Review-III

Recent Advances in Management of Intravascular Catheter Related Infections

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SUMMARY

Intravascular catheter-related infections are a major cause of morbidity and mortality. Coagulase-negative staphylo-cocci, Staphylo-coccus aureus, aerobic gram-negative bacilli and Candida albicans are the commonest microorganisms implicated in catheter-related infections. Management of catheter-related infections varies according to type of catheter involved. After appropriate cultures of blood and catheter samples are done, empirical intravenous antimicrobial therapy should be initiated on the basis of clinical picture, severity of the acute illness, underlying disease and the potential pathogens involved. When a catheter related infection is documented and a specific pathogen is identified, systemic antimicrobial therapy should be narrowed and consideration given for antibiotic lock therapy, if the central venous catheter or implantable device is not removed. In all cases of catheter-related bacteremia and fungemia, the catheter should be removed, if the infection is complicated with septic thrombosis, endocarditis and osteo-myelitis.

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INTRODUCTION

Intravascular devices are invaluable in modern day medical practice. They are used to administer IV fluids, medications, blood products, parenteral nutrition, and to monitor the hemodynamic status of critically ill patients. However the use of intravascular devices frequently is complicated by a variety of local or systemic infections. Complications including septic thrombophlebitis, endo-carditis, bloodstream infections and metastatic infections resulting from hematog-enous seeding from another body site by a colonized catheter. Approximately 5 million central venous catheters are inserted per year, and of these 3-8% lead to blood stream infection.[1] The attributable mortality of these blood stream infections is 12-25%.[2] A significant proportion of non –ICU patients have central venous catheters (e.g., patients on hematology –oncology wards), and many patients are discharged with central venous catheters in place. These patients are also at risk for serious catheter related infections.

Table 1. Micro-organisms commonly associated with peripheral vascular and CVC infection[5]

Gram-positive cocci	**Fungi**
Staphylococcus aureus	Candida species
Coagulase negative Staphylococcus	Aspergillus Species
Enterococcus faecalis/E.faecium	
Gram-negative bacilli	**Uncommon pathogens**
Escherichia coli and Klebsiella species	Corynebacterium species
Enterobacter species	Flavobacterium species
Acinetobacter species	Mycobacterium species
Stenotrophomonas maltophilla	
Pseudomonas aeruginosa	

Pathogenesis of Infection

The pathogenesis of catheter related infection is multifactorial and complex. The pathogenesis of nontunneled central venous catheter (CVC) is often related to extraluminal colonization of catheter, which originates from the skin and less commonly from the hematogenous seeding of the catheter tip, and/or intraluminal colonization of hub and lumen of the central venous catheter.[4] In comparison, for tunneled CVC or implantable devices contamination of catheter hub and intraluminal infection is the most common route of infection.[5]

Staphylococci, candida and some other microbes produce a slimy substance called biofilm. Biofilm is a filmy slimy layer, composed of multiple species of bacteria and their secreted polysaccharide matrix and components deposited from bodily fluids.[6, 7, 8] The first step in formation of catheter associated biofilm is deposition of a conditioning film on the surface of the device; rich in host derived proteins e.g. fibrin, fibronectin, thrombosdin and laminin, that act as adhesins.[9,10] Biofilms have major medical significance for two major reasons 1) biofilm decreases susceptibility to the antimicrobial agents 2) microbiology laboratory results based on planktonic organisms may not apply to sessile organisms embedded within a biofilm. Thus the organisms colonizing the catheter surface are attached to adhesins on the surfaces the catheter, are covered by a protective layer of biofilm, and are difficult to eradicate.

Definitions for Intravascular Catheter Related Infections.[11]

Catheter colonization: Growth of organisms from a catheter segment by either semiquantitative (≥15 colony forming units) or quantitative culture ($\geq 10^3$) from a proximal or distal catheter segment in the absence of accompanying clinical symptoms.

Exit site infection: Erythema, tenderness, induration or purulence within 2 cm of the skin at the exit site of the catheter.

Pocket infection: Erythema and necrosis of the skin over the reservoir of a totally implantable device (TID), or purulent exudates in the subcutaneous pocket containing the reservoir.

Tunnel Infection: Erythema, tenderness, induration in the tissue overlying catheter and > 2 cm from the exit site.

Catheter-related blood stream infection (CR-BSI): Isolation of the same organism from a semiquantitative or quantitative culture of a catheter segment and from the blood (preferably drawn from a peripheral vein) of a patient with accompanying clinical symptoms of blood-stream infection without any other apparent source of infection.

Infusate-related blood stream infection: Isolation of the same organism from infusate and from separate percutaneous blood cultures with no other identifiable source of infection.

Devices Used for Short-Term Vascular Access

- Peripheral venous catheter: It is the most commonly used intravascular device. Most peripheral venous catheters are currently made of polyurethane, Teflon or steel and are associated with a very low risk of bacteremia with less than 1 bacteremia per 500 devices.[12]
- Peripheral arterial catheters: are in wide spread use in critical care units for blood pressure monitoring and for obtaining arterial sample for blood gas determination. The incidence of bacteremia related to these devices is about 1%. The rate of significant colonization is about 5%.[13]
- Midline catheter: Peripheral catheter (size, 7.6-20 cm) is inserted via the antecubital fossa into the proximal basilica or cephalic veins, but it does not enter central veins; is associated with lower rates of phlebitis and infection than are CVCs.
- Nontunneled CVC: CVCs are estimated to account for over 90% of all catheter-related bacteremias. Prospective studies of noncuffed, short term single or multilumen catheters inserted into either the internal jugular or subclavian sites have found bacteremias rates of 1% to 5% and rates of significant colonization of the catheters (=15 CFU on semiquantitative culture) ranging between 5% and 30%[14] depending on the use and duration of the catheter plus the patient population. Peripherally inserted central catheters have the incidence of bacteremia to the tune of 1-2%.
- Pulmonary artery catheter: Incidence of bacteremia for these devices is 1%[15] as these are used for shorter duration.

Devices used for Long-Term Vascular Access[16]

- Tunneled CVC: Surgically implanted CVC with tunneled portion exiting the skin and a Dacron cuff just inside the exit site, the cuff inhibits migration of organisms into the catheter tract by stimulating growth of surrounding tissue. e.g. Hickman's catheter.
- Totally Implantable Device (TID): A subcutaneous reservoir with self sealing septum is tunneled beneath the skin and is accessed by a needle through intact skin.

Diagnosis:

Establishing a clinical diagnosis of catheter related infection (CRI) especially CR-BSI is often difficult. Diagnosis is typically based on clinical or laboratory criteria with each having significant diagnostic limitations.

Culture of the catheter is considered the "gold standard" for the diagnosis of catheter infection. Fever with or without chills has poor specificity. Inflammation or purulence around the intravascular device and blood stream infection has greater specificity but poor sensitivity.[5] Blood culture results that are positive for Staphylococcus aureus, coagulase negative Staphylococci or candida species, in absence of any other identifiable source of infection should increase the suspicion for CR-BSI.[11,17] Following are the various techniques used for diagnosis of CR-BSIs:

Rapid Diagnostic Techniques:

Gram staining of catheter segments may be helpful for the diagnosis of the local infections but is less sensitive than quantitative methods for the diagnosis of CR-BSI.

Cultures of Samples of IV Catheters:

Vortexing/sonicating or flushing the catheter lumen with broth catheter culture techniques are the most reliable diagnostic culture methodologies because they have greater specificity in the identification of catheter related infections compared with qualitative cultures, where a single contaminating microbe can result in a positive culture result.[18,19] The most widely used laboratory technique for the diagnosis of CRI is the semi quantitative method described by Maki et al,[20] in which the catheter segment is rolled across the surface of an agar plate and colony forming units (CFU) are counted after overnight incubation. To obtain the quantitative culture of a catheter, the catheter segment either flushed with, and then immersed in broth or placed in broth and vortexed/sonicated; quantitative cultures are done on the broth recovered from these procedures.

The limitation of the quantitative and semi quantitative catheter methods is that they require removal of the catheter to aid in the diagnosis of CR-BSIs.

Paired cultures of blood drawn percutaneously and through the IV catheter:

An alternative for diagnosis of CR-BSI in patients where catheter removal is undesirable because of limited vascular access. These techniques rely on quantitative culture of paired blood samples, one obtained through the central catheter and other from peripheral venipuncture site.

A colony count from the blood obtained from the catheter that is five to ten folds greater than the colony count from the blood obtained from a peripheral vein has been predictive of CR-BSI.

Endoluminal brush technique:

This technique involves brushing the lumen of the catheter and using an acridine orange leukocyte cytospin test on blood drawn through colonized catheter. Diagnosis of catheter related sepsis by the endoluminal brush method could be achieved without line sacrifice and was more sensitive (95%) and specific (84%) than extraluminal sampling of catheter tip by the Maki roll technique, 82% and 66% respectively.[21]

Differential time to positivity for CVC versus peripheral blood culture:

This new method, which correlates well with quantitative blood cultures, makes use of continuous blood culture monitoring for positivity (radiometric method) and compares the differential time to positivity (DTP) for qualitative cultures of blood samples drawn from the catheter and a peripheral vein.

Infusate related blood stream infection:

Samples are taken from both infusate and separate percutaneous blood culture for diagnosis of infusate related blood stream infection.

Management of catheter related infections:

Management of intravascular device associated infection depends on several variables, including; the type of infection, local or bacteremic; the organisms involved; the type of device, (peripheral or central catheters, totally implanted devices); and the severity of the illness of the patient.

Bacterial Coagulase negative Staphylococci

It is recommended to treat empirically with vancomycin and change to semisynthetic penicillin if the isolate is susceptible. Vancomycin is chosen most frequently because it is the only agent consistently acting against methicillin resistant staphylococcus aureus and coagulase negative staphylococci. A broad-spectrum penicillin such as piperacillin or piperacillin-tazobactum should be added for initial empiric therapy of catheter related sepsis while awaiting the results of cultures.

If the CVC is removed, appropriate systemic antibiotic therapy is recommended for 5-7 days.

Table 2. Risk Factors for Catheter Related Infection

Patient related factors:
Age (age ≤ 1 year or ≥ 60 yrs)
Loss of skin integrity
Presence of neutropenia (ANC ≤ 1000)
Chemotherapy and radiotherapy
Distant focus of infection
Severity of underlying disease
Device related risk factors:
Device material (steel, polyurethane, Teflon and silicone more resistant to adherence than polyethylene and polyvinyl chloride)
Frequency of surface irregularities
Thrombogenicity of catheter material
Antibiotic or antiseptic impregnated catheters
Microbe related risk factors:
Adherence properties (to fibronectin or to polymer),
Extracellular slime substance (antiphagocytic and may potentiate pathogenicity by acting as a barrier to antimicrobial penetration)
Host-microbe-device interaction risk factors:
Type of placement (cut down high risk than percutaneous)
Emergent placement high risk
Site of placement (jugular high risk than subclavian)
Duration of use
Aseptic technique at the time of insertion
Dense cutaneous colonization at entry site (high risk)
Dressing material (gauze dressing low risk than transparent dressing)
Skill of personnel
Antiseptic used for skin (chlorhexidine low risk than betadine)

If nontunneled CVC is retained and intraluminal infection is suspected, systemic antibiotics for 10-14 days and antibiotic lock therapy (ALT) are recommended.

A tunneled CVC or an ID can be retained, if necessary in patients with uncomplicated CR-BSI, patient should be treated with systemic antibiotics for 7 days and with ALT for 14 days.

Staphylococcus Aureus

β-lactam antibiotics should be the first choice for parenteral treatment of staphylococcus aureus bacteremia when the isolate is susceptible; for patients with serious allergy to β-lactams and for those with methicillin-resistant staphylococcus aureus, vancomycin is the drug of choice.[22]

Vancomycin should not be used when infection with β-lactam susceptible Staphylococcus aureus is diagnosed.

Nontunneled CVCs suspected to be the source of staphylococcus aureus bacteremia should be removed, and a new catheter should be reinserted at a different site.

Tunneled CVCs or IDs should be removed if there is evidence of tunnel, pocket or exit site infection.

Transesophageal echocardiography (TEE) should be done[16] for patients without contraindications, to identify those who have complicating endocarditis that require therapy for 4 to 6 weeks.

Sensitivity of transthoracic echocardiography is low and thus is not recommended for excluding the diagnosis of catheter related endocarditis if TEE can be done.

Patients who have negative TEE results and from whom the catheter is removed should be treated for 14 days with systemic antibiotic therapy.

Tunneled CVCs or IDs with uncomplicated intraluminal infection and staphylococcus aureus bacteremia should be removed, or in selected cases, retained and treated with appropriate systemic and antibiotic lock therapy for 14 days.

Gram–negative bacilli and miscellaneous pathogens

Patients with catheter related gram-negative bacteremia with nontunneled CVCs and no evidence of septic thrombosis or endocarditis should have the catheter removed and should receive appropriate antimicrobial therapy for 10-14 days.

Patients with tunneled CVCs or IDs that cannot be removed, who have suspected catheter related gram-negative bacteremia without associated organ dysfunction; hypoperfusion or hypotension can be treated for 14 days with systemic and antibiotic lock therapy.

For episodes of bacteremia due to Pseudomonas species other than Pseudomonas aeuruginosa, Burkholderia capacia, Stenotrophomonas species, Agrobacterium species and Acinetobacter baumanni, serious consideration should be given to catheter removal, especially if bacteremia continues despite appropriate antimicrobial therapy or if the patient becomes unstable.

Empirical antimicrobial therapy for systemic gram-negative, CR-BSI should include drugs that are active against Pseudomonas aeuruginosa especially in patients with neutropenia.

For patients with prolonged bacteremia after appropriate antimicrobial therapy and catheter removal, especially in the presence of underlying valvular heart disease, 4-6 weeks of antibiotic therapy should be undertaken.

Because the vast majority of CR-BSI infections caused by Bacillus and Corynebacterium species require catheter removal, catheter should be removed in these instances.

IV CRI due to mycobacteria such as mycobactrium fortuitum and mycobacterium chelonae require catheter removal.

Fungal:

Candida albicans and other fungi

All patients with candidemia should be treated; Amphotericin B is recommended for suspected catheter related candidemia in patients who are hemodynamically unstable or who have received prolonged fluconazole therapy, patients who are hemodynamically stable and who have not had recent therapy with fluconazole, or those who have a fluconazole susceptible organism, can be treated with fluconazole instead of Amphotericin-B.[23]

Duration of antifungal treatment for candidemia should be for 14 days after the last positive blood culture result and when signs and symptoms of infection have resolved. The recommended daily doses are 400 mg fluconazole and 0.5 to 0.6 mg/kg Amphotericin B.

Catheter related Candida krusei infection should be treated with Amphotericin B.

Tunneled CVCs or IDs should be removed in the presence of documented catheter related fungemia.

Salvage therapy for infected tunneled CVCs or IDs is not recommended for routine use because salvage rates with systemic fungal therapy and antibiotic lock therapy for candida species have been in the 30% range.[16].

Neutropenia Vs nonneutropenic:

The diagnosis of CR-BSI in cancer patients with febrile neutropenia remains difficult. Typical

clinical signs such as tenderness or purulent discharge at the insertion site, implicating the catheter as the source of infection, are frequently absent during neutropenia. Clinicians usually avoid removal of the catheter in patients with febrile neutropenia that would permit a semiquantitative or quantitative catheter tip culture because reinsertion of a new CVC carries a substantial bleeding risk. Consequently, existing data on the epidemiology of CR-BSI in cancer patients is restricted mainly to nonneutropenic patients with long term tunneled or nontunneled catheters or totally implanted ports that had been removed for diagnostic/or therapeutic purposes. Recently it has been demonstrated that differential time to positivity (DTP) technique is very useful for the in situ diagnosis of CR-BSI in neutropenic cancer patients.[24] This diagnostic method, which avoids unnecessary catheter removal, could be coupled with early targeted antimicrobial intervention such as antibiotic lock therapy and could result in improved patient care in this highly compromised patient population. It has been reported that in patients undergoing bone marrow transplant or intensive chemotherapy with difficult access who did not respond to antibiotics alone resolve their infection when the catheter was changed over a guidewire.[25]

Indications for removal of CVCs:

Nontunneled CVC

Catheter should be removed in patients with CR-BSIs, if the infection is complicated with septic thrombosis, endocarditis, osteomyelitis. Systemic antibiotic therapy is to be continued for 4-6 weeks.

In patients with uncomplicated CR-BSIs, catheter should be removed and systemic antibiotic therapy should be given for 5-7 days with coagulase negative staphylococcus infection and for 10-14 days in case of staphylococcus aureus and gram-negative bacilli.

In case of fungal infection, catheter should be removed and antifungal therapy is to be continued for 14 days.

Tunneled CVC/ID

Catheter should be removed if the infection is complicated with tunnel infection, port abscess, septic thrombosis, endocarditis and osteomyelitis.

Catheter can be retained with uncomplicated Staphylococcus aureus and gram-negative bacilli infection under cover of 10-14 days of systemic antimicrobial therapy with antibiotic lock therapy. These devices should be removed if there is clinical deterioration, persisting or relapsing bacteremia.

Salvage therapy for infected tunneled CVCs or IDs is not recommended for routine use in case of fungal infection because salvage rates with systemic fungal therapy and ALT for Candida species have been in the 30% range.

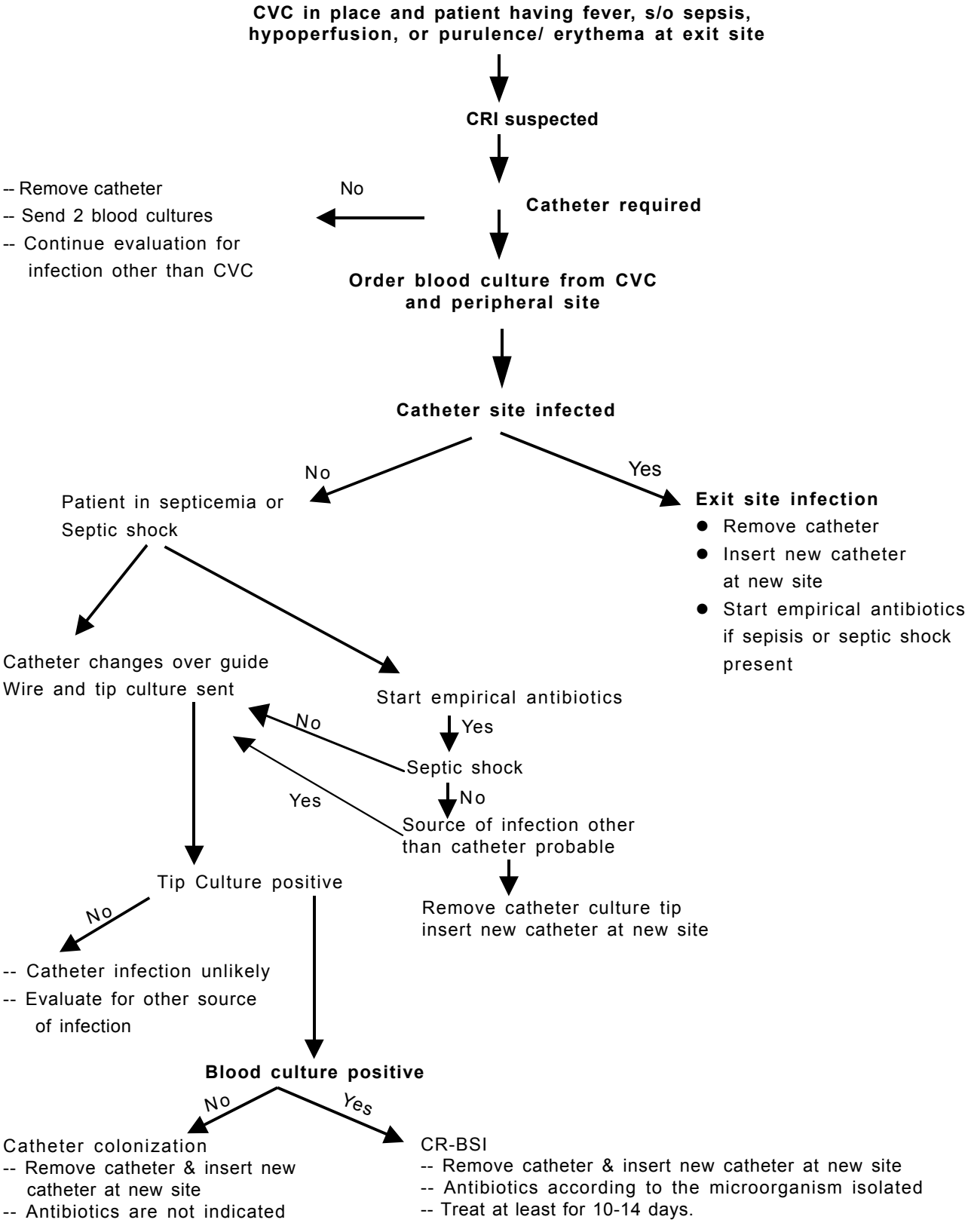
Antibiotic Lock Therapy (ALT)

Recent studies have demonstrated that antibiotic concentration must be 100-1000 times greater to kill sessile (biofilm) bacteria than to kill planktonic (in solution) bacteria.[26,27] A potential solution to this problem is based on this fact that majority of infection in tunneled catheters originate in catheter hub and spread to the catheter lumen. This fact prompted several investigators to try filling the catheter lumen with pharmacological concentrations of antibiotics and leaving them for hours or days, the so called “antibiotic lock therapy”.

Several open trials of antibiotic lock therapy of tunneled catheter related bacteremia, with or without concomitant parenteral therapy have reported response and catheter salvage without relapse in 82.6% cases.[28,29]

Antibiotic solutions that contain the desired antimicrobial agent in a concentration of 1-5 mg/ml are usually mixed with 50-100 units of heparin or (normal saline) in sufficient volume to fill the catheter lumen (usually 2-5 ml) and are installed or locked into the catheter lumen during periods when the catheter is not being used. For e.g. vancomycin has been used at a concentration of 1-5 mg/ml, gentamicin and amikacin 1-2 mg/ml and ciprofloxacin at 1-2 mg/ml. Two studies have suggested that two

Fig. : Management of Suspected Catheter Related Bloodstream Infection



weeks of antibiotic lock therapy alone may be as effective for intraluminal infection as a few days of systemic therapy followed by two weeks of antibiotic lock therapy.[30,31]

Antibiotic coated and antiseptic impregnated central catheters

Antibiotic coated and antiseptic impregnated central catheters appear to reduce catheter colonization and blood stream infection. Examples of antibiotics that have been used to coat catheters include cephazolin and minocycline-rifampin.[32] Although antibiotic coated catheters show promise clinically, the technical requirements for coating the catheter and concerns of antibiotic resistance may limit their wide spread use. Antiseptic impregnated catheters (chlorhexidine-silversulfadiazine) are less susceptible to antibiotic resistance as they do not require coating before insertion.[33]

Preventive strategies

Attention to detail in all aspects of placement and care of intravascular devices is necessary to minimize the risk of device related infection. This attention to detail is particularly important in critical care unit wherec the use of lines is intensive and patients, by nature of their underlying illness, are at high risk of device related infections. Although new scientific approaches to establishing improved techniques for catheter are necessary, and new technologic advances such as microbe resistant material will help to reduce the incidence of catheter related infections. There is no substitute for meticulous care and attention to detail in the care of the lines.

Conclusion

In conclusion, the management of CR-BSI, including early and accurate diagnosis, effective preventive strategies, and therapeutic clinical decisions related to catheter removal, must be guided by current understanding of pathogenesis of infections.

Considerable progress has been made in the field of intravascular catheter-associated infections. Recent studies have brought better understanding of the risk factors for intravascular catheter infections, have clarified preventive infection control strategies, and have introduced novel technologies such as antibiotic lock therapy and antimicrobial-impregnated vascular catheters.

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