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. Evidence based guidelines for the prevention of CR-BSI have recently been published by the Department of Health. 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. 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.

PATHOGENESIS
Venous catheters may become colonised with bacteria after 24 hours of insertion, and a fibrin sheath, with organisms originating from the skin exit site. In addition, bacteria growing on the luminal surface of the catheter will not be detected. The “Cleri flush” requires the tip of the catheter to be immersed in broth and the lumen flushed through. Vortexing or sonicaton 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. Clearly, both the Cleri flush and Cleri method provide only retrospective confirmation of CR-BSI, and inevitably involve catheter loss in up to 85% of cases where the catheter is not infected.

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. Standard qualitative peripheral blood culture remains the most commonly performed investigation for CR-BSI, but does not indicate the source or quantity of organisms and is subject to contamination. In combination, 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. This test relies on the fact that in CR-BSI, 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. 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.

Using an automated blood culture system (products of bacterial metabolism produce a colour change reaction),
time to positivity is proportional to the microbial bioload and the volume of blood taken. 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%. However, this technique is dependent on the patient not having received antibiotics and requires specialist 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. 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. 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 10^3–10^4 are seen. 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 cyto-spin test (AOLC) has been used for investigating CR-BSI in newborns and infants. 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.

Prevention

A proportion of cases of CR-BSI are potentially preventable, and both multidisciplinary nutritional care teams and appropriately trained nursing staff 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. Different hubs have been designed in an attempt to minimise the risk of infection, but while they may prevent organisms 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, but failed to show benefit in a more recent investigation. In randomised controlled trials in adult patients, catheters externally impregnated with chlorhexidine-silver sulphadiazine have been shown to reduce the incidence. Coating both the internal and external catheter surfaces with minocycline and rifampicin significantly reduces the risk of colonisation and CR-BSI, 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.

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 contamination with ceftazirole, gentamicin, and vancomycin and completely eliminate Gram negative colonisa- tion with aztreonam, ceftriaxone, and gentamicin. In addition, yeast colonisa- tion was completely eradicated by amphotericin B and significantly reduced by fluconazole. In both adults and children there are conflicting findings in relation to the effectiveness of catheter flushes containing vancomycin-heparin. A combination of vancomycin, ciprofloxacin, and heparin reduces CR-BSI in children, but use of this incompatible mixture may be inadvisable. 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. Frequent use of antibiotic flushes, especially those containing vancomycin, may lead to the emergence of resistant organisms. Minocycline and ethylendiaminetetra-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. 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, but not long term catheters. 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.

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. The most common bacteria implicated in translo- cation in surgical patients include Escherichia coli, Klebsiella oxytoca, and Bacteroides fragilis. 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 bacte- rial 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. Many children receiving long term PN have a dysmotive bowel and are susceptible to bacterial overgrowth. 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. Similar problems apply to probiotics. Although 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 infections and 70–90% of all catheter infections in young children can be eradicated with antibiotics. The initial combination must be broad spectrum (such as vancomycin and aztre- onam) and aimed at both coagulase negative staphylococci and Gram nega- tive organisms. The precise choice should
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. The CVC can continue to be used for giving 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.

ACKNOWLEDGEMENT

We are grateful to Dr Peter Kite for his helpful comments on this manuscript.


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