Iranian Journal of Clinical Infectious Diseases
2006;1(2):79-97

REVIEW ARTICLE

Catheter- related infections

Loannis Chatzinikolaou, Issam I Raad
The University of Texas, M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

Significance of Central Venous Catheters

The use of catheters has revolutionized the way cancer patients are treated and the advent of catheter technology is closely related to the improvement of the quality of cancer care and of the life of cancer patients.

The most common and life-threatening complication of catheters is infection. Catheter-related bloodstream infection (CRBSI) is the most common type of nosocomial infection, and it is associated with significant morbidity and mortality (1-6). Additionally, they contribute to the majority of nosocomial cases of septicemia caused by Staphylococcus epidermidis. Staphylococcus aureus, and Candida spp. (6-8). In cancer patients the risk of CRBSI is even higher than in other patients owing to a multitude of host factors (compromised skin due to radiation therapy or bioimmunotherapy such as interleukin- 2, increased use of intensive chemotherapeutic regimens leading to profound and prolonged neutropenia, and aggressive surgery).

Microbiology

Vascular catheters within a short time after insertion become uniformly colonized with biofilm, an architecturally complex structure that is rich in exopolysaccharids. Following their attachment on the catheter surface, microorganisms, such as S. aureus, coagulase-negative Staphylococci and candida parapsilosis, undergo phenotypic and enzymatic changes resulting in the production of exopolysaccharide, a major component of the biofilm (9-19). Recent studies on S. epidermidis have described a polysaccharide adhesion (PS/A) that is crucial to the pathogenesis of CRBSI (20). Similar work on Saccharomyces cerevisia and a genomic from C. albicans lead to the identification of the ALA gene, whose product play a crucial role in adherence to fibronectin, laminin, type IV collagen, and epithelial cells (21). Recently, the genetic control of biofilm production begun to be elucidated in S. epidermidis, S. aureus, and C. albicans (16,17,22,23). Synthesis of the capsular polysaccharide in Staphylococcus spp. is mediated by the ica operon. The key event in biofilm formation is a phenomenon called quorum sensing (24). Quorum sensing is an intermicrobial communication system vital for the regulation of a diverse array of processes, such as plasmid transfer, the activation of virulence factors, and biofilm formation. This communication is accomplished via chemical messengers like acyl-homoserine-lactone (25) and other peptides. Quorum sensing been reported in all the major pathogens involved in CRBSI (S. aureus,

Received: 20 February 2006 *Accepted*: 15 March 2006
Reprint or Correspondence: Issam I Raad, MD.
The University of Texas, MD Anderson Cancer Center, Houston, Texas, U.S.A.
E-mail: iraad@mdanderson.org

Staphylococcus epidermidis, and Candida spp.) (26-28). The microorganisms that are embedded in the biofilm layer become more resistant to different antibiotics (10,29,30), especially the glycopeptides (31), since they live in a microenvironment that acts as a barrier to circulating antibiotics.

The microorganisms most commonly implicated in CRBSI are predominantly skin organisms: S. aureus and coagulase-negative staphylococci (32). Staphylococcus aureus and coagulase-negative Staphylococci are considered to be introduced through the skin and contaminated hubs, whereas. C. albicans and C. parapsilosis are though to seed in the bloodstream from the gastrointestinal system (33), especially in cancer patients who receive cytotoxic immunosuppressive therapy. Other skin organisms such as Bacillus spp. and Corynebacterium spp. (especially the JK strains) have been reported frequently as the cause of CRBSI (34-36). Gram- negative microorganisms such as Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Acinetobacter spp. are frequent causes of CRBSI, since they can contaminate the hands of medical personnel, IV fluids, and other fomites of the hospital environment (37-39). Microorganisms emerging as CRBSI pathogens are Micrococcus spp. (40), Achromobacter spp. Rhodococcus spp. (41), Mycobacterium chelonei (42), Mycobacterium fortuitum (43), and fungi such as Rhodotorula spp. (44), Fusarium spp. (45-47), and Hansenula anomala (48,49).

Epidemiology

The incidence of CRBSI with long-term silicone catheters ranges from 1.4 to 1.9 episodes per 1,000 catheter-days (50-54). Tunneled catheters have been shown to predispose less to CRBSI than non-tunneled catheters (54-61). However, two studies, one randomized, failed to demonstrate any difference in the infection rates among tunneled and non-tunneled catheters (62,63). Additional data, from a center that maintains an infusion therapy team, showed that tunneled catheters have comparable rates of infectious complications when compared to non-tunneled catheters or PICC (64,65). Totally implantable intravascular devices (ports), being totally covered by the skin, have been associated with the lowest rate of infection when compared to other long- term catheters (66-76).

Multilumen catheters have been associated with a higher risk of infection than single lumen catheters (77-81), although in more than 50% of the triple lumen catheters only a single port is being used (82).

The catheter insertion site is another factor influencing the rate of CRBSI. In general, the internal jugular vein is related to higher risk for infections than the subclavian vein (83-88).

The role of neutropenia as an independent risk for CRBSI is controversial. In a study in cancer patients with long-term tunneled CVCs (53) nutropenia (< 500 neutrophils/ mm^3) was proven to be an independent risk factor for CRBSI, whereas a similar study conducted in M.D. Anderson Cancer Center (62), failed to show such an association. In the latter study (62) the only statistically significant risk factor for CRBSI was hematological malignancy, something that is supported by the study of Groeger et al. (66).

Clinical Manifestations

The clinical manifestations of CRBSI can be specific and nonspecific. Particularly in immunocompromised cancer patients, whose inability to launch an immune response to infectious stimuli obscures the signs and symptoms of any infectious process, the diagnosis of CRBSI can be a significant diagnostic challenge.

Nonspecific manifestations of CRCSI include fever, chills, and occasionally hypotension. Hypotension is often associated with CRBSIs caused by gram- negative bacilli or Canadida spp.

More specific signs, like inflammation and/ or purulence from the catheter site, palpable vessel

cord, and occasionally purulent secretions at the skin insertion site, indicate catheter exit site infection. A quantitative culture of the affected skin or of the excretions from the insertion site can help in distinguishing sterile inflammation from an exit site infection (89).

In tunneled catheters a greater than 2 cm inflammation extending proximally from the catheter exit site is an indication of tunnel infection. Pocket space abscess formation should be suspected in case of inflammation or cellulites overlying the catheter hub.

Although the majority of CRBSIs are uncomplicated, occasionally septic thrombophlebitis of deep-seated infections can occur (90). This is particularly true with virulent microorganisms like S. aureus, C. albicans, and Pseudomonas aeruginosa. Septic thrombosis is suspected in the presence of swelling above the site the thrombotic catheterized vein (swelling in the neck, shoulder or arm ipsilateral to the catheter insertion site). Imaging proof of the presence of thrombus (venography, or Doppler ultrasonography) in the vein with an indwelling catheter and positive blood cultures with clinical manifestations of septic or sepsis establish the diagnosis. Infrequently, deep-seated infections like endocarditis, osteomyelitis, septic pulmonary emboli, and retinitis (in case of candidemia) can complicate a CRBSI (90,91).

Diagnosis

Catheter-related bloodstream infection is to be suspected if a patient has; 1) clinical signs and symptoms of bloodstream infection (i.e., fever, chills, hypotension), 2) blood culture (s) positive for an organism often associated with CRBSIs, such as S. aureus, Bacillus spp., or C. parapsilosis, 3) the absence of any other source for the bloodstream infection except the catheter, and 4) local catheter infection, such as exit site inflammation, tunnel tract inflammation, a port pocket abscess formation associated with bloodstream infection (table 1).

Table 1. *Diagnosis of long- term catheter-related infections*

I. Criteria to suspect catheter- related infection
1. Clinical manifestations of infection (i.e., fever, chills)
2. Blood culture positive for likely organism (coagulase negative staphylococci, S. aureus, Bacillus spp., Corynevacterium spp., Candida spp.)
3. No apparent source of bacteremia other than the catheter
II. Criteria to confirm the diagnosis of catheter-related infection
1. Clinical evidence of catheter site and/ or tunnel infection/inflammation (purulent discharge, erythema, tenderness, warmth)
2. Response to antibiotic therapy within 48 hours after catheter removal; after 48 hours without response
3. 5:1 CFU* ratio of the same organism from CVC-blood culture compared to simultaneously collected peripheral blood culture
4. .>15 CFU (roll plate) or >1000 CFU (sonication) from CVC tip of the same organism as the one growing from peripheral blood culture
5. CVC collected blood culture is positive <2 hours prior to simultaneous peripheral blood culture

*CFU: colony forming units

Culture of the catheter was considered to be the gold standard for the diagnosis of catheter infection, especially in the absence of local catheter site infection. Usually the distal tip of the catheter (3-5 cm) is cultured. Culturing the subcutaneous catheter segment does not add to the diagnostic yield of the currently used methods of catheter (92). A number of different methods are available for culturing vascular catheters (93-95). The roll plate semiquantitative culture method is the most widely used (95). This involves aseptic removal of the catheter, rolling it across agar plate several times and counting the number of colonies of microorganisms after overnight incubation. The limiting factor of this method is that it cultures only the external surface of the catheters and does not retrieve organisms that are well embedded in the biofilm layer that covers the internal lumen of the

catheter. Consequently the roll-plate semi-quantitative technique is of limited usefulness in long-term catheters, in which the internal surface of the catheter is the predominant source of bloodstream infection (96).

Some laboratories use quantitative methods that are more labor intensive and more expensive. Such methods are 1) sonication (93), 2) vortexing a catheter segment (64), or 3) infusing the catheter luman with a known volume of broth (94). The cutoff point differs between the various methods. It is greater than 15 colony-forming units (CFUs) for the semi-quantitative (95) or at least 100 CFUs for the quantitative methods (97). Quantitative methods have been proven to be of higher sensitivity than semi-quantitative methods (97,98). The limitation of the semi-quantitative and quantitative catheter culture methods is that they require removal of the catheter (99), often resulting in wasteful removal of non-colonized catheters, increased medical costs, and patient inconvenience.

Catheter-related bloodstream infections can be diagnosed using simultaneous quantitative blood cultures without removing the catheter (100). This involves drawing one set of blood cultures through the catheter and one from a percutaneous site. If both blood cultures are positive for the same microorganism and the number of CFUs in the catheter-drawn specimen is at least 5 times (>5:1 ratio) higher than the number of CFUs from the peripheral venipuncture blood, this strongly suggests catheter-related bloodstream infection. The sensitivity of this method is higher in long-term catheter, where intraluminal transmission of microbes to the bloodstream is more common (96). The limitation of the method is that it is costly and labor intensive, so not many hospitals use quantitative culture in their microbiology laboratory.

A way to bypass the above-mentioned restriction and preserve the catheter in place is to use the differential time to positivity method. This requires simultaneous collection of blood through the catheter and through a peripheral venipuncture. If growth is detected in the catheter-drawn blood at least 2 hours earlier than in the simultaneously collected peripheral blood, this suggests CRBSI (101,102). This is a simple technique and can be practiced worldwide, since many laboratories have adopted the use of automated continuously monitored blood systems. The value of this approach has been challenged by a recent study involving a small number of patients in medical/ surgical ICUs (103). However, a large prospective clinical study at M.D. Anderson Cancer Center verified the value of this method in diagnosing CRBSI (104).

Catheter-related bloodstream infections can also be diagnosed using an endoluminal brush technique that involves brushing the lumen of the catheter and performing an acridine orange leukocyte cytospin (AOLC) test on blood drawn through colonized catheter (105). Although this approach has 95% specificity and 84% sensitivity, it has been associated with induction of transient bacteremia in 6% of the study patients. Staining catheter-drawn blood with AOLC was shown to be 96% specific and 92% sensitive when diagnosing CRBSI (106). Further larger studies are required to support such a finding.

Management

The optimal management of catheter-related infections requires taking many parameters into account, such as the condition of the host, the type of the infecting organism, and the site and severity of infection. Especially in cancer patients, a crucial question is added: Should we remove the catheter or not? The rationale for removing the catheter is to eliminate the nidus of infection that continuously sheds microorganisms in the bloodstream and possibly seeding other target organs. This action, however, may lead to increased morbidity and mortality, not to mention increased cost. Since the catheter is literally the lifeline of a cancer patient, removal of a long-term catheter usually

necessitates an insertion of a similar catheter at least at a different site, preferably after the infection is treated. In Hichman/Broviac or port-type catheters, this translates to another surgical procedure, which may be particularly hazardous in a patient who has thrombocytopenia or some other coagulopathy. An additional complication of insertion of new catheter is the possibility of pneumothorax.

Antibiotic lock therapy (ALT) is a new concept developed to reduce the need of catheter removal, when long-term catheters are infected. As stated earlier, the majority of these infections originate from microbes colonizing the internal lumen of the catheter. Recent studies have shown that many antibiotics are unable to kill microorganisms growing in biofilm, when used in therapeutic concentrations. Concentrations 100 to 1000 times greater are required in order to kill bacteria embedded in biofilm (sessile) than to kill planktonic (in solution) bacteria (107-110). ALT consists of installation and holding for hours or days pharmacological concentrations of antibiotics into the catheter lumen of the infected catheter. Antibiotic solutions that contain the desired antimicrobial agent are mixed with heparin or normal saline, in sufficient volume to fill the lumen (usually 2-5 ml) and are "locked" (installed) into the catheter lumen during periods when the catheter is not being used (e.g., during nighttime) (111,112). The volume of locked antibiotic is removed before infusion of the next dose of intravenous medication or fluids through the catheter. Although the duration of ALT varies, in the majority of clinical studies (112-119) it is most often done for 2 weeks. Antibiotics that are usually used in these solutions are vancomycin at a concentration of 1 to 5 mg/ml, gentamycin and amikacin (1 to 2 mg/ml), and ciprofloxacin (1 to 2 mg/ml) (120). Several trials of ALT on tunneled CRBSI, with or without concomitant intravenous antibiotic therapy, have reported response and catheter salvage rate in 82% of the episodes of CRBSI (120). Since the rationale behind ALT is to sterilize the lumen of the catheter, it should be used in cancer patients with long-term catheters, whose signs of catheter-related infection indicate an intraluminal source of infection.

Exit site infections can be cured by antibiotics locally and systemically, usually without removal of the catheter (54,121). If the infection persists for more than 48 hours, or if Pseudomonas spp. are cultured from the exit site, the removal of the catheter may be required for the eradication of the infection (54).

Tunnel infections and port pocket infections (abscesses) can sometimes be associated with significant local morbidity and even mortality. Catheter removal and 10 to 14 days of antibiotic therapy are required in order to cure the infection (120). In the treatment of Mycobacterium fortuitum and Mycobacterium chelonei infections, surgical excision of the infected tunnel may be required (122) in addition to CVC removal.

Managing catheter-related bloodstream infections means their categorization into three groups: low, moderate, and high risk. The risk stratification depends on the virulence of the organism involved and whether the CRBSI is complicated or uncomplicated. A CRBSI is characterized as complicated if: 1) the accompanying fever and/or positive blood culture(s) persist more than 48 hours despite appropriate antimicrobial therapy, 2) it is associated with hypotension, organ hypoperfusion, septic thrombosis, septic emboli, or deep-seated infections such as endocarditis (90,91) and 3) there is concurrent tunnel or port pocket infection.

A CRBSI is considered to be of low risk if it is uncomplicated and caused by a low-virulence microorganism, such as coagulase-negative staphylococci (123), the most frequent cause of bacteremia in neutropentc patients (124). These microorganisms are not usually associated with deep-seated infections, and their dramatic increase as pathogens parallels the use of long-term

catheters, accounting for the majority of CRBSI occurring annually (124-129). From the family of coagulase-negative staphylococci, S. epidermidis is most commonly isolated in bloodstream infections (124). In the case of a single positive blood culture for coagulase-negative staphylococci, the question arises if this represents a true bacteremia or just a catheter colonization or specimen contamination. Multiple positive blood cultures, isolation of the same microorganism from catheter and percutaneous blood cultures, as well as quantitative blood cultures collected through CVC, growing more than 100 CFU/ml, indicate true bloodstream infection (130). A low-risk CRBSI can be treated without removal of the long-term catheter (123,131), with systemic administration of appropriate antibiotics for usually 10 days (120). If the CVC is removed, appropriate systemic antibiotic therapy is recommended for 5 to 7 days (120). If the CVC is a high suspicion for intraluminal infection, patients should be treated with systemic antibiotics and antibiotic lock therapy for 10 to 14 days (120). Treatment failure manifesting as persistent fever, persistently positive blood cultures, or relapse of the infection after the antibiotic therapy has been completed is a clear indication for catheter removal (120). Vancomycin is the drug of choice in the case of methicillin resistant S. epidermidis. In patients who are either allergic to vancomycin or colonized with vancomycin-resistant enterococci, novel agents such as quinopristin-delfopristin or linezolid can be used (132-136). In the absence of methicillin-resistant microorganisms, pencillinase-resistant penicillins (nafcillin, oxacillin) or a first-generation cephalosporin may be used if the patient is not allergic to ß-lactam antibiotics. Staphylococcus haemolyticus is less frequently isolated from clinical specimens (125). Its resistance pattern to multiple antibiotics, including vancomycin (125), may impose catheter removal whenever S. haemolyticus is implicated in CRBSI.

A moderate-risk CRBSI is an uncomplicated CRBSI caused by moderate- to high-virulence microorganisms such as S. aureus and Candida spp.

These microorganisms can be associated with serious complications such as deep-seated infection or fatal septic shock (90,137). In such cases the CRBSI is considered to be a high-risk one, especially if it occurs in an immunocompromised patient (138,139).

Owing to its high virulence and high rates of complications, S. aureus CRBSI requires prompt antibiotic therapy and in most cases catheter removal (90,140). Serious complications such as deep-seated infections (endocarditis, septic thrombophlebitis, and osteomyelitis) or fatal septic shock occur at a frequency of 20 to 30% following CRBSI caused by S. aureus (140). In the case of uncomplicated CRBSI, a 10 to 14 day course of antibiotic therapy is sufficient to treat the infection after the catheter is removed (120,140,141). Removal of non-tunneled catheter that are infected with S. aureus has been associated with more rapid response to therapy and higher cure rate (90,138,141,142). If a new catheter has to be inserted, a different site has to be chosen. Tunneled CVCs or ports should definitely be removed if there is evidence of tunnel, pocket, or exit-site infection (120). However, in the case of patients with long-term tunneled catheters or implantable ports, in the absence of tunnel, pocket, or exit- site infection, owing to the difficulty and expenses involved with the removal of such catheters, they may be preserved, and antibiotic lock therapy may be considered in addition to 14 days of systemic antibiotic therapy (120). For patients who remain febrile and/or have positive blood cultures >3 days after appropriate antibiotic therapy has been instituted and/or the catheter has been removed, the possibility of a deep-seated infection, especially endocarditis, should be investigated (143,144). In this case, transesophageal echocardiography (TEE) may help in the decision to remove the catheter and to guide therapy (145). Provided that TEE is

available, the use of transthoracic echocardiography for excluding a diagnosis of catheter-related endocarditis is not recommended (120) because of its low sensitivity (146). For patients with TEE negative results, and from whom the catheter has been removed, a 14-day systemic antibiotic therapy is recommended (120). Staphylococcus aureus CRBSI complicated by a deep-seated infection, such as septic thrombosis, endocarditis, osteomyelitis, septic emboli abscesses, and arthritis, should be treated for 4 to 6 weeks (90,120). Determining the duration of therapy based on findings provided by TEE is a cost-effective alternative to the administration of therapy for 1 month to all patients with S. aureus bacteremia (145). The first choice for antibiotic therapy, of CRBSI caused by methicillin-susceptible S. aureus, should be intravenously administered ß-lactam antibiotics (penicillinase resistant penicillins, i. e., nafcillin or oxacillin (120). In case of penicillin allergy without anaphylaxis or angioedema, fist- or second-generation cephalosporins such as cefazolin or cefuroxime can be used (120). The addition of aminoglycosides (gentamycin) for the first 5 to 7 days of therapy may improve eradication of the S. aureus infection (6). For patients who are allergic to ß lactam antibiotics, and for those with methicillin- resistant S. aureus, vancomycin is the drug of choice (120). In case of S. aureus isolates with reduced susceptibility to vancomycin, the use of linezolid or quinopristin/dalfopristin is a therapeutic alternative.

All patients with candidemia should be treated (120). Candidemia is the third or fourth most common cause of nosocomial bloodstream infections. It occurs usually in seriously ill patients with multiple catheters and is associated with high attributable mortality rate, as high as 38% (147). Hemodynamically stable patients could be treated with fluconazole provided that it has not been recently used either prophylactically or therapeutically (148,149). A 14-day regimen of fluconazole (400 mg/day) has been proven as effective as and less toxin than amphotericin B (0.5mg/kg/day) given for the same length of time (148). Amphotericin B is recommended in patients with catheter-related candidemia who are hemodynamically unstable. Additionally, infections caused by fluconazole-resistant Candida spp. such as C. krusei should be treated with high-dose amphotericin B (1.0 mg/kg/day) (150-152). Treatment should be provided for 14 days after the last positive culture result and when signs and symptoms of infection have resolved (120). Since C.albicans and other candida species adhere avidly to materials used in vascular catheters (153), the removal of all central catheters from all patients with candidemia is considered to be standard practice and reinforced by recent consensus guidelines (120,150). In neutropenic cancer patients who have mucositis (acute leukemia, bone marrow transplantation), independent of the vascular catheter, the gastrointestinal system is an important source of C. albicans infection (154-157). Vascular catheters may, however, be the primary source of fungemia (158-160). Predictors of catheter-related candidemia include: quantitative blood cultures suggestive of CRBSI (>5:1 CFU ratio from blood collected through the catheter, compared to blood collected from a peripheral vein); indicative differential time to positivity (>2 hours for blood collected from a percutaneous venipuncture, compared with the one drawn through the CVC); isolation of C. parapsilosis from blood samples candidemia in a non-neutropenic patient who has a CVC in place and no other apparent source of bloodstream infection candidemia in a patient who is receiving TPN through the catheter; and persistent fungemia in a patient with a CVC, who is not responding to systemic antifungal therapy (120). Several studies have evaluated the impact of CVC removal on the outcome of candidemia (139,161-173). In the majority of these studies, catheter removal was associated with decreased duration of fungemia,

recurrence of infection, and improved survival (139,161-172). In a prospective observational study, in 145 cases of candidemia in patients with different underlying conditions, catheter retention was the only variable associated with increased risk of death on multivariate analysis (172). However, when the same scientific team looked into the risk factors for death in cancer patients with fungemia, the variables associated with an increased risk for death in multivariate analysis were older age, persistent neutropenia, and low performance status (165). In a large multicenter prospective observational study of 427 consecutive patients with candidemia, CVC retention was an independent risk factor for persistence of candidemia after 72 hours of antifungal therapy and was associated with higher mortality (161). In a review of the existing literature, with the notable absence of a prospective randomized study whose primary endpoint is the evaluation of the effect of vascular catheter removal in patients with candidemia, the consensus of catheter removal in all patients with candidemia was not substantiated (173). Given the limitations of the studies published today, and based on our experience, we believe that early therapy with a parenteral agent is important, since sustained fungemia is associated with poor outcome (139). An organism as adherent as Candida spp. to catheter can be more predictive of catheter-related candidemia (174), even in the setting of neutropenic cancer patients. Removal of the catheter is a common-sense therapeutic approach, especially if there is evidence implicating the catheter as the possible source of fungemia. Such predictors are: 1) no prior chemotherapy for the last month. Indicating the possible absence of gastrointestinal mucositis that enhances the risk of gut originating candidemia (156), 2) no prior steroid therapy, which has been associated with breakthrough candidemia (175,176), and 3) no other apparent source of the candidemia. Additionally, evidence of septic thrombophlebitis (through angiography) and invasion of the vascular wall (177) is another indication for catheter removal, since it may further increase the difficulty of eradicating the infection with medical therapy only. If the catheter is retained, the parenteral antifungal agents should be administered through all the lumens of the catheter, and the patient should be very closely monitored. If the patient is severely ill or has 72 hours of fungemia or persistent fever while on appropriate antifungal therapy, then removal of all CVCs is advised. Fungemia with C. parapsilosis is strongly associated with direct catheter infection (178) and would indicate catheter removal.

Malassezia furfur is a lipophic yeast that requires an exogenous lipid source to grow. Infection with this organism generally occurs in premature infants, but it has also been described in older children and adults, especially in critically ill patients hospitalized in ICU. Risk factors include the presence of a venous catheter and the administration of a lipid-enriched solution, like total parenteral nutrition. The basis of treatment is systemic administration of amphotericin B, discontinuation of the parenteral lipid supplements, and removal of the catheter, especially with non-tunneled catheter infections (120,179,180).

Although staphylococci and Candida spp. are the most frequent pathogens implicated in CRBSI, a number of other microorganisms have been reported as causing catheter-related bacteremia (181). The incidence of CRBSI due to gram-negative rods, including Pseudomonas spp., Acinetobacter spp., and Stenotrophomonas maltophilia is increasing, especially in cancer patients and immunocompromised hosts (182,183). They can cause infections associated with a high rate of failure when the catheter remains in place (37). There are no controlled trails evaluating the optimal antibiotics or the optimal duration of therapy for CRBSI caused by gram negatives. In addition, there is a similar lack of controlled trials encompassing the management of the catheter implicated in such infections. Catheter removal

within 48 to 72 hours of the onset of the CRBSI has been proven to prevent relapse of the infection (184). A course of 10 to 14 days of therapy with appropriate antibiotics is sufficient in the majority of cases (120). If the catheter cannot be removed and there is no evidence of tissue hypoperfusion, a combination of 14 days systemic therapy and antibiotic lock therapy is advised (120). In any case of persistence of and/or of positive blood cultures despite appropriate systemic antibiotic therapy, removal of the implicated catheter(s) should be seriously considered (120). Empirical antibiotic therapy, in cancer patients with gram-negative infections, should always cover P. aeruginosa (185).

Treatment of CRBSI caused by mycobacteria, notably M. fortuitum and M. chelonae, requires, in addition to systemic therapy with appropriate antibiotics, removal of the catheter (120,186).

Prevention

Most CVC infections are preventable. Several protective measures have been suggested to guard against long-term catheter CRBSI.

1- Precautions during catheter insertion

Careful hand washing and attention to aseptic technique during insertion is paramount for the prevention of infections in any type of catheter. For long-term central venous catheters, though, the level of precaution should be greater than just hand washing, wearing gloves, and using a small drape. The use of maximal sterile barriers (sterile gloves, mask, gown, cap, and a large drape) has been linked to a four-fold decrease in the rate of bacteremia related to pulmonary-artery catheters (187) and to a more than six-fold decrease in the rate of bacteremia related to CVCs (188).

2- Catheter-site care

The use of skin antiseptics at the insertion site is a very important measure for preventing CRBSI. The application of antimicrobial ointments to the catheter site at the time of catheter insertion or during routine dressing changes has been done to reduce the microbial burden at the skin insertion site. The use of a topical polyantibiotic regimen (polymyxin ß, neomycin, bacitracin) is associated with a significantly lower rate of CRBSI (189); but the overall protective effect of the topical antibiotic regimen is offset by a higher risk of catheter colonization and infection with Candida spp. (189,190). The use of mupirocin, a non-systemic anti-staphylococcal agent with proven efficacy in reducing staphylococcal spp. nasal carriage, has been proven to reduce five-fold the colonization of internal jugular catheter in cardiac surgery patients (191).

3- Tunneled catheters

Tunneling of short-term polyurethane internal jugular catheters reduces significantly the risk for CRBSI compared to non-tunneled catheters (192).

4-Intraluminal antibiotic locks

The intraluminal antibiotic lock consists of flushing and filling the lumen of the CVC with a combination of anticoagulant and antimicrobial agents. This flushing solution is then locked into the catheter for the time period that the catheter is not being used. This procedure is particularly useful for long-term catheter where hub contamination leads to lumen colonization and ultimately to bloodstream infection (193-195). Vancomycin in combination with heparin has been used as a daily flush solution for tunneled CVCs in five prospective randomized studies (196-200). Four of them have demonstrated the benefit of heparin-vancomycin lock solution in preventing CRBSI caused by vancomycin-susceptible microorganisms (196-199).

The major drawback of this lock solution is that the use of vancomycin, even in minute quantities, could lead to the emergence of vancomycin-resistant gram-positive organisms. A different antimicrobial/anticoagulant combination as a lock solution is the combination of minocycline with edetic-acid (EDTA). EDTA is a potent calcium and

iron chelator with anti-staphylococcal and anti-candidal activity, in addition to its anticoagulant properties (201,202).

5- Antimicrobial coating of catheters

Microorganisms can be prevented from colonizing catheter surfaces by coating the external and/or internal surfaces of the catheter with antimicrobial agents.

Catheters coated with chlorhexidine and silver sulfadiazine (CHSS) were two less likely to become colonized and were at least four times less likely to cause bacteremia than non-coated catheters (203). The catheters used in this study were coated only in the external surface (first-generation CHSS catheters) and thus do not provide the luminal protection that is needed in long-term catheters (>2 weeks) (204,205). Additionally, these catheters have a short antimicrobial durability (205). Several clinical studies reflect these weaknesses of the first-generation CHSS catheters, especially when used for longer than 2 weeks (204,206-208). A meta-analysis of 12 studies did show a benefit in using the first-generation CHSS catheters as short-term catheters (209), as these catheters are associated with a decrease in CRBSI (210). A second generation CHSS polyurethane catheter has been tested in an animal model (211). The second-generation CHSS catheter (CS2) has both the external and internal surfaces coated and may retain antimicrobial activity longer than the first-generation CHSS catheters (211). Clinical trials of this catheter are pending. Given that only short-term polyurethane CVCs are coated with CHSS, these catheters may not be useful in cancer patients requiring long-term catheterization.

Catheters impregnated with minocycline and rifampin (MR) have both their external and internal surfaces coated. The MR catheters have broad-spectrum activity against the most common microorganisms implicated in CRBSI, including C. albicans. In addition, these catheters demonstrated superior inhibitory activity against these microorganisms over the CHSS catheters (212,213). Both an animal model and large-multicenter prospective randomized clinical trial demonstrated that the MR catheters are safe and efficacious in preventing CRBSI (213,214). A prospective randomized multicenter trial comparing the MR and the CHSS catheters concluded that the MR catheters were 12 times less likely to be associated with CRBSI and three times less likely to be colonized than those coated only externally with CHSS (215). The MR catheters are coated both on the external surface and on their lumen, and the antimicrobial durability of these catheters extends to more than 4 weeks (216,217). No resistance thus far has been detected in the hundreds of MR catheters that have been studied. However the risk for development of such resistance still exists. Although an in vitro study suggests that the susceptibility of S. epidermidis to rifampin may decrease after repeated exposure of the organism to MR catheters (217), a surveillance study demonstrated that susceptibility patterns for minocycline and rifampin, among staphylococcal isolates from clinical service that uses the MR catheters, are comparable to those in patients not using antibiotic-coated catheters, in spite of a longer use of tetracyclines in the former group (218). The use of the MR catheters in the ICU of a cancer hospital resulted in a significant decrease in the frequency of nosocomial vancomycin- resistant enterococci- related bacteremia (219).

Antimicrobially coated catheters should be used when: 1) femoral or internal jugular vein insertion is desired (greater risk of infection than subclavian vein catheterization) (187), 2) catheterization expected to last longer than 4 days, 3) units with risk of CRBSI greater than 3% or 3.3/1000 catheter days, 4) patient with neutropenia or undergoing transplantation, 5) patients receiving TPN, 6) patients with burns, 7) patients undergoing hemodialysis, 8) patients with short bowel syndrome, 9) patients colonized with methicillin-

resistant S aurenus, 10) insertion or exchange in a patient with known infection or bacteremia.

REFERENCES

1. Maki DG. Infections due to infusion therapy. In: Bennett JV, Brachman PS, editors. Hospital infections. Boston: Little, Brown, 1995;p:849-98.

2. Pittet D, Tarara D, Eenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1995;271:1598-1601.

3. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infect Control Hosp Epidemiol 2000;21:510-5.

4. Soufir L, Timsit JF, Mahe C,et al. Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: a matched, risk-adjusted, cohort study. Infect Control Hosp Epidemiol 1999;20:396-401.

5. Javis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the Unites States. National Nosocomial Infections Surveillance System. Am J Med 1991;91:1855- 1910.

6. Raad II, Bodey GP. Infectious complications of indwelling vascular catheters. Clin Infect Dis 1992;15:197-208.

7. 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.

8. Fraser VJ, Jones M, Dunkel J, et al. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992;15:515-21.

9. Tojo M, Yamashita N, Goldmann DA, et al. Isolation and characterization of a capsular polysaccharide adhesion from Staphylococcus epidermidis. J Infect Dis 1988;157:713-22.

10. Sheth NK, Franson TR, Sohnle PG. Influence of bacterial adherence to intravascular catheters on in-vitro antibiotic susceptibility. Lancet 1985;2:1266-8.

11. Falcieri E, Vaudaux, P, Huggler E, et al. Role of bacterial exopolymers and host factors on adherence and phagocytosis of Staphylococcus aureus in foreign body infection. J Infect Dis 1987;155:524-31.

12. Costerton JW, Irvin RT, Cheng KJ. The bacterial glycocalyx in nature and disease. Annu Rev Microbial 1981;35:299-324.

13. Christensen GD, Simpson WA, Bisno AL, et al. Adherence of slime producing strains of Staphylococcus epidermidis to smooth surfaces. Infect Immun 1982;37:318-26.

14. Christensen GD, Simpson WA, Younger JJ, et al. Adherence of coagulase-negative staphylococci to plastic tissue culture plates: a quantitative model for the adherence of staphylococci to medical devices. J Clin Microbiol 1985;22:996-1006.

15. Montanaro L, Arciola CR, Borsetti, E, et al. A polymerase chain reaction (PCR) method for the identification of collagen adhesion gene (CNA) in Staphylococcus-induced prosthesis infections. New Microbiol 1998;21:359-63.

16. McKenney D, Pouliot KL, Wang Y, et al. Broadly protective vaccine for Staphylococcus aureus based on an in vitro-expressed antigen. Science 1999;284:1523-7.

17. Cramton SE, Gerko C, Schnell NF, et al. The intercellular adhesion (ica) hocus is present in Staphylococcus aureus and is required for biofilm formation. Infect Immun 1999;67:5427-33.

18. Arciola CR, Montanaro L, Baldassarri L, et al. Slime production by Staphylococci isolated from prosthesis-associated infections. New Microbiol 1999;22:337-41.

19. Ammendolia MG, Di Rosa R, Montanaro L, et al. Slime production and expression of the slime-associated antigen by staphylococcal clinical isolated. J Clin Microbiol 1999;37:3235-8.

20. McKenney D, Hubner J, Muller E, et al. The ica locus of Staphylococcus epidermidis encodes production of the capsular polysaccharide/adhesion. Infect Immun 1998;66:4711-20.

21. Gaur NK, Klotz SA. Expression, cloning, and characterization of a candida albicans gene, ALA1, that confers adherence properties upon Saccharmyces cerevisiae for extracellular matrix proteins. Infect Immun 1997;65:5289-94.

22. Gerke C, Kraft A, Sussmuth R, et al. Characterization of the N- acetyl glucosaminyl transferase activity involved in the biosynthesis of the Staphylococcus epidermidis polysaccharide intercellular adhesion. J Biol Chem 1998;273:18586- 93.

23. Lewis RE, Lo HJ, Raad II, et al. Lack of catheter infection by the efg1/ efg1 cph1 double- null mutant, a Candida albicans strain that is defective in filamentous growth. Antimicrob Agents Chemother 2002;46:1153-5.

24. Hardman AM, Stewart GS, Williams P. Quorum sensing and he cell-ceel communication dependent

regulation of gene expression in pathogenic and nonpathogenic bacteria. Antonie Van Leeuwengoek 1998;74:199-210.

25. Parsek MR, Val DL, Hanzelka BL, et al. Acyl homoserine-lactone quorum-sensing signal generation. Proc Natl Acad Sci USA 1999;96:4360-5.

26. Wesson CA, Liou LE, Todd KM, et al. Staphylococcus aureus Agr and Sar global regulators influence internalization and induction of apoptosis. Infect Immun 1998;66:5238-43.

27. Otto M, Sussmuth R, Jung G, et al. Structure of the phferomone peptide of the Staphylococcus epidermidis agr system. FEBS Lett 1998;424:89-94.

28. Hornby JM, Jensen EC, Lisec AD, et al. Quorum sensing in the dimorphic fungus Candida albicans is mediated by farnesol. Appl Environ Microbiol 2001;67:2982- 92.

29. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001;358:135-8.

30. Pfaller MA, Messer SA, Hollis RJ. Variations in DNA subtype, antifungal susceptibility, and slime production among clinical isolates of Candida parapsilosis. Diagn Microbiol Infect Dis 1995;21:9-14.

31. Farber BF, Kaplan MH, Clogston AG. Staphylococcus epidermidis extracted slime inhibits antimicrobial action of glycopeptide antibiotics. J Infect Dis 1990;16:37-40.

32. Maki DG. Infection caused by intravascular devices: pathogensis, strategies for prevention. London: Royal Society of Medicine Services, 1991.

33. Maki DG. Pathogenesis, prevention and management of infections due to intravascular devices used for infusion therapy. In: Bisno AL, Waldvogel FA, editors. Infections Associated wiht Indwelling Medical Devices. Washington: American Society for Microbiology, 1989:161-77.

34. Cotton DJ, Gill VJ, Marshall DJ, et al. Clinical features and therapeutic interventions in 17 cases of Bacillus bacteremia in an immunosuppressed patient population. J Clin Microbiol 1987;25:672-4.

35. Rieber W, Frantz N, Adelstein D, et al. Corynebacterium JK: a cause of nosocomial device-related infection. Rev Infect Dis 1986;8:42-9.

36. Saleh RA, Schorin MA. Bacillus spp. sepsis associated with Hickman catheters in patients with neoplastic disease. Pediatr Infect Dis J 1987;6:851-6.

37. Elting LS, Bodey GP. Septicemia due to Xanthomonas species and non-aeruginosa Pseudomons. Sepsis: increasing incidence of catheter-related infections. Medical (Baltimore) 1990;69:296-306.

38. Seifert H, Strate A, Pulverer G. Vascular catheter-related bloodstream infection due to Acinetobacter johnsonii (formerly Acinetobacter calcoaceticus var. Lwoffi): report of 13 cases. Clin Infect Dis 1993;17:632-6.

39. Ambler MW, Homans AC, O' Shea PA. An unusual central nervous system infection in a young immunocompromised host. Arch Pathol Lab Med 1986;110:497-501.

40. Hernandez JA, Martino R, Pericas R, et al. Achromobacter xylosoxidans bacteremia in patients with hematologic malignancies. Haematologica 1998; 83:284-5.

41. Chatzinilolaou I, Rolston K, Raad I. Central venous catheter-related Rhodococcus spp. Bacteremia in cancer patients. Fourth Decennial International Conference on Nosocomial and Healthcare- Associated Infections in Conjuction wiht the 10th Annual Meeting of SHEA, Atlanta, Georgia 2000.

42. Engler HD, Hass A, Hodes DS, et al. Mycobacterium chelonei infection of a Broviac catheter insertion site. Eur J Clin Microbiol Infect Dis 1989;8:521-3.

43. Swanson DS. Central venous catheter- related infections due to non-tuberculous Mycobacterium species. Pediatr Infect Dis J 1998;17:1163-4.

44. Chung JW, Kim BN, Kim YS. Central venous catheter-related Rhodotorula rubra. Fungemia. J Infect Chemother 2002;8:109-10.

45. Ammari LK, Puck JM, McGowan KL. Catheter-related Fudarium solani fungemia and pulmonary infection in a patient with leukemia in remission. Clin Infect Dis 1993;16:148-50.

46. Kiehn TE, Nelson PE, Bernard EM, et al. Catheter-associated fungemia caused by Fusarium chlamydosporum in a patient with lymphocytic lymphoma. J Clin Microbiol 1985;21:501-4.

47. Raad I, Hachem R. Treatment of central venous catheter- related fungemia due to Fusarium oxysporum. Clin Infect Dis 1995;20:709-11.

48. Klein AS, Tortora GT, Malowitz R, et al. Hansenula anomala: a new fungal pathogen. Two case reports and a review of the literature. Arch Intern Med 1988;148:1210-3.

49. Haron E, Anaissie E, Dumphy F, et al. Hansenula anomala fungemia. Rev Infect Dis 1988;10:1182-6.

50. Pearson ML. Guideline for prevention of intravascular device-related infections. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1996;17:438-73.

51. Clarke DE, Raffin TA. Infectious complications of indwelling long- term central venous catheters. Chest 1990; 97:966-72.

52. Decker MD, Edwards KM. Central venous catheter infections. Pediatr Clin North Am 1988;35:579-612.

53. Howell PB, Walters PE, Donowitz GR, et al. Risk factors for infection of adult patients with cancer who have tunneled central venous catheters. Cancer 1995;75:1367-75.

54. Press OW, Ramsey PG, Larson EB, et al. Hickman catheter infections in patients with malignancies. Medicine (Baltimore) 1984;63:189-200.

55. Abrahm JL, Mullen JL. A prospective study of prolonged central venous access in leukemia. JAMA 1982;248:2868-73.

56. Darbyshire PJ, Weightman NC, Speller DC. Problems associated with indwelling central venous catheters. Arch Dis Child 1985;60:129-34.

57. Pessa ME, Howard RJ. Complications of Hickman-Broviac catheters. Surg Gynecol Obstet 1985;161:257-60.

58. Schuman ES, Winters V, Gross GF, et al. Management of Hickman catheter sepsis. Am J Surg 1985;149:627-8.

59. Shapiro ED, Wald ER, Nelson KA, et al. Brovic catheter- related bacteremia in oncology patients. Am J Dis Child 1982;136:679-81.

60. Shulman RJ, Smith EO, Rahman S, et al. Single- vs. double-lumen central venous catheters in pediatric oncology patients. Am J Dis Child 1988;142:893-5.

61. Rannem T, Ladefoged K, Tvede M, et al. Catheter-related septicemia in patients receiving home parenteral nutrition. Scand J Gastroenterol 1986;21:455-60.

62. Raad I, Davis S, Becker M, et al. Low infection rate and long durability of non-tunneled silastic catheters. A safe and cost-effective alternative for long-term venous access. Arch Intern Med 1993;153:1791-6.

63. Andrivet P, Bacquer A, Ngoc CV, et al. Lack of clinical benefit from subcutaneous tunnel insertion of central venous catheters in immunocompromised patients. Clin Infect Dis 1994;18:199-206.

64. Raad I, Hanna H, McFadyen S, et al. Non-tunneled subclavian central venous catheters (NTSC) vs. tunneled central venous catheters. Interscience Conference on Antimicrobial Agents and Chemotheraphy (ICAAC). Chicago, IL, USA, 2001.

65. Hanna H, McFadyen S, Marts K, et al. Prospective evaluation of 1.67 million catheter-days peripherally inserted central catheters (PICCs) in cancer patients: long durability and low infection rate. Forty- first Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL, USA, 2001.

66. Groeger JS, Lucas AB, Thaler HT, et al. Infectious morbidity associated with long-term use of venous access devices in patients with cancer. Ann Intern Med 1993;119:1168-74.

67. Van der Pij1 H, Frissen PH. Experience with a totally implantable venous access device (Port- A- Cath) in patients with AIDS. AIDS 1992;6:709-13.

68. Khoury MD, Lioyd LR, Burrows J, et al. A totally implanted venous access system for the delivery of chemotherapy. Cancer 1985;65:1231-4.

69. Kappers-Klunne MC, Degener JE, Stijnen T, et al. Complication from long-term indwelling central venous catheters in hematologic patients with special reference to infection. Cancer 1989;64:1747-52.

70. Carde P, Cosset-Delaigue MF, Laplanceh A, et al. Classical external indwelling central venous catheter versus totally implanted venous access systems for chemotherapy administration: a randomized trial in 100 patients with solid tumors. Eur J Cancer Clin Oncol 1989;25:939-44.

71. Brincker H, Saeter G. Fifty-five patient years' experience with a totally implanted system for intravenous chemotherapy. Cancer 1986;57:1124-9.

72. Gives JW, Ensminger WD, Niederhuber JE, et al. A totally implanted infection port system for blood sampling and chemotherapy administration. JAMA 1984;251:2538-41.

73. Lokich JJ, Both A Jr, Benotti P, et al. Complications and management of implanted venous access catheters. J Clin Oncol 1985;3:710-17.

74. Pegues D, Axelrod P, McClarren C, et al. Comparison of infections in Hickman and implanted port catheters in adult solid tumor patients. J Surg Oncol 1992;49:156-62.

75. McDowell HP, Hart CA, Martin J. Implantable subcutaneous venous catheters. Arch Dis Child 1996;61:1037-8.

76. Wurzel CL, Halom K, Feldman JG, et al. Infection rates of Broviac Hickman catheters and implantable venous devices. Am J Dis Child 1988;142:536-40.

77. Clark-Cgristoff N, Watters VA, Sparks W, et al. Use of triple-lumen subclavian catheters for administration of total parenteral nutrition. J Parenter Enteral Nutr 1992;16:403-7.

78. Hilton E, Haslet TM, Borenstein MT, et al. Central catheter infections: single- versus triple- lumen catheters. Influence of guide wires on infection rates when used for replacement of catheters. Am J Med 1988;84:667-72.

79. McCarthy MC, Shives JK, Robison RJ, et al. Perspective evaluation of single and triple lumen catheters in total parenteral nutrition. J Parenter Enternal Nutr 1987;11:259-62.

80. 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.

81. Yeung C, May J, Hughes R. Infection rate for single lumen v. triple lumen subclavian catheters. Infect Control Hosp Epidemiol 1988;9:154-8.

82. Lee RB, Buckner M, Sharp KW. Do multi- lumen catheters increase central venous catheter sepsis compared to single- lumen catheters? J Trauma 1988;28:1472-5.

83. Farkas JC, Liu N, Bleriot JP, et al. Single- vs triple-lumen central catheter-related sepsis: a prospective randomized study in a critically ill population. Am J Med 1992;93:277-82.

84. Collignon PJ, Soni N, Pearson IY, et al. Is semiquantitative culture of central vein catheter tips useful in the diagnosis of catheter-associated bacteremia? J Clin Microbiol 1986;24:532-5.

85. Brun-Buisson C, Abrouk F, Legrand P, et al. Diagnosis of central venous catheter- related sepsis. Critical level of quantitative tip- cultures. Arch Intern Med 1987;147:873-7.

86. Prager RL, Silva J Jr. Colonization of central venous catheters. South Med J 1984;77:458-61.

87. Richet H, Hubert B, Nitemberg G, et al. Perspective 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.

88. Snydman DR, Gorbea HF, Pober BR, et al. Predictive value of surveillance skin cultures in total-parenteral- nutrition- related infection. Lancet 1982;21:1385-8.

89. Radd II, Baba M, Bodey GP. Diagnosis of catheter-related infections: the role of surveillance and targeted quantitative skin cultures. Clin Infect Dis 1995;20:593-7.

90. Raad I, Narro J, Khan A, et al. Serious complications of vascular catheter-related Staphylococcus aureus bacteremia in cancer patients. Eur J Clin Microbiol Infect Dis 1992;11:675-82.

91. Strinden WD, Helgerson RB, Maki DG. Candida septic thrombosis of the great central veins associated with central catheters. Clinical features and management. Ann Surg 1985;202:653-8.

92. Raad II, Hanna HA, Darouiche RO. Diagnosis of catheter- related bloodstream infections: is it necessary to culture the subcutaneous catheter segment? Eur J Clin Microbiol Infect Dis 2001;20:560-8.

93. Sheretz RJ, Raad II, Belani A, et al. Three-year experience with sonicated vascular catheter cultures in a clinical microbiology laboratory. J Clin Microbiol 1990;28:76-82.

94. Cleri DJ, Corrado ML, Seligman SJ. Quantitative culture of intravenous catheters and other intravascular inserts. J Infect Dis 1980;141:781-6.

95. Maki DG, Weise CE, Sarafin HW. A semi-quantitative culture method for identifying intravenous-catheter- related infection. N Engl J Med 1977;296:1305-9.

96. Raad I, Costerton W, Sabharwal U, et al. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. J Infect Dis 1993;168:400-7.

97. Sheretz RJ, Heard SO, Raad II. Diagnosis of triple-lumen catheter infection: comparison of roll plate, sonication, and flushing methodologies. J Clin Microbiol 1997;35:641-6.

98. Siegman-Igra Y, Anglim AM, Shapiro DE, et al. Diagnosis of vascular catheter- related bloodstream infection: a meta- analysis. J Clin Microbiol 1997;35:928-36.

99. Widmer AF, Nettleman M, Flint K, et al. The clinical impact of culturing central venous catheters. A prospective study. Arch Intern Med 1992;152:1299-1302.

100. Capdevila JA, Planes AM, Palomar M, et al. Value of differential quantitative blood cultures in the diagnosis of catheter-related sepsis. Eur J Clin Microbiol Infect Dis 1992;11:403-7.

101. Blot F, Scchmidt E, Nitenberg G, et al. Earlier positivity of central-venous- versus peripheral-blood cultures is highly predictive of catheter- related sepsis. J Clin Micribiol 1998;36:105-9.

102.Blot F, Nitenberg G, Chachaty E, et al. Diagnosis of catheter- related bacteremia: a prospective comparison of the time to positivity of hup- blood versus peripheral-blood cultures. Lancet 1999;354:1071-7.

103.Rijnders BJ, Verwaest C, Peetermans WE, et al. Difference in time to positivity of hub- blood versus nonhub- blood cultures is not useful for the diagnosis of catheter- related bloodstream infection in critically ill patients. Cirt Care Med 2001;29:1399-1403.

104.Raad I, Hanna H, Alakech B, et al. Diagnosis of catheter- related bloodstream infections (CRBSI): correlation of differential time to positivity (DTP) with quantitative blood cultures (QBC) for short- and long-term central venous catheters (CVC). Fortieth Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Toronto, Ontario, Canada, 2000.

105.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.

106.Kite P, Dobbins BM, Wilcox MH, et al. Rapid diagnosis of central venous- catheter- related bloodstream infection without catheter removal. Lancet 1999; 354:1504-7.

107.Pascual A, Ramirez de Arellano E, Martinez Martinez L, et al. Effect of polyurethane catheters and bacterial biofilm on the in- vitro activity of antimicrobials against Staphylococcus epidermidis. J Hosp Infect 1993;24:211-8.

108.Guggenbichler JP, Berchtold D, Allerberger F, et al. In vitro effect of antibiotics on catheters colonized by staphylococci. Eur J Clin Microbiol Infect Dis 1992;11:408-15.

109.Ramirez de Arellano E, Pascual A, Martinez L, et al. Activity of eight antibacterial agents on Staphylococcus epidermidis attached to Teflon catheters. J Med Microbiol 1994;40:43-7.

110.Gaillard JL, Merlino R, Pajot N, et al. Conventional and nonconventional modes of vancomycin administration to decontaminate the internal surface of catheters colonized with coagulase negative staphylococci. J Parenter Enteral Nutr 1990;14:593-7.

111.Cowan CE. Antibiotic lock technique. J Intraven Nurs 1990;15:283-7.

112.Messing B, Peitra- Cohen S, Debur A, et al. Antibiotic- lock technique: a new approach patients. J Parenter Enternal Nutr 1988;12:185-9.

113.Douard MC, Arlet G, Longuet P, et al. Diagnosis of venous access port-related infections. Clin Infect Dis 1999;29(5):1197-202.

114.Johnson DC, Johnson FL, Goldman S. Preliminary results treating persistent central venous catheter infections with the antibiotic lock technique in pediatric patients. Pediatr Infect Dis J 1994;13:930-1.

115.Williams N, Carlson GL, Scott NA, et al. Incidence and management of catheter- related sepsis in patients receiving home parenteral nutrition. Br J Surg 1994;81:392-4.

116.Benoit JL, Carandang G, Sitrin M, et al. Intraluminal antibiotic treatment of central venous catheter infections in patients receiving parenteral nutrition at home. Clin Infect Dis 1995;21:1286-8.

117.Krzywda EA, Andris DA, Edmistion CE Jr, et al. Treatment of Hickman catheter sepsis using antibiotic lock technique. Infect Control Hosp Epidemiol 1995;16:596-8.

118.Capdevila JA, Segarra A, Planes AM, et al. Successful treatment of haemodialysis catheter- related sepsis without catheter removal. Nephrol Dial Transplant 1993;8:231-4.

119.Rao JS, O' Meara A, Harvey T, et al. A new approach to the management of Broviac catheter infection. J Hosp Infect 1992;22:109-16.

120.Mermel LA, Farr BM, Sheretz RJ, et al. Guidelines for the management of intravascular catheter- related infections. Clin Infect Dis 2001;32:1249-72.

121.Raad I, Davis S, Khan A, et al. Impact of central venous catheter removal on the recurrence of catheter-relate coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol 1992;13:215-21.

122.Raad II, Vartivarian S, Khan A, et al. Catheter-related infections caused by the Mycobacterium fortuitum complex: 15 cases and review. Rev Infect Dis 1991;13:1120-5.

123.Fidalgo S, Vazquez F, Mendoza MC, et al. Bacteremia due to Staphylococcus epidermidis: microbiologic, epidemiologic, clinical, and prognostic features. Rev Infect Dis 1990; 12: 5820-528.

124.Rupp ME, Archer GL. Coagulase- negative staphylococci: pathogents associated with medical progress. Clin Infect Dis 1994;91:231-243; quiz 244-235.

125.Frogatt JW, Hohnston JL, Galetto DW, et al. Antimicrobial resistance in nosocomial isolated of Staphylococcus haemolyticus. Antimicrob Atgents Chemother 1989;33:460-6.

126.Christensen GD, Bisno AL, Parisi JT, et al. Nosocomial septicemia due to multiply antibiotic-resistants Staphylococcus epidermididis. Ann Intern Med 1982;96:1-10.

127.Winston DJ, Chapian M, Ho WG, et al. Coagulase-negative staphylococcal bacteremia in patients receiving immunosuppressive therapy. Arch Intern Med 1983;143:32-36.

128.Sattler FR, Foderato JB. Aber RC. Staphylococcus epidermidis bactermia associated with vascular catheter: an important cause of febrile morbidity in hospitalized patients. Infect Control 1984;5:279-83.

129.Sheretz RJ, Falk RJ, Huffman KA, et al. Infections associated with subclavian Uldall catheters. Arch Intern Med 1983;143:52-6.

130.Herwaldt LA, Geiss M, Kao C, et al. The positive predictive value of isolating coagulase- negative staphylococci from blood cultures. Clin Infect Dis 1996; 22:14-20.

131.Raad I, Davis S, Khan A, et al. Impact of central venous catheter- removal on the recurrence of catheter-related coagulase- negative staphylococcal bactermia. Infect Control Hosp Epidemiol 1992; 13: 215- 221.

132.Raad I, Bompart F, Hachem R. Prospective, randomized dose- ranging open phase II pilot study of quinupristin/dalfopristin versus vancomycin in the treatment of catheter- related staphylococcal bacteremia. Eur J Clin Microbiol Infect Dis 1999; 18: 199- 202.

133.Garcia R, Raad I. In vitro study of the potential role of quinupristin/ dalfopristin in the treatment of catheter-related staphyloccal infections. Eur J Clin Microbiol Infect Dis 1996; 15: 933- 936.

134.Jones RN, Johnson DM, Erwin ME. In vitro antimicrobial activities and spectra of U- 100592 and U-100766, two novel fluorinated oxazolidinones. Antimicrob Agents Chemother 1996;40:720-6.

135.Kaatz GW, Seo SM. In vitro activities of oxazolidinone compounds U 100592 and U 100766 against Staphylococcus aureus and Staphylococcus epidermidis. Antimicrob Agents Chemother 1996;40: 799- 801.

136.Moellering RC Jr. A novel antimicrobial agent joins the battle against resistant bacteria. Ann Intern Med 1999;130:155-7.

137.Rose HD. Venous catheter- associated candidemia. Am I Med Sci 1978;275:265-9.

138.Dugdale DC, Ramsey PG. Staphylococcus aureus bacteremia in patients with Hickman catheters. Am J Med 1990;89:137-41.

139.Lecciones JA, Lee JW, Navarro EE, et al. Vascular catheter- associated fungemia in patient with cancer: analysis of 155 episodes. Clin Infect Dis 1992;14:875-83.

140.Raad II, Sabagh MF. Optimal duration of therapy for catheter- related Staphylococcus aureus bacteremia: a study of 55 cases and review. Clin Infect Dis 1992;14: 75-7.

141.Malanoski GJ, Samore MH, Pefanis A, et al. Staphylococcus aureus catheter- associated bacteremia. Minimal effective therapy and unusual infectious complications associated with arterial sheath catheters. Arch Intern Med 1992;155:1161-6.

142.Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis 1998;27:478-86.

143.Libman H, Arbeit RD. Complications associated with Staphylococcus aureus bacteremia. Arch Intern Med 1984;144:541-5.

144.Maki DG, McCormick RD, Uman SJ, et al. Septic endarteritis due to intra- arterial catheters for cancer chemotherapy. I. Evaluation of an outbreak. II. Risk factors, clinical features and management. III. Guidelines for prevention. Cancer 1979;44:1228-240.

145.Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter- associated Staphylococcus aureus bacteremia. Ann Intern Med 1993;130:810-20.

146.Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with Staphylococcus aureus bacteremia: experience in 103 patients. I Am Coll Cardio 1997;30:1072-78.

147.Wey SB, Mori M, Pfaller MA, et al. Hospital-acquired candidemia. The attributable mortality and excess of stay. Arch Intern Med 1988;148:2642-5.

148.Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Insititute. N Engl J Med 1994;331:13255-30.

149.Anaissie EJ, Vartivarian SE, Abi-Said D, et al. Fluconazole versus amphotericin B in the treatment of hematogenous candidiasis: a matched cohort study. Am J Med 1996;101:170-6.

150.Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious

Diseases Society of America. Clin Infect Dis 2000;30: 662-78.

151.Beeouane YF, Hollis RJ, Pfall MA. Strain variation among and antifungal susceptibilities of isolates of Candida krusei. J Clin Microbiol 1996;34:1856-8.

152.Pfall MA, Barrey AL. In vitro susceptibilities of clinical yeast isolates to three antifungal agents determined by the microdilution method. Mycopathologia 1995;130:3-9.

153.Chandrea J, Kuhn DM, Mukherjee PK, et al. Biofilm formation by the fungal pathogen Candida albicans: development architecture, and drug resistance. Journal of Bacteriology 2001;183:5385-94.

154.Cole GT, Halawa AA, Anaissie EJ. The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. Clin Infect Dis 1996;22(Suppl 2): S73- S88.

155.Pittet D, Monod M, Suter PM, et al. Candida colonization and subsequent infections in critically ill surgical patients. Annals of Surgery 1994;220:751-8.

156.Reagan DR, Pfaller MA, Hollis RJ, et al. Characterization of the sequence of colinization and nosocomial candidemia using DNA fingerprinting and a DNA probe. Journal of Clinical Microbioligy 1990;28:2733-8.

157.Walsh TJ, Merz WG. Pathologic features in the human alimentary tract associated with invasiveness of Candida tropicalis. Am J Clin Pathol 1986;85:498-502.

158.McNeil MM, Lasker BA, Lott TJ, et al. Postsurgical Candida albicans infections associated with an extrinsically contaminated intravenous anesthetic agent. Journal of Clinical Microbiology 1999;37:1398-1403.

159.Solomon SL, Alexander H, Eley JW, et al. Nosocomial fungemia in neonates associated with intravascular pressure- monitoring device. Pediatr Infect Dis 1986;5:680-5.

160.Solomon SL, Khabbaz RF, Parker RH, et al. An outbreak of Candida parapsilosis bloodstream infections in patients receiving parenteral nutrition. J Infect Dis 1984;149:98-102.

161.Nguyen MH, Peacock JE Jr, Tanner DC, et al. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, perspective, observational study. Arch Intern Med 1995;155:2429-35.

162.Nucci M, Colombo AL, Silveria F, et al. Risk factors for death in patients with candidemia. Infect Control Hosp Epidemiol 1998;19:846-50.

163.Hung CC, Chen YC, Chang SC, et al. Nosocomial candidemia in a university hospital in Taiwan. J Jormos Med Assoc 1996;95:19-28.

164.Rex JH, Bennett JE, Sugar AM, et al. Intravascular catheter exchange and duration of candidemia. NIAID Mycoses Study Group and the Candidemia Study Group. Clin Infect Dis 1995;21:994-96.

165.Nucci M, Silveria MI, Spector N, et al. Risk factors for death among cancer patients with fungemia. Clin Infect Dis 1998;27: 107-11.

166.Karlowicz MG, Hashimoto LN, Kelley RE Jr, et al. should central venous catheters be removed as soon as candidemia is detected in neonates? Pediatrics 2000; 106: E63.

167.Anaissie EJ, Rex JH, Uzun O, et al. Predictors of adverse outcome in cancer patients with candidemia. Am J Med 1998;104:238-45.

168.Luzzati R, Amalfitano G, Lazzarini L, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. Eur J Clin Microbiol Infect 2000;19:602-7.

169.Girmenia C, Martino P, De Bernardis F, et al. Rising incidence of Candida parapsilosis fungemia in patients with hematologic malignancies: clinical aspects, predisposing factors. And differential pathogenicity of the causative strains. Clin Infect Dis 1996;23:506-14.

170.Stamos JK, Rowley AH. Candidemia in a pediatric population. Clin Infect Dis 1995;20:571-5.

171.Dato VM, Dajani AS. Candidemia in children with central venous catheters: role of catheter removal and amphoteridcin B therapy. Pediatr Infect Dis J 1990;9:309-14.

172.Eppes SC, Troutman JL, Gutman LT. Outcome of treatment of candidemia in children whose central catheters were removed or retained. Pediatr Infect Dis J 1989;8:99-104.

173.Nucci M, Anaissie E. Should vascular catheters be removed from all patients with candidemia? An evidence- based review. Clin Infect Dis 2002;34:591- 9.

174.Telenti A, Steckelberg JM, Stockman L, et al. Quantitative blood cultures in candidemia. Mayo Clin Proc 1991;66:1120-3.

175.Uzun O, Ascioglu, S, Anaissie EJ, et al. Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. Clin Infect Dis 2001;32:1713-7.

176.Nucci M, Colombo AL. Risk factors for breakthrough candidemia. Eur J Clin Microbiol Infect Dis 2002;21:209-11.

177.Anaissie E. Opportunistic mycoses in the immunocompromised host: experience at a cancer center and review. Clin Infect Dis 1992;14 (suppl 1): S43-S53.

178.Abi-Said D, Anaissie E, Uzun O, et al. The epidemiology of hematogenous candidiasis caused by different Candida species. Clin Infect Dis 1997;24:1122-8.

179.Barder GR, Brown AE, Kiehn TE, et al. Catheter-related Malassezia furfur fungemia in immunocompromised patients. Am J Med 1993;95:365-70.

180.Macron MJ, Powell DA. Human infections due to Malassezia spp. Microbiol Rev 1992;5:101-19.

181.Kiehn TE, Armstrong D. Changes in the spectrum of organisms causing causing bacteremia and fungemia in immunocompromised patients due to venous access devices. Eur J Clin Microbiol Infect Dis 1990;9:869- 72.

182.Seifert H. Catheter- related infectious due to gram-negative bacilli. In: Seifert H, Jansen B, Farr BM, eds. Catheter- related Infections. New York: Marcel Dekker, 1997: 111- 138.

183.Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennett JV, Barchman PS, eds. Hospital Infections. Philadelphia: Lippincott- Raven, 1998; 689-724.

184.Afif C, Hanna H, Alakech B, et al. Central venous catheter- related gram negative bacteremia (CRGNB): significance of catheter removal in preventing relapse. Thirty- ninth Annual Meeting of the Infectious Disease Society of America (IDSA) , San Francisco, California, USA, 2001.

185.Chatzinikolaou I, Abi-Said D, Bodey GP, et al. Recent experience with Pseudomonas aeruginosa bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch Intern Med 2000;160:501-9.

186.Voss A. Miscellaneous organisms. In: Seifert H, Jansen B, Farr BM, eds. Catheter- Related Infections. New York: Marcel Dekker, 1997: 157-182.

187.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.

188.Raad II, Hohn DC, Gilbreath BJ, Suleiman N, Hill LA, Bruso PA, Marts K. Mansfield PF, Bodey GP. Prevention of central venous catheter- related infections by susing maximal sterile barrier precautions during insertion. Infect Control Hosp Epidemiol 1994; 15: 231-238. See comments.

189.Maki DG, Band JD. A comparative study of polyantibiotic and iodophor ointments in prevention of vascular catheter- related infection. Am J Med 1981;70:739-44.

190.Zinner SH, Denny- Brown BC, Braun P, et al. Risk of infection with intravenous indwelling catheters: effect of application of antibiotic ointment. J Infect Dis 1969; 120:616-9.

191.Hill RL, Fisher AP, Ware RJ, et al. Mupirocin for the reduction of colonization of internal jugular cannulae- a randomized controlled trial. J Hosp Infect 1990; 15: 311- 321.

192.Timsit JF, Sebille V, Farkas JC, et al. Effect of subcuataneous tunneling on internal jugular catheter-related sepsis in critically ill patients: a prospective randomized multicenter study. JAMA 1996;276:1416-20.

193.Salzman MB, Isenberg HD, Shapiro JF, et al. A prospective study of the catheter hub as the portal of entry for microorganisms causing catheter- related sepsis in neonates. J Infect Dis 1993;167:487- 90.

194.Linares J, Sitges-Serra A, Garau J, et al. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hup and segments. J Clin Microbiol 1985;21:357- 60.

195.Sitges-Serra A, Puig P, Linares, J, et al. Hub colonization as the initial step in an outbreak of catheter-related sepsis due to coagulase negative staphylococci during parenteral nutrition. J Parenter Enternal Nutr 1984; 8:668-72.

196.Schwartz C, Henrickson KJ, Roghmann K, Powell K. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin- susceptible organisms. J Clin Oncol 1990; 8:1591-7.

197.Henrickson KJ, Axtell RA, Hoover SM, et al. Prevention of central venous catheter- related infectious and thrombotic events in immunocompromised children by the use of vancomycin/ ciprofloxacin/ heparin flush solution: a randomized, multicenter, double- blind trial. J Clin Oncol 2000;18:1269-78.

198.Carratala J, Niubo J, Fernandez-Sevilla- A, et al. Randomized, double-blind trial of an antibiotic- lock technique for prevention of gram- positive central venous catheter- related infection in neutropenic patients with cancer. Antimicrob Agents Chemother 1999;43:2200-4.

199.Maki D, Garland J, Alec C, et al. A randomized trial of a vancomycin- heparin lock solution (VHLS) for prevention of catheter- related bloodstream infection (CRBSI) in a NNICU. Twelfth Annual Scientific

Meeting of the Society for Healthcare Epidemiology of America (SHEA) , Salt Lake City, Uth, USA, Apr 6- 9, 2002.

200.Rackoff WR, Weiman M, Jakobowski D, et al. A randomized, controlled trial of the efficacy of a heparin and vancomycin solution in preventing central venous catheter infections in children. J Pediatr 1995;127:147-51.

201.Gil ML, Casanova M, Martinez JP. Changes in the cell wall glycoprotein composition of Candida albicans associated to the inhibition of germ tube formation by EDTA. Arch Microbiol 1994; 161: 489-94.

202.Root JL, McIntyre OR, Jacobs NJ, et al. Inhibitory effect of disodium EDTA upon the growth of Staphylococcus epidermidis in vitro: relation to infection prophylaxis of Hickman catheters. Antimicrob Agents Chemother 1988;32:1627-31.

203.Maki DG, Stolz SM, Wheeler S, et al. Prevention of central venous catheter- related bloodstream infection by use of an antiseptic- impregnated catheter. A randomized, controlled trial. Ann Intern Med 1997;37:145-56.

204.Logghe C, Van Ossel C, D' Hoore W, et al. Evaluation of chlorhexidine and silver- sulfadiazine impregnated central venous catheter for the prevention of bloodstream infection in leukaemic patients: a randomized controlled trial. J Hosp Infect 1997;37:145-56.

205.Bach A, Schmidt H, Bottiger B, et al. Retention of antibacterial activity and bacterial colonization of antiseptic- bonded central venous catheters. J Antimicrob Chemother 1996;37:315-22.

206.Ciresi DL, Alberecht RM, Volkers PA, et al. Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. Am Surg 1996;62:641-6.

207.Heard SO, Wagle M, Vijayakumar E, et al. Influence of triple-lumen central venous catheter coated with chlorhexidine and silver sulfadiazine on the incidence of catheter- related bacteremia. Arch Intern Med 1998;158:81-87.

208.Pemberton LB, Ross V, Cuddy P, et al. No difference in catheter sepsis between standard and antiseptic central venous catheters. A prospective randomized trial. Arch Surg 1996;131:986-9.

209.Veenstra DL, Saint S, Saha S, et al. Efficacy of antiseptic impregnated central venous catheter in preventing catheter- related bloodstream infection: a meta- analysis. JAMA 1996;281:261-7.

210.Mermel LA. Prevention of intravascular catheter-related infections. Ann Intern Med 2000;132:391-402.

211.Bassetti S, Hu J, D' Agostino RB Jr, et al. Prolonged antimicrobial activity of a catheter containing chlorhexidine- silver sulfadiazine extends protection against catheter infections in vivo. Antimicrob Agents Chemother 2001;45:1535-8.

212.Raad I, Darouiche R, Hachem R, et al. Antibiotics and prevention of microbial colonization of catheters. Antimicrob Agents Chemother 1995;39:2397-400.

213.Raad I, Darouche R, Hachem R, et al. The broad-spectrum activity and efficacy of catheters coated with minocycline and rifampin. J Infect Dis 1996;173:418-24.

214.Raad I, Darouche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter- related colonization and bloodstream infections. A randomized, double- blind trial. Texas Medical Center Catheter Study Group, Ann Intern Med 1997;127:267-74.

215.Darouiche RO, Raad II, Heard SO, et al. A comparison of two antimicrobial- impregnated central venous catheters. Catheter Study Group. N Engl J Med 1999;340:1-8.

216.Raad II, Darouiche RO, Hachem R, et al. Antimicrobial durability and rare ultrastructural colonization of indwelling central catheters coated with minocylcline and rifampin. Crit Care Med 1998;26:219-24.

217.Tambe SM, Sampath L, Modak SM. In vitro evaluation of the risk of developing bacterial resistance to antiseptics and antibiotics used in medical devices. J Antimicrob Chemother 2001;47:589-98.

218.Hanna H, Graviss L, Chaiban G, t al. Susceptibility patterns of Staphylococcus organisms in leukemia and bone marrow transplant (BMT) services after the use of minocycline / rifampin- impregnated central venous catheters (MR- CVCs) in a cancer hospital. Forty – Second Annual Conference of the Interscience Conference on Antimicribial Agents and Chemotherapy (ICAAC), San Diego, CA, USA, 2002.

219.Raad II, Hachett B, Hanna HA, et al. Use of antibiotic impregnated catheters associated with significant decrease in nosocomial bloodstream infections in critically ill cancer patients. Programs and Abstracts of the 4th Decennial Conference on Nososcomial and Healthcare- Associated Infections, in conjunction with the 10th Annual Meeting of the Society for Healthcare Epidemiology of America, Atlanta, Georgia, 2000.