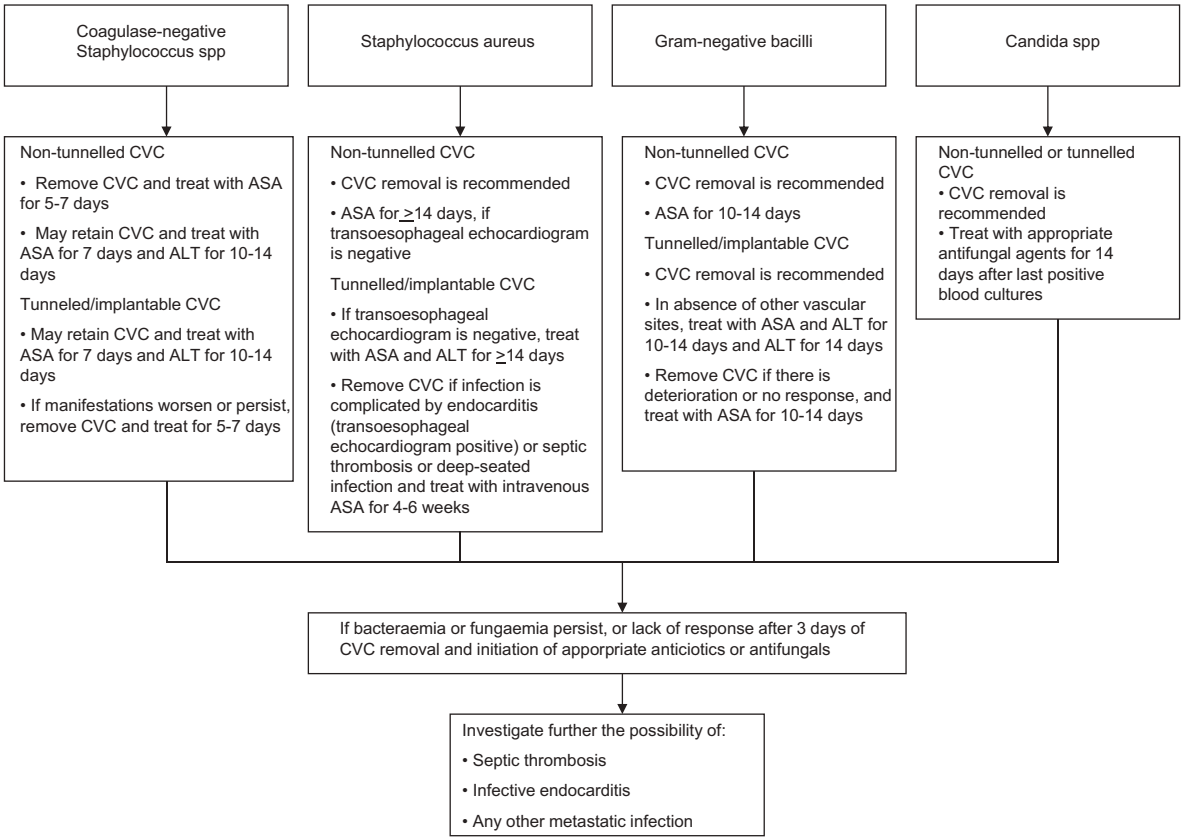

Fig. 2. Management of catheter-related bloodstream infections. ALT, antibiotic-lock therapy; ASA, appropriate systemic antibiotic; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter. (*From* Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis 2007;7:645–57; with permission.)

Box 2
Risk factors for infusion-related sepsis

Patient-Related Factors

1. Extremes of age (neonates or age greater than 65 years)
2. Critical illness/sepsis
3. Remote active infection with coincident vascular catheter
4. Impaired host defenses
5. Major trauma
6. Major surgery
7. Major burn injury
8. Malnutrition
9. Immunosuppressive diseases (eg, diabetes mellitus, uremia, chronic alcoholism, liver disease, neutropenia)
10. Interruption of anatomic barriers (eg, severe psoriasis or eczema, major burns or wounds, mucositis)

Therapy-Related Factors

1. Catheter insertion or maintenance by other than a dedicated team
2. Multiple invasive devices
3. Hospitalization in intensive care unit
4. Use of immunosuppressive or antibiotic drugs
5. Use of total parenteral nutrition
6. Excessive time intervals (longer than 5 days) between replacements of components of the delivery system
7. Excessive time intervals between dressing changes (longer than 3 days) or failure to change dressings when soiled
8. Faulty decontamination of transducer between patients (reusable transducers)

Catheter-Specific Factors

1. Open surgical placement (cutdown rather than percutaneous)
2. Emergent rather than elective catheter insertion
3. Use of polyvinyl chloride or polyethylene catheters, polyurethane, or Teflon (for peripheral intravenous catheters)
4. Complex closed delivery system with multiple stopcocks and other ports
5. Interruption of closed fluid-filled system or need for catheter manipulation after initial insertion
6. Prolonged intravascular retention (longer than 5 days)
7. Suboptimal skin decontamination (2% chlorhexidine is superior to 10% povidone-iodine or 70% alcohol)
8. Use of multilumen rather than single-lumen catheter (possible)
9. Failure to use antiseptic or antibiotic-bonded catheter
10. Failure to use catheter with silver-impregnated tissue cuff
11. Internal jugular rather than subclavian insertion site (femoral site risk intermediate)

CATHETER MATERIAL

The major infectious risk factor is whether the catheter material provides an attractive surface for adherence by pathogenic microorganisms, such as *S epidermidis*.[57,58] Most published research linking type of catheter material and infection risk has been done in peripheral intravenous catheters. In vitro studies have shown that Teflon, silicone, and polyurethane are more resistant to adherence by CNS than polyvinyl chloride and polyethylene.[59,60] Although conflicting, current data do not support conclusions linking central venous catheter materials to risk of infection.[10]

The development of intravascular catheters and implantable devices that resist microbial adherence as well as fibrin formation, while retaining desired flexibility characteristics, must receive high priority. This goal remains a major challenge to manufacturers.

SPECIFIC CENTRAL VENOUS CATHETER INSERTION SITES

Studies of pulmonary artery and central venous catheters have revealed that there is an increased risk of CRS with insertion in the jugular vein in comparison with insertion in the subclavian vein.[61–63] This risk may be caused by heavier skin colonization with gram-negative rods and yeasts, owing to the catheter being placed close to the openings of the respiratory tract (tracheostomy tube, nose, mouth).

Placement in the femoral veins is generally not preferred because of the heavy growth of bacteria and yeast in the area, the likelihood of site contamination if the patient is involuntary of stool and/or incontinent of urine, the difficulty in keeping the groin dressing intact and sterile, and the difficulty in immobilizing the patient's leg and the risk of deep venous thrombosis incited by the presence of the catheter. Some data suggest an increased infection risk with femoral venous catheterization in comparison with subclavian and internal jugular sites.[64] Peripherally inserted central catheters (PICCs), despite suggestions to the contrary, appear to be associated with an infection risk comparable with that of standard central venous catheters when assessed in comparable (high-risk) groups of patients.[65,66]

SEPTIC RISK SPECIFIC TO TYPES OF VASCULAR CATHETERS

Catheter-related bacteremia or fungemia is the most frequent serious complication of these devices. In fact, 80% to 90% of intravascular device–related bacteremias and candidemias arise from central venous catheters,[63,67,68] and central venous catheterization is the single greatest risk factor for nosocomial candidemia.[69–71] The rate of catheter-related infection with central venous catheters is far higher than with peripheral venous catheters, which is in the range of 2% to 7%.[12,14,15,23–25,27,28,72–78]

Except for pulmonary artery catheters, central venous catheters generally have either single or triple lumens. Studies have reported inconsistent results regarding the risk of infection with single-lumen versus triple-lumen catheters. For example, one study[74] reported an incidence of catheter-associated bacteremia of 3.1% with triple-lumen catheters; all bacteremias were caused by *S epidermidis*. However, this study concluded that catheter-related infection occurred with similar frequency between single-lumen and triple-lumen catheters. A meta-analysis/systematic review, however, demonstrated that triple-lumen catheters were associated with an increased incidence of CRS when compared with single-lumen catheters.[79] In this analysis, 1 CR-BSI was prevented for every 20 single-lumen (rather than triple-lumen) catheter inserted. An important factor to consider is that in this latter study, the patients with triple-lumen catheters were more ill, and therefore at greater risk of CRS, than patients

with single-lumen catheters. A single trial has suggested that infection risk is unaffected when TPN is delivered by single-, double-, or triple-lumen catheters.[80]

Among the variety of central venous catheters, hemodialysis catheters are associated with the highest risk of CRS, at approximately 10%.[81–83] The lowest risk of infection is with cuffed, tunneled, surgically implanted devices (eg, Hickman, Broviac) with infection risks of 0.2% to 0.5%.[36] PICCs have been reputed to carry an extremely low (<1%) risk of infection,[66] and this is certainly the case in the usual, low-risk outpatient setting. However, in recent years such catheters have become more commonly used in high-risk ICU patients. Safdar and Maki[65] have shown that use of PICCs in such patients is associated in infection rates similar to those for standard central venous catheters.

Pulmonary artery catheters, once a hallmark of critical care management, have substantially declined in usage given a large body of evidence that invasive devices do not decrease mortality. Mermel[61] previously had estimated the rate of CRS to be 0.7%. The investigators concluded that with "reasonable care" the risk of bacteremic infection is low, generally in the range of 1.0%.

Arterial pressure monitoring with arterial catheters, on the other hand, remains an essential component in the management of more than 80% of the 4 to 5 million patients cared for in the ICUs in United States hospitals each year. Maki and Ringer[11] conducted a prospective study of 489 percutaneously inserted arterial catheters in a large medical-surgical ICU, using microbiological methods for identification of all potential sources of infusion-related infection. The septic risk was found to be very low, with local catheter-related infection at 3.1% and infusate-related or hub-related infections at 0.8%. This rate of invasive infection is 3- to 6-fold lower than that encountered with central venous catheters used in similar ICU patients for a comparable period of time in situ.[20,33] Although the rate of infection with arterial catheters was low in this large study, other studies have suggested an equivalent infection risk with arterial catheters when compared with central venous catheters.[84] Flush solutions used for hemodynamic monitoring are vulnerable to contamination, and are the most important cause of epidemic infusion-related gram-negative bacteremia in ICU patients.

MANAGEMENT OF CATHETER-RELATED AND INFUSION-RELATED SEPSIS

A common error seen in management of catheter colonization is the assumption that a colonizing organism does not represent infection or high risk of infection. The question of how to handle catheter asymptomatic colonization of intravascular catheters (semiquantitative count >15 CFU) in the absence of positive blood cultures is difficult, owing to the lack of randomized trials. Certainly routine screening of cultures from extracted catheters frequently yields evidence of colonization with commensals in asymptomatic patients. Most of these do not require therapy. However, catheter tip colony counts of greater than 15 CFU with certain pathogens are clearly associated with increased risk of CR-BSIs.[85,86] As a consequence, catheter colonization with pathogenic noncommensals including *S aureus*, gram negatives, and *Candida* species require empiric antimicrobial therapy even in the absence of signs of clinical infection and positive blood cultures.

Without evidence of clinical sepsis or documented bacteremia, most clinicians will not treat patients with antibiotics if catheter colonization with commensal organisms is found following catheter removal. On the other hand, such catheters are sometimes switched over a guide wire. If the original catheter tip grows to greater than 15 CFU, any new catheter placed into the same site over a guide wire should be removed.

In all cases, patients who have experienced high-grade catheter-related bacteremia or candidemia should always be assessed carefully for the development of late complications, including endocarditis or other metastatic complications.[36] This aspect is particularly important for infections with *Candida* species and *S aureus* and for those patients with intravascular prosthetic devices including heart valves.

Recent data suggest that many infected central venous catheters, particularly those infected with coagulase-negative staphylococci, can be effectively treated without catheter removal. However, there is a significant risk of recurrent bacteremia (approximately 20% after 3 weeks vs 3% if the catheter is removed).[87] Because the presence of an infected catheter puts the patient at risk for serious septic complications including septic thrombosis and endocarditis, such an approach should be reserved only for those catheters that cannot be easily and safely replaced. As a general rule, any short-term intravascular catheter suspected of being the source of sepsis (unexplained fever, local inflammation, cryptogenic staphylococcal bacteremia, or candidemia) should be removed and replaced. Exceptions should be limited to those patients with severe coagulopathy/thrombocytopenia or exceptional problems with venous access whereby removal and/or replacement is untenable.

By contrast, CRS associated with surgically implanted catheters (eg, Hickman, Broviac) can be assessed for in situ antibiotic treatment. An attempt at antibiotic treatment with retention of the catheter may be worthwhile if there is no evidence of a persistent exit-site infection, tunnel infection, endocarditis, septic thrombosis, or septic shock; if the infecting organism is other than *Corynebacterium jeikeium*, *S aureus*, *Bacillus* species, *Stenotrophomonas* species, yeast, fungus or mycobacteria; and if bacteremia or candidemia has persisted for less than 3 days.[36] Up to two-thirds of CRS in surgically implanted catheters (apart from those conditions listed here) may be cured with antibiotics administered through the device for 7 to 10 days.[71,88–93] Bacteremia caused by CRS in such devices may be cured even more simply by locking a concentrated antibiotic-containing solution (usually vancomycin or an aminoglycoside) into the lumen of the catheter for 12 hours per day for 2 weeks.[94,95] If this approach is attempted, early initiation of therapy is important to maximize chances of cure.[96]

The role of local thrombolytics in in situ therapy for catheter-related infection is unclear. Some advocate such an approach as part of therapy for retained catheters, because local thrombosis is known to be associated with catheter infections and should theoretically make it more difficult to clear an infection.[93,97] However, to date no randomized trial has been performed to definitively answer this question. For this reason, there are no uniformly accepted recommendations regarding this issue.

PREVENTION OF CATHETER-RELATED AND INFUSION-RELATED SEPSIS

Infection and infectious sequelae, such as sepsis and multiple system organ failure, are the most common causes of death in surgical and trauma ICUs. It has been estimated that the ICU incidence of nosocomial sepsis is 24 times higher than that of general medical-surgical areas.[98] One major reason for this high incidence of health care–associated infection in the ICU is that invasive devices, which are a major risk factor for sepsis, are a standard part of ICU patient care; their use should, therefore, be kept to a minimum. The importance of meticulously following sepsis prophylaxis in all aspects of patient care cannot be overstated. An advisory statement on prevention of intravascular catheter-related infection has been published and is recommended for those requiring a detailed analysis.[8] A simple “golden rule” on this issue is never

to insert an intravascular device without a clear indication and never retain that device longer than the minimum period required. Abbreviated suggestions for the prophylaxis and management of infusion-related sepsis are discussed here.

Hand Washing

Infusion-related infections may originate from microorganisms present on the hands of medical personnel inserting or manipulating the devices. The hands of the caregiver are a primary source of antibiotic-resistant bacterial contamination that causes health care–associated infection. Vigorous rubbing together of all lathered hand surfaces for a minimum of 10 seconds (preferably for 30 seconds) is one of the oldest yet most important infection control measures before and after manipulating any invasive device. Wearing gloves may provide an additional measure of patient safety when the closed fluid system requires disruption (changing connecting tubing or stopcocks, and/or aspiration of blood).

Antiseptic hand-washing soaps do not reduce the amount of time, friction, or water required for effective hand degerming. Consistent, careful hand-washing technique and gloving also protects caregivers from acquiring transferable diseases such as hepatitis, acquired immune deficiency diseases, and herpetic infections.

Dedicated Infusion Therapy Team/Training

Many studies have conclusively demonstrated that the use of a dedicated infusion therapy team for intravascular catheter placement and care can substantially reduce the risk of IRS by up to 8-fold.[53,99] If such a team is not possible, rigorous training of nurses and physicians involved in catheter insertion and care, along with meticulous adherence to catheter care protocols, can achieve similar results.[100,101] This latter approach is specifically recommended in an advisory statement by a group of experts in the field.[8]

Skin Disinfection

A strong concordance exists between microorganisms colonizing catheters and the skin at the catheter-insertion site.[11,12,24,25] The data in related studies suggest that the importance of reliable suppression of the skin microflora with an antiseptic solution before catheter insertion and the follow-up care of the insertion site cannot be overemphasized.

The ideal means of skin disinfection (nonirritating and effective in antimicrobial activity) has not yet been identified. In a study by Maki and colleagues,[102] insertion sites were disinfected with 70% alcohol, 10% povidone-iodine, or 2% aqueous chlorhexidine, by random allocation. Alcohol and povidone-iodine were equivalent in protection against infection but significantly less effective than chlorhexidine in preventing catheter-related infection.[102] Although other studies have failed to show such a difference,[103] chlorhexidine has been recommended as the first-line antiseptic for prevention of infection with percutaneously inserted intravascular devices of all types.[103] Other studies demonstrate a decreased risk of CRS with use of a topical polyantibiotic regiment (polymyxin B, neomycin, bacitracin) or mupirocin (an antistaphylococcal agent).[104,105] One study has shown superiority of 5% povidone-iodine in 70% ethanol over the 10% aqueous form.[106] Future studies should examine other agents for cutaneous disinfection to improve the effectiveness and duration of flora suppression at the catheter-insertion site. Even with adequate suppression of skin microflora at the time of insertion, the suppressed microorganisms can rapidly grow back and invade the wound.

SURGICAL ASEPTIC TECHNIQUE FOR INTRAVASCULAR CATHETER INSERTION

For central venous catheter insertion, the operator and assistant should wear gown, gloves, and mask, and the patient should be surgically draped. All those assisting in the room should wear a surgical mask and cap. When possible, the door to the room should be closed during the insertion procedure, and the number of persons entering and leaving the room should be limited. The use of maximal barrier precautions has been shown to result in a highly significant 4- to 6-fold decrease in the risk of catheter-related infections.[33,61,107]

INTRAVASCULAR CATHETER DRESSING PROTOCOL

To prevent contamination of the insertion site, a sterile occlusive dressing should be applied. The dressing and not the tape should cover the wound. The date of catheter insertion should be recorded where it can be easily found, such as in the medical record and, if possible, directly on the dressing or tape.

As discussed earlier, there is a strong correlation between microorganisms present at the catheter-insertion site and microorganisms implicated in CRS. In the past it was believed that frequent dressing changes at the site would reduce the incidence of CRS. Studies regarding dressing material and frequency of dressing changes have produced conflicting results. At this point, the CDC has no recommendation on the frequency of dressing changes or the type of dressing material.[10] However, dressings should be changed also whenever wet, soiled with drainage, or disrupted. Wet dressings particularly favor bacterial growth.

A semipermeable clear membrane dressing has been introduced in recent years. Vasquez and Jarrad[108] studied one such dressing, Opsite, and found an overall CRS rate of 1% for the 100 patients studied. It was concluded that Opsite was both a safe and cost-effective dressing for central venous catheters. Young and colleagues[109] also compared a standard protocol of gauze changed 3 times per week with Opsite changed 3 times per week, or every 7 to 10 days. Sepsis rates were low in all groups. It was concluded by these investigators that Opsite could be safely left in place for up to 7 days. However, 2 studies[110,111] have revealed a much higher incidence of catheter-related infection and sepsis when transparent dressings were used for central venous catheters. Patients were found to have higher rates of colonization of the subcutaneous tract and subsequent bacteremia that coincided with microorganisms found at the catheter-insertion site.[111] Bacterial colonization may actually be enhanced when moisture accumulates under the transparent dressing. Transparent dressings are less bulky and allow for visualization of the site while being vapor-permeable and waterproof. Further studies are required to determine the safety and efficacy of transparent polyurethane dressings. Sterile gauze and an antimicrobial ointment are currently acceptable and economical dressings.

The recent development of a chlorhexidine sponge of about 1-inch (2.5 cm) diameter that can be affixed over the catheter-insertion site has shown promise in at least one study.[112] In another meta-analysis, a trend toward decreased vascular and epidural catheter infection was shown.[113] However, other studies have been contradictory, and guidelines do not support this approach at this time.

Regular maintenance and observation of the intravenous site are important for prevention or early detection of intravenous-related complications.[114] Intravenous sites should be inspected at least every 24 hours. If visual inspection is not possible, the insertion site should be gently palpated to detect pain, tenderness, or swelling. At each dressing change and at catheter removal, the insertion site should be observed for erythema, purulence, swelling, and tenderness.

INFUSION SYSTEM PROTOCOLS

Intraluminal antibiotic locks as part of routine catheter care may be effective in reducing intraluminal colonization and infection rates.[115–117] Antibiotics that can be locked into the infusion ports with a reduction in IRS include aminoglycosides and minocycline.[117] A recent meta-analysis has demonstrated that this vancomycin lock can halve the incidence of CR-BSI.[118] Despite this, vancomycin locking is not currently recommended because of the risk of the development of vancomycin-resistant organisms (especially enterococci).

Most IRS is, in fact, CRS. However, contamination of the infusate may occur, often in the setting of a cluster. Historically, United States hospital practice has been to routinely replace the entire infusion delivery system on a 24- to 48-hour basis to reduce the risk from extrinsically contaminated fluid.[20] This action minimizes the opportunity of any potential organisms in the infusate to grow to numbers large enough to cause adverse effects. However, recent studies suggest that the infusate delivery systems do not require replacement more than every 72 hours.[19,119,120] Exceptions may be made for infusion sets used for delivery of blood products, lipid emulsions, or arterial pressure monitoring, whereby more frequent changes may be prudent.[36]

CATHETER-DESIGN IMPROVEMENTS/ANTISEPTIC-ANTIMICROBIAL BONDING

Improvements in catheter design have been intrinsic to improvement in rates of CRS. Methods to prevent invasion of the transcutaneous tract by skin flora following catheter insertion have been studied. Surgically implanted, tunneled, Dacron-cuffed devices such as Hickman and Broviac catheters used for long-term vascular access are an example. Both tunneling and the cuff limit the migration of cutaneous microorganisms to the bloodstream. An attachable subcutaneous cuff constructed of a biodegradable collagen matrix impregnated with bactericidal silver was studied by Maki and colleagues,[12] who found that the silver-impregnated cuff can confer a 3-fold reduction of catheter-related infection with PICCs. Antiseptic hubs and in-line filters have also been studied.[9,36] In addition, needleless luer-activated devices (ports) are an important source of catheter infection, and improvements in their design and materials can be expected to reduce rates of infusion-related sepsis.[121,122]

Three different commercially available antiseptic-/antibiotic-bonded central venous catheters exist: (1) minocycline-/rifampicin-bonded catheters; (2) chlorhexidine-/silver sulfadiazine–impregnated catheters; and (3) platinum/silver/carbon iontophoretic catheters. Each device is currently available in the United States. A series of studies and meta-analyses have demonstrated that antiseptic and antimicrobial bonded intravascular catheters are effective in reducing the risk of catheter colonization and infection.[123] Recent data suggest that the use of antiseptic (chlorhexidine and silver sulfadiazine)-bonded and antibiotic (minocycline and rifampin)-bonded catheters results in a 3- to 4-fold reduction in the risk of CRS.[124–126] A single head-to-head comparison of the 2 types of catheter has favored the antibiotic-bonded device.[125,127]

Despite data showing a decrease in catheter colonization with the silver/platinum iontophoretic catheter, 2 studies have failed to demonstrate any reduction in CR-BSI with these devices.[9,128,129] Irrespective of these data, no formal recommendation favoring one type of catheter over another has been adopted in formal consensus advisories.[8] Their use in general has been recommended in institutions where catheter infection risk remains high despite implementation of other recommendations in high-risk patients.

New antiseptic and antimicrobial catheters continue to be developed, including catheters coated or bonded with new combinations or formulations of chlorhexidine, silver, vancomycin, and miconazole.[128,130–133]

INSERTION SITE

Because studies of pulmonary artery catheters and central venous catheters have shown that there is an increased risk of CRS with insertion in the jugular vein compared with insertion in the subclavian vein,[61–63] the subclavian venous site is the preferred insertion site as regards the prevention of CRS. Recent data suggest an increased CRS risk using the femoral insertion site.[5,64]

DURATION OF INTRAVASCULAR CATHETERIZATION

Previous studies have indicated that the duration of vascular catheterization[134–137] is related to the incidence of both catheter colonization and CRS. In general, an in situ duration of more than 72 hours significantly increases the risk of catheter-related infection. Consequently, it had been generally recommended that central venous catheters be changed routinely every 3 to 5 days (most clinicians use 5 days). Other studies support the theory that both arterial and pulmonary catheters can remain in place as long as needed, provided there are no signs or symptoms of CRS occurring more than 48 hours after catheter insertion, local signs of infection at the insertion site, or positive blood cultures.[61,64,138–140] The most recent consensus recommendations suggest that in the absence of evidence of colonization/infection, routine replacement of central venous catheters is not required.[8]

INTEGRATIVE, MULTIFACTORIAL PROTOCOLS (BUNDLES)

A series of studies have shown that increasing nursing workload substantially increases the probability of acquiring CR-BSI.[52] The mechanism of this effect is likely to be a multifactorial deterioration in standard infection-prevention techniques. At least 2 major studies have now demonstrated astonishing decreases in incidence of catheter-related infection through an implementation of central-line "bundles" (a broad group of proven standard infection-control methods endorsed by the Institute of Healthcare Improvement [IHI]) as previously discussed.[141,142] Care bundles, in general, are groupings of best practices with respect to a disease process that individually improve care, but when applied together result in substantially greater improvement. The science supporting the bundle components is sufficiently established to be considered standard of care. The key elements of the catheter bundles are hand hygiene, routine use of maximum barrier precautions during insertion, chlorhexidine as the preferred antiseptic, the subclavian vein as the preferred access, and daily assessment for continued retention of intravascular catheters. One simple way to ensure compliance with these elements is to use a standard checklist.[142] Of note, these studies indicated that once these efforts were effectively implemented, the benefits were sustainable if the protocols were incorporated into hospital guidelines.

REFERENCES

1. Maki DG. Infections due to infusion therapy. In: Bennett JV, Brachman PS, editors. Hospital infections. Boston: Little Brown & Co; 1986. p. 849–98.
2. Raad I, Darouiche RO. Catheter-related septicemia: risk reduction. Infect Med 1996;13:807–23.

3. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 1995;274(8):639–44.
4. Vincent J, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302(21):2323–9.
5. Mermel LA. Prevention of intravascular catheter-related infections. Ann Intern Med 2000;132:391–402.
6. Srinivasan A, Wise M, Bel M, et al. Vital signs: central line-associated blood stream infections - United States, 2001, 2008, and 2009. MMWR Morb Mortal Wkly Rep 2011;60(8):243–8.
7. Scott RD. The direct medical cost of healthcare-associated infections in U.S. hospitals and the benefits of prevention. Atlanta (GA): Center for Disease Control; 2010.
8. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Infect Control Hosp Epidemiol 2002; 23(12):759–69.
9. Raad I, Hanna H, Maki D, et al. Intravascular catheter-related infections: advances in diagnosis, prevention, and management [166 refs]. Lancet Infect Dis 2007;7(10):645–57.
10. Pearson ML. Hospital Infection Control Practice Advisory Committee: guidelines for prevention of intravascular-device-related infections. Infect Control Hosp Epidemiol 1996;17:438–73.
11. Maki DG, Ringer M. Evaluation of dressing regimens for prevention of infection with peripheral intravenous catheters. JAMA 1987;258:2396–403.
12. Maki DG, Cobb L, Garman JK, et al. An attachable silver-impregnated cuff for prevention of infection with central venous catheters: a prospective randomised multicenter trial. Am J Med 1988;85:307–14.
13. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous catheter-related infection. N Engl J Med 1977;296:1305–9.
14. Snydman DR, Murray SA, Kornfeld SJ. Total parental nutrition-related infections. Prospective epidemiologic study using semiquantitative methods. Am J Med 1982;73:695–9.
15. Collignon PJ, Soni N, Pearson IY. Is semiquantitative culture of central vein catheter tips useful in the diagnosis of catheter-associated bacteremia? J Clin Microbiol 1986;24:532–5.
16. Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis 1987;141:781–6.
17. Sherertz RJ, Raad I, Belani A, et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiologic laboratory. J Clin Microbiol 1990;28:76–82.
18. Raad I, Sabbagh MF, Rand KH, et al. Quantitative tip culture methods and the diagnosis of central venous catheter-related infections. Diagn Microbiol Infect Dis 1992;15:13–20.
19. Band JD, Maki DG. Safety of changing intravenous delivery systems at longer than 24-hour intervals. Ann Intern Med 1979;91:173–8.
20. Maki DG, Goldman DA, Rhame FS. Infection control in intravenous therapy. Ann Intern Med 1973;79:867–87.
21. Maki DG. Infections associated with intravascular lines. In: Swartz M, Remington JS, editors. Current topics in clinical infectious disease. New York: McGraw Hill; 1982. p. 309–63.

22. Maki DG. Nosocomial bacteremia: an epidemiologic overview. Am J Med 1981; 70:719–32.
23. McGeer A, Righter J. Improving our ability to diagnose infections associated with central venous catheters: value of Gram's staining and culture of entry site swabs. Can Med Assoc J 1987;137:1009–15.
24. Snydman DR, Pober BR, Murray SA. Predictive values of surveillance skin cultures in total-parenteral-nutrition-related infection. Lancet 1982;2:1385.
25. Bjornson HS, Colley R, Bower RH. Association between microorganism growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery 1982;92:720–7.
26. Kovacevich DS, Faubion WC, Bender JM, et al. Association of parenteral nutrition catheter sepsis with urinary tract infections. JPEN J Parenter Enteral Nutr 1986;10:639–41.
27. Pettigrew RA, Lang SD, Haydock DA. Catheter-related sepsis in patients on intravenous nutrition: a prospective study of quantitative catheter cultures and guidewire changes for suspected sepsis. Br J Surg 1985;72:52–5.
28. Sitges-Serra A, Linares J, Garau J. Catheter sepsis: the clue is the hub. Surgery 1985;97:355–7.
29. Raad I, Costerton W, Sabharwal U. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis 1993;168:400–7.
30. Maki DG, Rhame FS. Nationwide epidemic of septicemia caused by contaminated intravenous products. Am J Med 1977;60:471–85.
31. Hamory BH. Nosocomial bloodstream and intravascular device-related infections. In: Wenzel R, editor. Prevention and control of nosocomial infections. Baltimore (MD): Williams and Wilkins; 1987. p. 283.
32. Bennett SN, McNeil MM, Bland LA, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med 1995;333: 147–54.
33. Goldman DG, Martin WT, Worthington JW. Growth of bacteria and fungi in total parenteral nutrition solutions. Am J Surg 1973;126:314–8.
34. Freeman J, Goldmann DA, Smith NE, et al. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. N Engl J Med 1990;323:301–8.
35. Safdar N, Maki DG. Inflammation at the insertion site is not predictive of catheter-related bloodstream infection with short-term, noncuffed central venous catheters. Crit Care Med 2002;30(12):2632–5.
36. Maki DG. Infections caused by intravascular devices used for infusion therapy: pathogenesis, prevention, and management. In: Bisno AL, Waldvogel FA, editors. Infections associated with indwelling medical devices. Washington, DC: American Society for Microbiology; 1994. p. 155–212.
37. Ascher DP, Shoupe BA, Robb M, et al. Comparison of standard and quantitative blood cultures in the evaluation of children with suspected central venous line sepsis. Diagn Microbiol Infect Dis 1992;15:499–503.
38. Benezra D, Kiehn T, Gold JW, et al. Prospective study of infections in indwelling central venous catheters using quantitative blood cultures. Am J Med 1988;85: 495–8.
39. Vanhuynegem L, Parmentier P, Potvliege C. In situ bacteriologic diagnosis of total parenteral nutrition catheter infection. Surgery 1987;103:174–7.
40. Raad I. Intravascular-catheter-related infections. Lancet 1998;351(9106): 893–8.

41. Kite P, Dobbins BM, Wilcox MH, et al. Evaluation of a novel endoluminal brush method for in situ diagnosis of catheter related sepsis. J Clin Pathol 1997;50: 278–82.
42. Rushforth JA, Hoy CM, Kite P, et al. Rapid diagnosis of central venous catheter sepsis. Lancet 1993;342:402–3.
43. Millar MR, Johnson G, Wilks M, et al. Molecular diagnosis of vascular access device-associated infection in children being treated for cancer or leukaemia. Clin Microbiol Infect 2008;14(3):213–20.
44. Guerti K, Ieven M, Mahieu L. Diagnosis of catheter-related bloodstream infection in neonates: a study on the value of differential time to positivity of paired blood cultures. Pediatr Crit Care Med 2007;8(5):470–5.
45. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med 2004;140(1):18–25 [Erratum Ann Intern Med. 2004 Jan 6;140(1):I39; PMID: 14706995].
46. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. Ann Intern Med 2005;142(6): 451–66 [Erratum appears in Ann Intern Med. 2005 May 3;142(9):803].
47. Telenti A, Steckelberg JM, Stockman L, et al. Quantitative blood cultures in candidemia. Mayo Clin Proc 1991;66:1120–3.
48. Craven DE, Kunches LM, Lictenberg DA. Nosocomial infections and fatality in medical and surgical intensive care unit patients. Arch Intern Med 1988;148: 1161–8.
49. Freeman J, McGowan JE. Risk factors for nosocomial infection. J Infect Dis 1978;138:811–9.
50. Armstrong CW, Mayhall CG, Miller KB. Prospective study of catheter replacement and other risk factors for infection of hyperalimentation catheters. J Infect Dis 1986;154:808–16.
51. Yilmaz G, Koksal I, Aydin K, et al. Risk factors of catheter-related bloodstream infections in parenteral nutrition catheterization. JPEN J Parenter Enteral Nutr 2007;31(4):284–7.
52. Hugonnet S, Chevrolet JC, Pittet D. The effect of workload on infection risk in critically ill patients. Crit Care Med 2007;35(1):76–81.
53. Faubion WC, Wesley JR, Khalidi N, et al. Total parenteral nutrition catheter sepsis: impact of the team approach. JPEN J Parenter Enteral Nutr 1986;10: 642–5.
54. Nelson DB, Kien CL, Mohr B. Dressing changes by specialized personnel reduced infection rates in patients receiving central venous parenteral nutrition. JPEN J Parenter Enteral Nutr 1986;10:220–2.
55. Tomford JW, Hershey CO, McLaren CE. Intravenous therapy team and peripheral venous catheter-associated complications: a prospective controlled study. Arch Intern Med 1984;144:1191–4.
56. Mermel LA, Maki DG. Infectious complications of Swan-Ganz pulmonary artery catheters. Pathogenesis, epidemiology, prevention and management. Am J Respir Crit Care Med 1994;149:1020–36.
57. Christensen GD, Simpson WA, Beachey EH. Adherence of slime-producing strains of *Staphylococcus epidermidis* to smooth surfaces. Infect Immun 1982;37:318–26.
58. Peters G, Locci R, Pulverer G. Adherence and growth of coagulase-negative staphylococci on surfaces of intravenous catheters. J Infect Dis 1982;146: 479–82.

59. Sheth NK, Rose HD, Franson TR. In vitro quantitative adherence of bacteria to intravascular catheters. J Surg Res 1983;34:213–8.
60. Sheth NK, Franson TR, Rose HD. Colonization of bacteria on polyvinyl chloride and Teflon intravenous catheters in hospitalized patients. J Clin Microbiol 1983; 18:1061–3.
61. Mermel LA, McCormick RD, Springman SR, et al. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. Am J Med 1991;91: 197S–205S.
62. Pinilla JC, Ross DF, Martin T, et al. Study of the incidence of intravascular catheter infection and associated septicemia in critically ill patients. Crit Care Med 1983;11:21–5.
63. Richet H, Hubert B, Netemberg G. Prospective multicenter study of vascular catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. J Clin Microbiol 1990;28:2520–5.
64. Norwood S, Ruby A, Civetta J, et al. Catheter-related infections and associated septicemia. Chest 1988;99:968–75.
65. Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients [54 refs]. Chest 2005;128(2):489–95.
66. Graham DR, Keldermans MM, Klemm LW, et al. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. Am J Med 1991;91(Suppl 3B): 95S–100S.
67. Maki DG. The epidemiology and prevention of nosocomial bloodstream infections. In: Program and abstracts of the third international conference on nosocomial infections 1990. Atlanta, (GA): Centers for Disease Control. The National Foundation for Infectious Disease and the American Society for Microbiology; 1990. p. 20.
68. Nystrom B, Olesen Larsen S, Daschner F, et al. Bacteraemia in surgical patients with intravenous devices: a European multicentre incidence study. J Hosp Infect 1983;4:338–49.
69. Bross J, Talbot GH, Maislin G, et al. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. Am J Med 1989;87:614–20.
70. Komshian SV, Uwaydah AK, Sobel JD, et al. Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989;3: 379–90.
71. Wang EE, Prober CG, Ford-Jones L, et al. The management of central intravenous catheter infections. Pediatr Infect Dis 1984;3:110–3.
72. Capell S, Linares J, Sitges-Serra A. Catheter sepsis due to coagulase-negative staphylococci in patients on total parental nutrition. Eur J Clin Microbiol 1985;5: 40–2.
73. Linares J, Sitges-Serra A, Garau J. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter and hub segments. J Clin Microbiol 1985;21:357–60.
74. Kelly CS, Ligas JR, Smith CA. Sepsis due to triple lumen central venous catheters. Surg Gynecol Obstet 1986;163:14–6.
75. Pemberton LB, Lyman B, Lander V, et al. Sepsis from triple vs. single-lumen catheters during total parenteral nutrition in surgical or critically ill patients. Arch Surg 1986;121:591–4.

76. Padberg FT, Ruggiero J, Blackburn GL, et al. Central venous catheterization for parenteral nutrition. Ann Surg 1981;193:264–70.
77. Bozzetti F, Terno G, Bonfanti G. Prevention and treatment of central venous catheter sepsis by exchange via a guidewire. A prospective controlled trial. Ann Surg 1983;198:48–52.
78. Sitzmann JV, Townsend TR, Siler MC, et al. Septic and technical complications of central venous catheterization. A prospective study of 200 consecutive patients. Ann Surg 1985;202:766–70.
79. Zurcher M, Tramer MR, Walder B. Colonization and bloodstream infection with single- versus multi-lumen central venous catheters: a quantitative systematic review [58 refs]. Anesth Analg 2004;99(1):177–82.
80. Ma TY, Yoshinaka R, Banaag A, et al. Total parenteral nutrition via multilumen catheters does not increase the risk of catheter-related sepsis: a randomized, prospective study. Clin Infect Dis 1998;27(3):500–3.
81. Cheesbrough JS, Finch RG, Burden RP. A prospective study of the mechanisms of infection associated with hemodialysis catheters. J Infect Dis 1986;154: 579–89.
82. Pezzarossi HE, Ponce de Leon S, Calva JJ, et al. High incidence of subclavian dialysis catheter-related bacteremias. Infect Control 1986;7:596–9.
83. Sherertz RJ, Falk RJ, Huffman KA, et al. Infections associated with subclavian Uldall catheters. Arch Intern Med 1983;143:52–6.
84. Traore O, Liotier J, Souweine B, et al. Prospective study of arterial and central venous catheter colonization and of arterial- and central venous catheter-related bacteremia in intensive care units. Crit Care Med 2005;33(6):1276–80.
85. O'Grady NP, Barie PS, Bartlett J, et al. Practice parameters for evaluating new fever in critically ill adult patients. Crit Care Med 1998;26(2):392–408.
86. Ekkelenkamp MB, van der BT, van de Vijver DA, et al. Bacteremic complications of intravascular catheters colonized with *Staphylococcus aureus*. Clin Infect Dis 2008;46(1):114–8.
87. Raad I, Davis S, Khan A, et al. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol 1992;13:215–21.
88. Cappello M, De Pauw L, Bastin G, et al. Central venous access for haemodialysis using the Hickman catheter. Nephrol Dial Transplant 1989;4:988–92.
89. Hartman GE, Shochat SJ. Management of septic complications associated with silastic catheters in childhood malignancy. Pediatr Infect Dis 1987;6:1042–7.
90. Johnson PR, Decker MD, Edwards KM, et al. Frequency of Broviac catheter infections in pediatric oncology patients. J Infect Dis 1986;154:570–8.
91. Press OW, Ramsey PG, Larson EB, et al. Hickman catheter infections in patients with malignancies. Medicine 1984;63:189–200.
92. Prince A, Heller B, Jevy J, et al. Management of fever in patients with central vein catheters. Pediatr Infect Dis 1986;5:20–4.
93. Schuman ES, Winters V, Gross GF, et al. Management of Hickman catheter sepsis. Am J Surg 1985;149:627–8.
94. Douard MC, Leverger G, Paulien R, et al. Quantitative blood cultures for diagnosis and management of catheter-related sepsis in pediatric hematology and oncology patients. Intensive Care Med 1991;17:30–5.
95. Messing B, Peitra-Cohen S, Debure A, et al. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. JPEN J Parenter Enteral Nutr 1988;12:185–9.

96. Onder AM, Chandar J, Billings AA, et al. Comparison of early versus late use of antibiotic locks in the treatment of catheter-related bacteremia. Clin J Am Soc Nephrol 2008;3(4):1048–56.
97. Jones GR, Konsler GK, Dunaway RP, et al. Prospective analysis of urokinase in the treatment of catheter sepsis in pediatric hematology-oncology patients. J Pediatr Surg 1993;28:350–8.
98. Wenzel RP, Osterman CA, Donowitz LG, et al. Identification of procedure-related nosocomial infections in high-risk patients. Rev Infect Dis 1981;3:701–7.
99. Maki DG. Yes, Virginia, aseptic technique is very important: maximal barrier precautions during insertion reduce the risk of central venous catheter-related bacteremia. Infect Control Hosp Epidemiol 1994;15:227–30.
100. Puntis JW, Holden CE, Smallman S, et al. Staff training: a key factor in reducing intravascular catheter sepsis. Arch Dis Child 1990;65:335–7.
101. Vanherweghem JL, Dhaene M, Goldman M, et al. Infections associated with subclavian dialysis catheters: the key role of nurse training. Nephron 1986;42: 116–9.
102. Maki DG, Alvarado CJ, Ringer M. A prospective, randomized trial of povidone-iodine, alcohol and chlorhexidine for prevention of infection with central venous and arterial catheters. Lancet 1991;338:339–43.
103. Humar A, Ostromecki A, Direnfeld J, et al. Prospective randomized trial of 10% povidone-iodine versus 0.5% tincture of chlorhexidine as cutaneous antisepsis for prevention of central venous catheter infection. Clin Infect Dis 2000;31(4): 1001–7.
104. Hill RL, Fisher AP, Ware RJ, et al. Mupirocin for the reduction of colonization of internal jugular cannulae-a randomised controlled trial. J Hosp Infect 1990;15: 311–21.
105. Maki DG, Band JD. A comparative study of polyantitotic and iodophor ointments in prevention of vascular catheter-related infection. Am J Med 1981;70: 739–44.
106. Parienti JJ, du Cheyron D, Ramakers M, et al. Members of the NSG. Alcoholic povidone-iodine to prevent central venous catheter colonization: a randomized unit-crossover study. Crit Care Med 2004;32(3):708–13.
107. Raad I, Hohn DC, Gilbreath J. Prevention of central venous catheter-related infections using maximal barrier precautions during insertion. Infect Control Hosp Epidemiol 1994;15:231–8.
108. Vasquez RM, Jarrad MM. Care of the central venous catheterization site: the use of a transparent polyurethane film. JPEN J Parenter Enteral Nutr 1984;8: 181–6.
109. Young GP, Alexeyeff M, Russell DM, et al. Catheter sepsis during parenteral nutrition: the safety of longterm Opsite dressing. JPEN J Parenter Enteral Nutr 1988;12:365–70.
110. Conly JM, Grieves K, Peters B. A prospective randomized study comparing transparent and dry gauze dressings for central venous catheters. J Infect Dis 1989;159:310–9.
111. Dickerson N, Horton P, Smith S, et al. Clinically significant central venous catheter infections in a community hospital: association with type of dressing. J Infect Dis 1989;160:720–2.
112. Maki DG, Mermel LA, Kluger D, et al. The efficacy of a chlorhexidine-impregnated sponge (Biopatch TM) for the prevention of intravascular catheter-related infection: a prospective, randomized controlled multicenter study. 40th Interscience

Conference on Antimicrobial Agents and Chemotherapy. Toronto (ON), September 17–20, 2000.
113. Ho KM, Litton E. Use of chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. J Antimicrob Chemother 2006;58(2):281–7.
114. Simmons BP. CDC guidelines for the prevention and control of nosocomial infections. Guidelines for prevention of intravascular infections. Am J Infect Control 1983;11:183–99.
115. Jaffer Y, Selby NM, Taal MW, et al. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. Am J Kidney Dis 2008;51(2):233–41.
116. Schwartz C, Henrickson KJ, Roghmann K, et al. Prevention of bacteraemia attributed to luminal colonization of tunnelled central venous catheters with vancomycin-susceptible organisms. J Clin Oncol 1990;80:591–7.
117. Raad I, Buzaid A, Rhyne J, et al. Minocycline and ethylenediaminetetraacetate for the prevention of recurrent vascular catheter infections. Clin Infect Dis 1997; 25:149–51.
118. Safdar N, Maki DG. Use of vancomycin-containing lock or flush solutions for prevention of bloodstream infection associated with central venous access devices: a meta-analysis of prospective, randomized trials. Clin Infect Dis 2006;43(4):474–84.
119. Buxton AE, Highsmith AK, Garner JS. Contamination of intravenous fluid: effects of changing administration sets. Ann Intern Med 1979;90:764–8.
120. Gorbea HF, Snydman DR, Delaney A. Intravenous tubing with burettes can be safely changed at 48-hour intervals. JAMA 1984;251:2112–5.
121. Menyhay SZ, Maki DG. Disinfection of needleless catheter connectors and access ports with alcohol may not prevent microbial entry: the promise of a novel antiseptic-barrier cap. Infect Control Hosp Epidemiol 2006;27(1): 23–7.
122. Maragakis LL, Bradley KL, Song X, et al. Increased catheter-related bloodstream infection rates after the introduction of a new mechanical valve intravenous access port. Infect Control Hosp Epidemiol 2006;27(1):67–70.
123. Falagas ME, Fragoulis K, Bliziotis IA, et al. Rifampicin-impregnated central venous catheters: a meta-analysis of randomized controlled trials. J Antimicrob Chemother 2007;59(3):359–69.
124. Maki DG, Stolz SM, Wheeler S, et al. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomised, controlled trial. Ann Intern Med 1997;127:257–66.
125. Raad I, Darouiche RO, Hachem R, et al. The broad spectrum activity and efficacy of catheters coated with minocycline and rifampicin. J Infect Dis 1996; 173:418–24.
126. Raad I, Darouiche RO, Dupuis J. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infection: a randomised, double-blind trial. Ann Intern Med 1997;127: 267–74.
127. Darouiche RO, Raad I, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. N Engl J Med 1999;340:1–8.
128. Bong JJ, Kite P, Wilco MH, et al. Prevention of catheter related bloodstream infection by silver iontophoretic central venous catheters: a randomised controlled trial. J Clin Pathol 2003;56(10):731–5.

129. Moretti EW, Ofstead CL, Kristy RM, et al. Impact of central venous catheter type and methods on catheter-related colonization and bacteraemia. J Hosp Infect 2005;61(2):139–45.
130. Yucel N, Lefering R, Maegele M, et al. Reduced colonization and infection with miconazole-rifampicin modified central venous catheters: a randomized controlled clinical trial. J Antimicrob Chemother 2004;54(6):1109–15.
131. Brun-Buisson C, Doyon F, Sollet JP, et al. Prevention of intravascular catheter-related infection with newer chlorhexidine-silver sulfadiazine-coated catheters: a randomized controlled trial. Intensive Care Med 2004;30(5):837–43.
132. Rupp ME, Lisco SJ, Lipsett PA, et al. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections: a randomized, controlled trial. Ann Intern Med 2005;143(8): 570–80 [Erratum Ann Intern Med. 2005 Oct 18;143(8):I36; PMID: 16230719].
133. Thornton J, Todd NJ, Webster NR. Central venous line sepsis in the intensive care unit. A study comparing antibiotic coated catheters with plain catheters. Anaesthesia 1996;51(11):1018–20 [Erratum appears in Anaesthesia 1997 Feb;52(2):192].
134. Gil RT, Krause JA, Thill-Baharozian MC. Triple vs single lumen central venous catheters. Arch Intern Med 1989;149:1139–43.
135. Roy O, Billiau V, Beuscart C. Nosocomial infections associated with long-term radial artery cannulation. Intensive Care Med 1989;15:241–6.
136. Band JD, Maki DG. Infections caused by arterial catheters used for hemodynamic monitoring. Am J Med 1979;67:735–41.
137. Applefeld JJ, Caruthers TE, Reno DJ. Assessment of the sterility of long-term cardiac catheterization using thermodilution Swan-Ganz catheter. Chest 1978; 74:377–80.
138. Eyer S, Brummitt C, Crossley K. Catheter-related sepsis: prospective randomized study of three methods of long-term catheter maintenance. Crit Care Med 1990;18:1073–9.
139. Snyder RH, Ardrer FJ, Endy T. Catheter infection: comparison of two catheter maintenance techniques. Ann Surg 1988;208:651–3.
140. Mermel LA, Maki DG. Epidemic bloodstream infections from hemodynamic pressure monitoring: signs of the times. Infect Control Hosp Epidemiol 1989; 10(2):47–53.
141. Eggimann P, Harbarth S, Constantin MN, et al. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. Lancet 2000;355(9218):1864–8.
142. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 2006; 355(26):2725–32.