

Infection

Diagnosis, prevention, and management of catheter related bloodstream infection during long term parenteral nutrition

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Central venous catheter related bloodstream infection is an important cause of morbidity and mortality

Central venous catheters (CVC) are widely used in children receiving long term parenteral nutrition (PN). They provide secure venous access and allow safe administration of hypertonic solutions. However, catheter related bloodstream infection (CR-BSI) is a serious and potentially life threatening complication.^{1,2} Evidence based guidelines for the prevention of CR-BSI have recently been published by the Department of Health.³ These focus on hospital acquired infection in patients of 4 years and above, and do not address the important issues of diagnosis and treatment. The clinical features are often non-specific and up to 85% of those catheters removed on clinical grounds alone are subsequently proven to be sterile.⁴ The clinician suspecting CR-BSI is presented with a difficult dilemma given that CVC removal results in loss of venous access, while an infected catheter left in situ may lead to overwhelming sepsis. Until recently, standard techniques for diagnosing CR-BSI involved catheter removal. However, the development of novel diagnostic tests currently allows earlier and more accurate diagnosis with the CVC left in place. In addition, management of CR-BSI with through-catheter antibiotics has become accepted practice and can lead to a high proportion of infected catheters being successfully salvaged.⁵

PATHOGENESIS

Venous catheters may become colonised with bacteria after 24 hours of insertion, the outer surface with organisms originating from the skin at the time of placement, and the lumen usually later, from those entering the catheter hub during connection and disconnection. CVCs may also become infected as a result of haematological seeding from a distal site, and occasionally from contaminated infusate. Electron microscopy of CVCs reveals a biofilm adherent to the internal lumen, and a fibrin sheath, which forms extraluminally. Bacteria

colonising the catheter lumen exist in two forms: sessile organisms embedded in the biofilm, and free floating "planktonic" organisms which detach from the biofilm surface. Positive blood cultures drawn through a CVC may represent "colonisation" and represent latent infection. External tip colonisation has been defined as a growth of at least 15 colony forming units (CFU) on a semi-quantitative culture obtained by rolling the catheter tip over an agar plate in the absence of clinical signs of sepsis.⁶ Whether or not colonisation inevitably progresses to CR-BSI is unclear.

Aetiological organisms in the adult population in order of frequency include coagulase negative staphylococci, *Staphylococcus aureus*, *Candida* spp, enterococci, *Pseudomonas aeruginosa*, and *Enterobacter* spp.⁷ Similar organisms are seen in young children with CR-BSI, but there is an increased frequency of Gram negative isolates, such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae*,⁵ possibly as a result of increased translocation of organisms from the gastrointestinal tract. Children receiving long term PN may well have impaired gut barrier function related to primary mucosal pathology, gastrointestinal surgery, or lack of enteral nutrition.

DIAGNOSIS

In clinical practice the diagnosis of CR-BSI is usually based on positive blood culture in a patient with suggestive symptoms and absence of focal infection, although direct culture of the CVC tip has traditionally provided the definitive diagnosis.² The "Maki roll", described in 1977,⁸ involves rolling the catheter tip across an agar plate and thereby inoculating those organisms adherent to the outer surface, ≥ 15 CFU being indicative of catheter colonisation. A major disadvantage of this technique is that the catheter may be contaminated by commensals as it is pulled through the skin exit site. In addition, bacteria growing on the luminal surface of the

catheter will not be detected. The "Cleri flush"⁹ requires the tip of the catheter to be immersed in broth and the lumen flushed through. Vortexing¹⁰ or sonication¹¹ of the catheter tip are aimed at dislodging microorganisms embedded in the CVC biofilm, giving a higher sensitivity of culture. However, a positive culture may still reflect only contamination of the outer surface of the catheter. A further modification involves treating the outer surface of the catheter with chlorhexidine prior to flushing the lumen.¹² Clearly, both the Maki roll and Cleri flush methods provide only retrospective confirmation of CR-BSI, and inevitably involve catheter loss in up to 85% of cases where the catheter is not infected.¹³

As maintaining long term central venous access is a high priority in infants and children with gastrointestinal failure, diagnostic tests that leave the catheter in place are potentially of considerable value. Such catheter sparing investigations rely on obtaining blood through the CVC. However, this is not always possible, with only 50% of CVC found to bleed back in one study.¹⁴ Standard qualitative peripheral blood culture remains the most commonly performed investigation for CR-BSI,¹⁵ but does not indicate the source or quantity of organisms and is subject to contamination. In contrast, paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein represent a considerable refinement, but impose a much greater burden on the laboratory.¹⁶ This test relies on the fact that in CR-BSI, blood taken through the CVC should contain far higher numbers of organisms than blood drawn from a peripheral vein after haemodilution and filtering of organisms by the pulmonary vascular bed. A differential in colony counts of 5–10:1 (CVC:peripheral vein) is taken as being diagnostic of catheter sepsis.^{17,18} When possible, peripheral and central venous blood samples should be taken for bacterial culture at the time the child is febrile. One small study in infants has suggested that repeated quantitative spread plate blood cultures drawn repeatedly from a CVC two to three times a week over the duration of catheterisation may predict some cases of CR-BSI (30%) prior to the development of clinical symptoms, and also help monitor response to antibiotics.¹⁹

Using an automated blood culture system (products of bacterial metabolism produce a colour change reaction),

Abbreviations: AOLC, acridine orange leucocyte cytospin test; CFU, colony forming unit; CR-BSI, catheter related bloodstream infection; CVC, central venous catheter; PN, parenteral nutrition

time to positivity is proportional to the microbial bioload and the volume of blood taken.²⁰ A recent investigation in adult oncology patients compared the time to positivity of paired blood cultures taken simultaneously from CVC and peripheral blood. CVC blood culture becoming positive at least two hours before the peripheral culture was found to be diagnostic of CR-BSI, with a specificity of 100% and a sensitivity of 96.4%.²¹ However, this technique is dependent on the patient not having received antibiotics and requires specialised laboratory automated blood culture equipment. An indirect enzyme linked immunosorbent assay (ELISA) has been developed for the detection of antibodies against a novel short chain lipoteichoic acid antigen produced by coagulase negative staphylococci. Adult patients with CR-BSI were found to have significantly higher IgG and IgM antibody levels compared with controls.²² Larger studies are needed to assess the full potential for this test.

Direct sampling of the intraluminal surface of the catheter using an endoluminal brush was first described in 1983.²³ This technique involves passing a guidewire with a nylon brush down the catheter to its distal end, withdrawal then resulting in sampling of the catheter biofilm. The brush is vortexed with phosphate buffered saline and plated onto agar; colony counts of 100 CFU/ml are significant, although in most cases of CR-BSI much higher colony counts of 10^3 – 10^6 are seen.^{12, 24} This technique has not yet been evaluated in children, although brushes are now available for catheters down to 1 mm internal diameter. The acridine orange leucocyte cytopspin test (AOLC) has been used for investigating CR-BSI in newborns and infants.²⁵ The test involves taking a through-catheter blood sample into EDTA, lysing the red blood cells with hypotonic formol saline, pelleting the leucocytes by centrifugation, staining the cellular monolayer with acridine orange, and examining under ultraviolet light. If any bacteria are seen (in plasma or within polymorphs) the result is positive. A separate sample is treated the same way but is Gram stained for bacterial characterisation. It has the major advantage of only requiring small volumes of blood, and results can be available within one hour. In a newborn/infant population this test was shown to be 87% sensitive and 94% specific compared with quantitative blood cultures.²⁵ Subsequent studies in adult patients of the AOLC test combined with a Gram stain after catheter brushing have shown a sensitivity of 96% and a specificity of 92%.²⁶ The labour intensive nature of this test makes it unlikely to be widely embraced by service laboratories.

PREVENTION

A proportion of cases of CR-BSI are potentially preventable, and both multidisciplinary nutritional care teams²⁷ and appropriately trained nursing staff^{28, 29} play an important role. Broviac type CVCs should be inserted in theatre under strict aseptic conditions by a restricted number of skilled operators. Manipulation of the catheter hub is responsible for the majority of iatrogenic cases.³⁰ Different hubs have been designed in an attempt to minimise the risk of infection, but while they may prevent organisms from migrating along the intraluminal surface of the catheter, they cannot prevent organisms migrating from the skin along the extraluminal surface. A hub including an iodine–alcohol reservoir was shown to reduce CR-BSI fourfold in one study,³¹ but failed to show benefit in a more recent investigation.³² In randomised controlled trials in adult patients, catheters externally impregnated with chlorhexidine–silver sulphadiazine have been shown to reduce the incidence.^{33–35} Coating both the internal and external catheter surfaces with minocycline and rifampicin significantly reduces the risk of colonisation and CR-BSI,³⁶ although this protection is short lived as the antibiotics are washed off. A study comparing chlorhexidine–silver sulphadiazine with minocycline–rifampicin coating has shown the antibiotic combination to be more effective.³⁷

Studies have addressed the effect of instilling high concentrations of antibiotic containing “flush” into the CVC. In vitro, it is possible to significantly decrease staphylococcal colonisation with ceftriaxone, gentamicin, and vancomycin and completely eliminate Gram negative colonisation with aztreonam, ceftriaxone, and gentamicin. In addition, yeast colonisation was completely eradicated by amphotericin B and significantly reduced by fluconazole.³⁸ In both adults and children there are conflicting findings in relation to the effectiveness of catheter flushes containing vancomycin–heparin.^{39–41} A combination of vancomycin, ciprofloxacin, and heparin reduces CR-BSI in children,⁴⁰ but use of this incompatible mixture may be inadvisable.⁴² Theoretically, thrombolytics should help break down CVC biofilm releasing adherent microorganisms; however, the use of urokinase as an adjuvant to antibiotics in the treatment of CR-BSI is of doubtful value.⁴³ Frequent use of antibiotic flushes, especially those containing vancomycin, may lead to the emergence of resistant organisms. Minocycline and ethylenediaminetetra-acetate (EDTA) flush provides broad spectrum antimicrobial activity against Gram positive and Gram negative bacteria and candida, and has been shown to be successful in preventing recurrent CR-BSI in three

adult patients.⁴⁴ At present there is no uniform practise among units in the UK. Chelated silver ions impregnating subcutaneous collagen cuffs confer antimicrobial properties, the cuff also providing a physical barrier to the migration of microorganisms along the external surface of the catheter. Their use has been shown to reduce the incidence of infection in short,⁴⁵ but not long term catheters.^{46, 47} Over time however, the collagen cuff is degraded and protection is lost. Subcutaneous tunnelling reduces the incidence of CR-BSI in short term CVC that are not used to sample blood.⁴⁸

It is thought that a proportion of cases follow translocation of bacteria from the bowel lumen. Normal host defences to bacterial translocation include the gut mucosal barrier, natural host immunity, and a protective gut flora.⁴⁹ The most common bacteria implicated in translocation in surgical patients include *Escherichia coli*, *Klebsiella oxytoca*, and *Bacteroides fragilis*.⁵⁰ Children receiving long term PN may be at increased risk of bacterial translocation as they are more likely to have abnormalities of the gut mucosa, abnormal immunity, and bacterial overgrowth with pathogenic bacteria. Trophic feeding in the premature newborn has been shown to reduce the risk of septic episodes, possibly by maintaining gut mucosal integrity.⁵¹ Many children receiving long term PN have a dysmotile bowel and are susceptible to bacterial overgrowth.⁵² In such patients, cyclical antibiotics given enterally may encourage the growth of antibiotic resistant organisms or fungi, and the role of this treatment in preventing CR-BSI is uncertain. Similarly, a prophylactic role for probiotics remains to be established. In an animal model, the addition of glutamine to total PN has been shown to reduce both the rate of bacterial translocation from the gastrointestinal tract and CVC infection.⁵³ In the same model, short chain fatty acids, while having no effect on bacterial translocation, also reduced the rate of infection.⁵³ The addition of epidermal growth factor to total PN has been shown to reduce gut mucosal atrophy, bacterial translocation, and the incidence of CR-BSI in rats,⁵⁴ but the potential clinical application of these various nutritional interventions in terms of reducing the incidence in humans has yet to be clarified.

TREATMENT

Up to 80% of coagulase negative staphylococci infections⁵⁵ and 70–90% of all catheter infections in young children can be eradicated with antibiotics.^{5, 20} The initial combination must be broad spectrum (such as vancomycin and aztreonam) and aimed at both coagulase negative staphylococci and Gram negative organisms. The precise choice should

Recommendations for prevention of catheter related bloodstream infection

- Limited number of experienced operators for CVC insertion, following strict aseptic technique
- CVC "dedicated" to PN (not to be used as a routing for blood sampling, giving drugs or other fluids)
- Unit protocols for accessing the CVC, and dealing with complications such as suspected sepsis, blockage, or fracture
- Overview of PN patients by nurse specialist in nutrition support, working as part of a multidisciplinary nutritional care team
- Recurrent audit of CVC related complications, including sepsis
- Regular training in CVC care for medical and nursing staff looking after patients receiving parenteral nutrition

depend on known patterns of isolates and sensitivities in individual units. The duration of through-CVC antibiotic treatment required to achieve microbial clearance is unknown, but 10 days is probably adequate in most cases once repeat blood cultures are negative.⁵ The CVC can continue to be used for giving PN, but should be removed if there is clinical deterioration despite appropriate antibiotic treatment, or (in most circumstances) if blood cultures remain positive or yeasts are isolated.

SUMMARY

CR-BSI is an important cause of morbidity and mortality in children receiving PN. An important proportion of cases are iatrogenic and potentially preventable. Dedicated nutrition teams have been shown to reduce the incidence of CR-BSI, and units caring for children requiring long term PN should have standardised protocols for catheter care and management. The incidence of the condition should be regularly audited. The AOLC test combined with qualitative or automated paired peripheral vein/catheter cultures provides the most rapid and accurate diagnosis with the catheter in situ. Local first line "blind" antibiotic regimens should be established in combination with the microbiology department, and "through-catheter" treatment given. Advances in catheter design have proven effective in adult patients, but further studies to assess their role in the paediatric population are needed.

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