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Diagnosis and Treatment of Catheter-related Blood Stream Infection in Neonates and Children

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Abstract This article provides an overview on the current management of catheter-related blood stream infection in neonates and children. New techniques, such as acridine orange stain and differential time to positivity, are useful in diagnosing catheter-related bacterial infections without catheter removal. Furthermore, they are feasible for those hospitals with limited manpower and budget in microbiology service. Management of catheter-related infections depends on bacterial, device (type of device, nature of the infusate) and host factors (age, birth weight, gestation and underlying diseases). Bacterial factor is probably the most important consideration for the decision of catheter removal, choice of antibiotics and duration of therapy. Catheter-salvaging strategies including antibiotic-lock therapy and urokinase had been suggested but only the former is still useful in patients with uncomplicated infections involving implantable devices or tunneled catheters. In addition, changing of a catheter over a guidewire because of concern about losing venous access is not recommended.

Key words Antibiotic-lock therapy; Catheter-related blood stream infection; Central venous catheters; Urokinase

Introduction

The use of central venous catheter (CVC) has increased greatly in hospitals nowadays. It is especially useful in neonates and infants with chronic medical conditions requiring frequent venous access. In our neonatal intensive care unit, umbilical venous catheters (UVC) and peripheral-inserted central venous catheters (PICC) are used for total parenteral nutrition (TPN) administration in premature babies. In our paediatric high dependent unit, PICC is mainly used for inotropes infusion. Hence from time to time we do encounter complications related to the central venous catheters, namely blood stream infections. The difficulties in making the diagnosis and treating catheter-related infections have resulted in the unnecessary removal of CVC causing venous access problem and inappropriate use of antibiotics, thereby further encouraging emergence of microbial resistance. Conversely, misdiagnosis of catheter-related blood stream infection (CR-BSI) would cause the development of other complications, ranging from thrombophlebitis to osteomyelitis and endocarditis. Moreover, controlled trials and even management guidelines only provide limited information regarding appropriate catheter-related infection management in neonates and children. This review article therefore will discuss the issues and controversies in the management of catheter-related blood stream infection.

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Definitions

Catheter-related infections can be divided into superficial infections (involving the exit site or tunnel tract) and septic infections (catheter-related blood stream infection). The

latter can occur with or without the evidence of superficial infection.

The definition of exit site infection is the presence of erythema, tenderness, induration and purulence within 2 cm of the skin exit of the catheter or within 2 cm from any edge of a subcutaneous port. The latter is also called a "pocket" infection. Tunnel tract infection is the development of erythema, tenderness, and induration along the subcutaneous tract of the Broviac or Hickman catheter at a distance greater than 2 cm from skin exit site with or without signs of exit site infection. This definition applies to subcutaneous port infection as well.[1,2] Table 1 summarises the definitions of catheter-related blood stream infection (CR-BSI) and colonisation.

Diagnosis of Infection

Contamination or True Bacteremia?

National Nosocomial Infections Surveillance System in United States showed that 88% blood stream infections among neonates in high-risk nurseries were associated with umbilical or central vascular catheters. Coagulase-negative staphylococci (CoNS) accounted for 51% of these infections.[3] In paediatric intensive care units, 37.8% blood stream infection was caused by CoNS (Table 2).[4] CoNS is a normal skin flora and its presence in blood culture is frequently encountered as contaminants. In general CoNS bacteremia should be suspected if more than 2 blood cultures are positive for CoNS within 24 hours, have

Table 1 Definitions of colonisation and catheter-related blood stream infection

Catheter colonisation:
Significant growth of a microorganism in a quantitative or semiquantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub.

Catheter related blood stream infection:
1. Bacteremia or fungemia in a patient who has an intravascular device and ≥1 positive result of culture of blood samples obtained from the peripheral vein.
2. Clinical manifestations of infection (e.g., fever, chills, and/or hypotension).
3. No apparent source for bloodstream infection (with the exception of the catheter).
4. One of the following should be present:
   - a positive result of semiquantitative (≥15 cfu per catheter segment) or quantitative (≥10^2 cfu per catheter segment) catheter culture, whereby the same organism (species and antibiogram) is isolated from a catheter segment and a peripheral blood sample
   - simultaneous quantitative cultures of blood samples with a ratio of ≥5 : 1 (CVC vs. peripheral)
   - differential time to positivity (i.e., a positive result of culture from a CVC is obtained at least 2 hours earlier than is a positive result of culture from peripheral blood)

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

Table 2 Blood stream infection rate and common pathogens isolated from blood stream infection in neonates and children

	Neonates		Paediatric patients	
	NNIS Study[3]	NICHD Study[32]	Decker, 1988#	NNIS Study[4]
% of blood stream infection in nosocomial infections	79-87	11.5-32.4		28
% of blood stream infection associated with umbilical venous catheters or central venous catheters	88	The rate of infection increased with an increasing duration of central venous catheters use		91
Major pathogens associated with blood stream infection (%)				
- Coagulase-negative staphylococcus	51	55	36	37.8
- Group B streptococcus	7.9	2	4	-
- Staphylococcus aureus	7.5	9	16	9.3
- Enterococcus	6.2	5	5	11.2
- Enterobacter spp.	2.9	4	4	6.2
- Candida spp.	6.9	7	5	5.5
- Pseudomonas spp.	-	2	4	4.9
- Klebsiella spp.	2.5	4	5	4.1
- Escherichia coli	4.3	4	5	2.9

#Decker MD and Edwards KM summarised blood isolates from 13 studies of Broviac catheter sepsis involving paediatric patients.[24]
NNIS: national nosocomial infections surveillance system; NICHD: national institute of child health and human development neonatal research network.

identical antibiogram, and genotypic analysis demonstrates that they are monoclonal, i.e. same strain.[5] On the contrary blood cultures with multiple CoNS strains are usually regarded as contaminants. However, this belief has been challenged recently. Van Eldere reported a case of polyclonal (4 clones with 2 different antibiograms) CoNS endocarditis in an 82-year-old man. Furthermore he also demonstrated genetic variation of CoNS in a rat model of catheter-associated infection.[6] Therefore the interpretation of blood cultures positive for CoNS becomes even more complicated. Hence, Elloitt et al used enzyme linked immunosorbent assay (ELISA) for the serological diagnosis of CVC-related sepsis in adult patients. It based on a novel short-chain lipoteichoic acid antigen isolated from CoNS which was used to determine the patient's IgG and IgM response to CVC sepsis caused by CoNS. There was a significant increase in the antibody levels, both IgG and IgM, to the short-chain lipoteichoic acid in patients with CVC-associated staphylococcal sepsis as compared to those with a CVC in situ but had no evidence of sepsis.[7]

From a practical point of view, antibiotics should be instituted when there is doubt about the significance of a commensal organism isolated from the blood of a neonate with signs and symptoms suggestive of infection or second blood culture positive for the same organism, taken within 24 hours of the first.[8]

Diagnostic Techniques (Table 3)

There are few available data regarding different diagnostic methods of intravascular catheter-related infection in children. Therefore the following diagnostic techniques are derived from studies on adult patients in surgical units or from those in oncology wards.

Diagnosis with catheter in situ. Qualitative paired blood cultures (i.e., only show what organism in the blood rather than the quantity of organism in the blood) drawn through the central catheter and peripheral vein for the diagnosis of CR-BSI is a common practice but the result is not reliable. DesJardin showed that the positive predictive value of qualitative blood cultures from catheter and peripheral blood was 63% and 73%, and the negative predictive value was 99% and 98% respectively. He concluded that culture of blood drawn through either the central catheter or peripheral vein showed excellent negative predictive value. Therefore, a positive result from a catheter needed clinical interpretation and might require confirmation.[9] Thus diagnosis of catheter-related blood stream infection without the removal of CVC relies on simultaneous quantitative blood culture from the CVC and peripheral vein. This is done by means of the direct inoculation of blood on to an agar plate (pour-plate method) to permit counting. Catheter infection is likely if the number of colonies isolated from the blood culture obtained via the catheter is 7 fold more than that in the blood obtained peripherally.[10] If the quantitative blood culture from the CVC yields at least 100 cfu/ml, it may be diagnostic even without the peripheral blood culture.[1] However this method is not routinely used in clinical practice because it is time-consuming, complex and expensive. The differential time to positivity (DTTP) for CVC versus peripheral blood culture may be helpful in

Table 3 Comparisons among different diagnostic methods of catheter-related blood stream infection without the removal of central venous catheter

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Quantitative paired blood cultures				
1. pour-plate method[10]	77.8	100	100	88.2
Qualitative paired blood cultures[9]				
1. from central venous catheter	89	95	63	99
2. from peripheral veins	78	97	73	98
Differential time to positivity (cut-off point 120 minutes)[11]	91	94	94	91
Acridine-orange leucocyte cytospin test (AOLC) + Gram stain[12]	96	92	91	97
Serological test on short-chain lipoteichoic acid antigen of CoNS[7]				
1. IgM titre (cut-off point 5,000)	52	85		
2. IgG titre (cut-off point 20,000)	75	90		

the above scenario. Diagnosis of catheter-related blood stream infection could be made on a patient who has a positive blood culture from the CVC 120 minutes earlier than that from the peripheral vein. Overall sensitivity is 91% and specificity is 94%.[11] Recently the acridine-orange leukocyte cytospin test (AOLC) of blood drawn through the catheter in combination with gram stain shows a sensitivity of 96% and a specificity of 92%. These two tests are rapid (30 min), inexpensive, and require only 100 microlitre of catheter blood and the use of light and ultraviolet microscopy.[12]

Diagnosis with catheter removal. Culture of organisms on the catheter tip is useful in confirming the infection that is catheter related. A 5 cm distal segment of the removed catheter is rolled across the culture media (roll-plate method) for semiquantitative culture.[13] However the culture results can be misleading because the external surface of the catheter may become contaminated with skin commensals on removal, hence the false positive rate is high. Quantitative catheter culture, in particular using the sonication method, can retrieve microorganisms from the external and internal surfaces of the CVC. Therefore it has higher diagnostic value than the roll-plate method. A count of ≥15 colonies by roll-plate method or ≥100 colonies by means of quantitative culture is indicative of significant colonisation of the catheter, whereas fewer colonies are consistent with contamination during removal.

Treatment

Remove the Line, Change the Line or Keep the Line? (Table 4)

The traditional approach to the infected line is to remove it immediately and give appropriate antibiotics for patients who have clinical sepsis. This is an appropriate approach for patients who have short term, easily resited lines, but for patients who have precious lines that are critical to their further care, a trial of treatment with the line in situ is usually warranted. This applies to children with tunneled catheters and implantable devices, and infants who would pose technical difficulties in reinserting the lines.

Catheter tip colonisation. Catheter colonisation is much more frequent than bacteremia and usually precedes seeding of the blood stream. A biofilm forms on the inner lumen of the catheter and the embedded bacteria or fungi are protected from the action of antibiotics. This occurs in the catheter with long-term use. The presence of the catheter tip in the blood vessel can damage the intima of the vessel and often results in thrombosis. Infection of the thrombus leads to septic thrombophlebitis. This occurs on the external surface of the catheter and is commonly seen in short-term use catheters. In these 2 situations, the embedded microorganisms can be dislodged resulting in haematogenous spread.[14,15]

If the patient has severe systemic sepsis, erythema and

Table 4 Factors to be considered when treating an infected line in situ[33]

Factor	Outcome		
	Likely success	**Unlikely success**	**Risk of distant infections**
Organisms[20, 21, 23-26]	CoNS Diphtheroids Enterococcus	Fungi Pseudomonas Multi-resistant organisms (MRSA) Stenotrophomonas maltophilia Bacillus species Atypical mycobacteria Presence of multi organisms	Candida species Staphylococcus aureus
Site of infection[25]	Local exit site	Tunnel infection Pocket infection Frank pus from exit site	
Line factors	Line functioning well	Impaired flow	
Host factors[1]	No evidence of systemic sepsis	Severe systemic sepsis	Abnormal heart valves

purulence at the catheter exit site and no source of fever identified, the catheter should be removed and cultured.[1] In case a catheter is important for the patient's further care, whether to replace it with another catheter at a different insertion site or use a guide wire to change the catheter at the same site remains debatable. In the sheep model, Olson showed that replacement of a biofilm-colonised central venous catheter over a guide wire was associated with rapid colonisation of the new catheter within 48 hours, and all eighteen sheep had embolic pneumonia and vegetative endocarditis at autopsy.[16] A systemic review of 12 randomised controlled trials by Cook concluded that the guide wire exchange technique on critically ill adult patients might be associated with a greater risk of catheter-related infection but fewer mechanical complications than new-site replacement.[17] Hence recent guideline suggests that "change over a guide wire" technique for malfunctioning catheter is safe with fewer mechanical complications and less discomfort but it is not recommended in the presence of bacteremia.[18] Another problem that physicians face from time to time is PICC cannot always be advanced to a central location for various reasons such as venospasm, venous tortuosity and venous valves. Racadio et al showed that non-centrally placed catheter tips were associated with more leakage, occlusion and phlebitis than centrally placed catheter tips, but there was no significant difference in the infection rate between these 2 groups.[19]

There is no data in the literature regarding the use of antibiotics for patients whose catheter tip culture reveals significant growth but without culture proven bacteremia or fungemia. Nevertheless, a short course (5-7 days) of antibiotics may be indicated if the patient has valvular heart diseases, neutropenia or catheter tip cultures reveal significant growth of Staphylococcus aureus or Candida albicans.[1]

Routine or scheduled replacement of intravascular catheter as a measure to prevent infection without a clinical indication is not necessary. It does not reduce the rate of catheter colonisation or the rate of CR-BSI.[2,18]

Catheter-related blood stream infection. Benjamin et al believed that the species of bacterium was important to the decision of catheter removal. He suggested that for CR-BSI in neonates, removal of the catheter should be considered to avoid complicated bacteremia if the infection involving *S. aureus* and gram negative rods. Catheter sterilisation, i.e. appropriate antibiotics given through the central catheter, could be attempted in neonates who were infected with Enterococcus or CoNS. Follow-up blood cultures should be obtained on day 3 and day 4. If both follow-up blood cultures were still positive for these organisms, then the catheter should be removed.[20]

A more recent study by Karlowicz showed that CoNS bacteremia lasted 3 to 4 days in neonates was successfully treated with vancomycin without removal of CVCs in 46% of cases but the number needed to harm was 3.3, i.e. for every 3 infants with CoNS bacteremia from whom CVCs were not removed within 3 days of the first positive blood culture, 1 infant had prolonged bacteremia. CVCs should therefore be removed in cases of CoNS bacteremia lasting > 4 days. There were no cases of osteomyelitis, endocarditis or serious focal infections in association with CoNS bacteremia.[21] Surprisingly, Nazemi et al found that Enterobacteriaceae (ENTB) bacteremia could also be treated successfully with gentamicin or tobramycin without removing CVCs in 45% of cases. However the lines should be removed immediately if ENTB bacteremia cases were associated with severe thrombocytopenia, or subsequent blood cultures (24 to 48 hours after initial blood culture) showed persistent bacteremia despite appropriate antibiotic treatment.[22]

For catheter-related candidemia, the mortality, morbidity and the persistence of candidemia are associated with attempts to maintain the catheters. Immediate removal of the catheters and the initiation of antifungal treatment are warranted.[23] Other organisms that may be difficult to eradicate include bacillus species, methicillin-resistant staphylococcus aureus, atypical mycobacteria and malassezia species.[24-26]

Exit-site infection can be successfully treated with local care, i.e. frequent change of dressing, even without the addition of antibiotic. However if it is caused by Pseudomonas aeruginosa, which is more difficult to eradicate than other organisms, the catheter may need to be removed. For tunnel-tract infection and pocket infection, they are difficult to treat successfully if the line is not removed. Only one third of the tunnel tract infection and one half of the pocket infection can be cured without removing the line.[25]

Apart from considering the specific pathogen involved, the catheter should be removed if one or more of the following conditions are met: 1) the patient's condition deteriorates; 2) the presence of complications, such as endocarditis, septic thrombosis, tunnel infection, or metastatic seeding;[1] 3) relapse of infection after antibiotics have been discontinued; 4) persistent positive blood cultures; or 5) the catheter is not necessary.[26]

Antibiotics

In immunocompetent patients, the initial empirical therapy should include antibiotics against staphylococci (oxacillin, nafcillin, or vancomycin, depending on the prevalence of methicillin-resistant staphalococci) plus an agent active against hospital-acquired gram negative rod species (usually 3rd generation cephalosporin, such as cefotaxime, ceftriaxone, or ceftazidime, or an aminoglycoside, such as gentamicin or tobramycin).

For immunocompromised patients, some experts recommend both a cephalosporin and an aminoglycoside for better gram negative bacilli coverage. Vancomycin should also be included in the initial empiric regimen.[27] Peripheral and catheter blood cultures should be repeated 24-48 hours after the initiation of therapy. Antibiotic therapy should be adjusted on the identification and susceptibility testing of the causative pathogen(s).

In general, if catheter-related sepsis is diagnosed, antibiotics should be administered through the catheter for 10-14 days. However the duration of treatment depends on specific pathogens, associated complications, whether the catheter is removed and whether the catheter is tunneled.

For coagulase negative staphylococci CR-BSI, infection may resolve without antibiotic if the catheter is removed. Nevertheless many experts suggest that antibiotic is still necessary. If the CVC is removed, appropriate systemic antibiotic therapy is recommended for 5-7 days. If the non-tunneled catheter is retained, duration of the systemic antibiotic treatment should be extended to 10-14 days. The duration of treatment could be shortened to 7 days if the catheter is tunneled.

For Staphylococus aureus CR-BSI, repeated positive blood culture results and/or unchanged clinical status for 3 days after catheter removal usually indicate complications of CR-BSI such as septic thrombosis, endocarditis or metastatic foci of infection. Septic thrombosis and endocarditis should be treated with antibiotics for 4-6 weeks and 6-8 weeks for osteomyelitis.

The duration of antibiotics treating gram negative bacilli CR-BSI is usually 14 days. Catheter removal should be considered if the bacteremia is due to Pseudomonas species other than Pseudomonas aeruginosa, Burkholderia cepacia, Stenotrophomonas species, Agrobacterium species and Acinetobacter baumannii.

The duration of antifungal treatment for candidemia should be 14 days after the last positive blood culture result.

Antibiotic Lock Therapy

Antibiotic lock technique (ALT) is a method of sterilising intravascular catheters by using high concentration of antibiotics infused into the portion of the catheter between the hub and the vessel entry. The solution is allowed to dwell within the catheter segment for several hours. It can be used as an adjuvant therapy with parenteral systemic antibiotics for the treatment of uncomplicated tunneled catheter-related or implantable device-related blood stream infections. This technique can also salvage non-tunneled CVC in CoNS catheter infection.[1]

Johnson et al successfully treated 10 of 12 episodes of persistent CVC infections by antibiotic lock technique in 11 children. He injected 2 mg/ml antibiotic solution of 3 to 4 ml (vancomycin, mezlocillin, amphotericin B, amikacin or combination of ampicillin and gentamicin) into the catheter lumen. The catheters were capped so as to dwell the antibiotic in the line every 12 hours per day for 10 to 14 days. He reported that this type of therapy was successful after the failure of conventional intravenous antibiotic therapy.[28] Spafford suggested a TPN solution containing 25 μg of vancomycin per ml could effectively reduce catheter-related sepsis in the neonatal intensive care unit and offer other potential benefits such as the need for fewer catheters and earlier weight gain. The colonisation of catheters by coagulase-negative staphylococci was reduced from 40% to 22% in the vancomycin group; catheter-related sepsis was reduced from 15% to no cases. Fewer infants required CVC reinsertion in the vancomycin-treated group, who also regained birth weight earlier (13.4 vs 17.1 days). Adverse effects of vancomycin infusion were not observed.[29]

In general, ALT solutions that contain antimicrobial agent in a concentration of 1-5 mg/ml (e.g. 1-5 mg/ml for vancomycin, 1-2 mg/ml for gentamicin and amikacin) are usually mixed with 50-100 U of heparin or normal saline in sufficient volume to fill the catheter lumen (usually 2-5 ml) and "locked" into the lumen during the periods when the catheter is not being used. The duration of ALT most often is 2 weeks.[1]

Antibiotic-lock therapy is useful in patients receiving total parenteral nutrition. It offers several advantages: 1) minimal side effects of the systemic antibiotics; 2) salvage of the CVCs; and 3) the therapy can be administrated in an outpatient setting thereby reducing hospital costs. But it also has drawbacks: 1) for patients who require multiple infusions through the CVCs other than nutrition, the antibiotic lock therapy may reduce the time

available for other infusates; 2) fungal infections have been suppressed but not eliminated with this technique; 3) it is inadequate for extraluminal infection; and 4) the high concentration of antibiotic installation may cause the emergence of antibiotic-resistant organisms.

Urokinase

The use of urokinase as an adjuvant therapy to antibiotics has been proposed.

Urokinase may dissolve the fibrin sheath around the catheter that harbours microorganisms, making them susceptible to antibiotics and host defenses. However 2 randomised double-blind trials failed to demonstrate improved infection clearance with urokinase in the treatment of Hickman catheter sepsis.[30,31] The trial by LaQuaglia was stopped early because of fever, chills and hypotension in several patients in spite of a slow-push urokinase or placebo infusion.

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