A review of the literature of central venous catheters: placement and management in infants admitted to a neonatal intensive care unit.
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Background

Nosocomial infection in the newborn infant is a major cause of morbidity and mortality and results in substantial health care costs (Makhoul, 2007; Rogowski, 2004; Stoll, 2003, 2004). Premature and/or sick infants are at particular risk because they have a naïve immune system, immature gut and deficient barrier function of the skin (Schanler, 2000; Rutter, 2000). The environment in which they are managed may also increase their risk of infection. The use of incubators restricts straightforward access and increases the potential for contamination of sterile equipment used in procedures. The use of high ambient humidity in the first few weeks of life may encourage organism multiplication within the incubator. Furthermore infants are exposed to multiple invasive procedures and treated with intravenous medications and fluids that increase the risk of acquiring an infection (Brady, 2005).

Bloodstream infection (BSI) is a common nosocomial infection in the newborn population. Stoll et al (2003) reports sepsis rates from 2 large cohort studies with very low birth weight (VLBW) infants: one between 1991-1993 and the other 1998-2000. Early onset sepsis (≤ 72 hours of life) for the 2 time points was 1.9% (147/7606 infants) and 1.5% (84/5447 infants) respectively; in those who survived beyond 72 hours of life, 25% (1696/6911 infants) and 21% (1313/6215 infants) respectively had one or more episodes of blood culture-proven sepsis. However in the extremely immature infant where rate of late onset infection is higher than in any other birth weight group, the incidence over time has increased from approximately 31 to 48% (Stoll, 2003). The high prevalence in this group and the increasing incidence over time is probably a reflection of increasing survival rates, extreme immaturity and continuing need for intensive and prolonged medical intervention.

Several risk factors are associated with BSI: low birth weight and gestational age, use of total parenteral nutrition (TPN), the presence of an intravascular device (peripheral or central), use of mechanical ventilatory support and duration of stay (Holmes, 2007; Perlman, 2007; Couto, 2006; Van Der Zwet, 2005; Stoll, 2003; Chien, 2002).

The purpose of this review is to examine the literature on interventions related to the insertion and management of central venous catheters which may have an effect on blood stream infection in the newborn. Central venous catheters (CVCs) are essential in the management of newborn infants undergoing intensive care treatment as they guarantee reliable vascular access. This is especially so in the VLBW where access to peripheral veins is limited, use of hypertonic solutions or drugs with low pH over a prolonged period of time is not unusual and where infiltration of these solutions can lead to local skin ulceration, secondary infection and scarring (Ainsworth, 2001). The placement of a CVC is not without
risk: complications are mainly mechanical, thrombotic and infectious with catheter related bloodstream infection being the most frequently occurring complication. The incidences of catheter related BSI in the newborn population varies depending on the criteria used in defining infection and the population studied. Reported incidences range from 4%-44% with higher rates occurring in the most immature infants (Aly, 2005; Pessoa-Silva, 2004; Klein, 2003; Chien, 2002; Mahieu, 2001a; Yeung, 1998; Trotter, 1996; Lander, 1991). The most common organisms leading to catheter related BSI are Gram positive bacteria (Perlman, 2007). BSI associated with CVC use is attributable to four major sources: colonisation from the skin leading to extraluminal contamination; hub/intraluminal contamination; translocation/seeding from another source and contamination of infusate.
Method

Definitions
For the purposes of this review a central venous catheter is defined as a catheter that is passed through a vein to be in a position in the thoracic portion of the vena cava or in the right atrium. They may be characterised by: site of insertion [e.g. via umbilical, subclavian, femoral, internal jugular veins or peripherally via basilica, cephalic, brachial or saphenous veins (PICC)]; intended life span [temporary or short-term vs. permanent or long-term]; pathway from skin to vessel [e.g. tunnelled vs. non-tunnelled] and length [short vs. long] (O’Grady, 2002).
Search strategy

The PICO framework was used to initiate the literature search (Schardt, 2007).

- Patient group - neonate(s), infant, newborn, baby, preterm, premature, immature, low birth weight
- Intervention - central venous catheter (CVC), central line, central venous therapy, peripherally inserted central catheter (PICC), long line, non-tunnelled/tunnelled catheter, surgical, umbilical
- Comparison -
  - hands and hand hygiene (products, gloves, nails, jewellery)
  - barrier precautions (maximal, minimal, sterile, aseptic, gown, glove, mask, hat, no-touch)
  - skin antiseptic preparation (antibacterial, antimicrobial, chlorhexidine, alcohol, povidone iodine)
  - catheter type (PICC, umbilical, surgical) and duration of use (long, short)
  - site of insertion (upper and lower limb, umbilicus)
  - manipulations and connectors (multi-lumen, single, double, triple, hub, needleless connector, three way tap, in-line filters)
  - catheter dressings (gauze, transparent, hydrocolloid, iodine, sponge, frequency)
  - infusate solutions (dextrose, amino acid, lipid, total parenteral nutrition [TPN]),
  - personnel (dedicated, doctor, nurse, expert, physician, team, grade)
  - use of antibiotics (prophylactic, therapeutic line treatment)

Outcome measures: colonisation of catheter, bloodstream infection, sepsis

Date range: 1990-2007
Types of studies: randomised controlled trials, case control and cohort studies, observational studies, systematic reviews and recommendations from expert bodies.
Databases: Biomed Central, British Nursing Index, Cinahl, Cochrane Libraray, Embase, Highwire Press, Medline, National Library of Medicine, Nursing and Allied, Ovid, Pub-med, Proquest Medical Library
Limits: English language, human studies, electronic or local accessibility
Number of retrievals: 1448 articles. The abstracts of all retrievals were examined for relevance. Duplications and those with no relevance to the neonatal population were discarded.
Number evaluated: 283
The evidence was assessed using an adapted scheme that was developed at the Oxford Centre for Evidence-based Medicine (http://www.cebm.net/?o=1011).

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<th>Level</th>
<th>Source of evidence</th>
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<tr>
<td>1a</td>
<td>SR with homogeneity of RCTs</td>
<td>A</td>
<td>consistent level 1 studies = good evidence</td>
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<tr>
<td>1b</td>
<td>Individual RCT with narrow Confidence Interval</td>
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<tr>
<td>2a</td>
<td>SR with homogeneity of cohort studies</td>
<td>B</td>
<td>consistent level 2 or 3 studies or extrapolations from level 1 studies = moderately good evidence</td>
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<tr>
<td>2b</td>
<td>Individual cohort study including low quality RCT; e.g., &lt;80% follow-up</td>
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<tr>
<td>3a</td>
<td>SR with homogeneity of case-control studies</td>
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<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
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<tr>
<td>4</td>
<td>Case-series and poor quality cohort and case-control studies</td>
<td>C</td>
<td>level 4 studies or extrapolations from level 2 or 3 studies = poor evidence</td>
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<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
<td>D</td>
<td>level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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SR - Systematic Review
RCT - Randomised Controlled Trial
Hand hygiene

Products
Hand hygiene is emphasised as being the simplest, single most effective measure in any infection control program for preventing nosocomial infection (Boyce, 2002). Effective hand hygiene (hand washing and/or hand disinfection) involves removing both resident and transient organisms from the skin. Hand washing with a plain soap and water for a minimum of 15 seconds can remove 90% of loosely adherent transient flora but may also increase bacterial counts where there is irritated or damaged skin (Boyce, 2002). Plain soaps may also become contaminated and lead to the colonization of hands of personnel with Gram negative bacilli (Sartor, 2000; Winnefeld, 2000).

The in vitro/in vivo activity of alcohols against Gram positive and negative bacteria and certain viruses (herpes simplex virus, human immunodeficiency virus, influenza virus, respiratory syncytial virus, hepatitis B and A, rotavirus, adenovirus, and rhinovirus) is well established (Boyce, 2002). The effectiveness of alcohol based hand rub products is dependant on the alcohol concentration, the amount of time that hands are exposed to the alcohol and organism and are not appropriate for use when hands are visibly dirty or contaminated with proteinaceous materials. Re-growth of bacteria on the skin occurs slowly after use of alcohol-based hand antiseptics but the addition of other products, for example chlorhexidine, can result in persistent activity. Alcohol-based products are more effective for standard hand washing than soap but may cause skin irritation and dryness.

Hand colonisation
A variety of organisms colonise the environment and the hands of staff working in the NICU and in the course of working may be transmitted to and between infants and staff (Cook, 2007; Pessoa-Silva, 2004). Data from the observational study by Pessoa-Silva (2004) show that direct and indirect care activities associated with the newborn are all associated with a significant increase in hand colony count: skin contact (p=0.004), nappy change (p<0.001), respiratory tract care (p<0.001) and contact with equipment (p=0.015) and manipulation of CVC device (p<0.004).

In a series of papers reporting various aspects of a prospective cross over design study examining the effects of hand hygiene practices on healthcare associated infection in 2 high risk neonatal populations, differences were noted between the Gram status of organisms, hand colonisation of staff and BSI in the neonate (Perlman, 2007; Cook, 2007; Larsen, 2005; Waters, 2004; Milisavljevic, 2005). Over a 2 year period data were collected from 2935 infants and 119 nurses (Perlman, 2007). Of the 2935 infants, 205 (7%) developed a bacterial BSI. Of these episodes 179 were caused by Gram positive organisms and 57 Gram negative organisms (n=236 isolates).
Significantly more Gram positive BSI were associated with the presence of a CVC than compared to Gram negative BSI (77% [138/179] and 61% [35/57] respectively, p=0.03). To explore the relationship between staff hand colonisation and transmission of organisms, 834 hand cultures from 119 nurses were available for analysis. From these cultures, 1442 isolates were typed; most (89%) were Gram positive bacteria, 7% were Gram negative bacteria and 5% were fungi (Cook, 2007). In determining the transmission rate between an infant and the hands of nurses of the most frequently occurring organism, Milisavljevic et al (2005) analysed the genetic relatedness of Staphylococcus epidermidis from the 2 groups. Of the 173 isolates of Staphylococcus epidermidis that were typed, the majority, (78% n=135/173), were common to both infant and nurse. In contrast, the presence of a CVC was not associated with Gram negative BSI (Larsen, 2005). Additionally, there was little relationship between the strains causing BSI and those cultured from nurse’s hands (Larsen, 2005; Waters, 2004). Waters et al (2004) found that only 9% of neonatal infections were associated with the same strain identified on the hands of nurses. Of these, Klebsiella pneumoniae and Serratia marcescens were significantly more likely to be shared as compared to the other 3 detected strains: Escherichia coli, Enterobacter cloacae and Pseudomonas aeruginosa (p=0.002). A number of conclusions are drawn from these papers. Catheter related sepsis is more likely to be caused by Gram positive than Gram negative organisms and the mechanism of acquiring a catheter related sepsis is different according to organism type. Because of the genetic relatedness between Gram positive organisms in infants with catheter related BSI and the organisms on nurses’ hands, it is thought that the mode of transmission occurs with insertion and subsequent manipulation of the catheter. However, because the presence of a CVC is unrelated to gram negative sepsis and there is little relationship between the type of Gram negative organism associated with BSI and those found on the hands of nurses, it is thought that transmission of these bacteria is more likely to occur from other sources e.g. the gastrointestinal tract.

Nails and Jewellery
There are no specific data on infection rates and the wearing of artificial nails. However survey data and data from outbreak investigations show a relationship between artificial nails and organism growth. Cultures obtained before and after hand washing from the fingertips of 56 nurses wearing artificial nails and 56 nurses with natural nails showed higher numbers of colony-forming units of Gram negative organisms from those nurses with artificial nails than from those with natural nails (41% vs 9% respectively). There were no significant differences in other types of organisms (Pottinger, 1989). Data from an outbreak investigation of Klebsiella pneumoniae infection in a NICU showed that 68% (13/19) of affected infants carried Clone A. In multivariate analysis, exposure to a health care worker wearing artificial nails was associated with infection and/or colonization with the organism (OR, 7.87; 95% CI, 1.75 to 35.36; Gupta, 2004).
Because of these increasing concerns, the CDC guidelines for hand hygiene in healthcare settings state that artificial fingernails or extenders should not be worn when having contact with high-risk patients, for example those in intensive-care units. Natural nail tips should be less than 0.5 cm long (McCleskey, 2003).

The literature on wearing hand jewellery is limited and the various study designs make it difficult to draw conclusions (Al-Allak, 2008; Yildirim, 2008; Fagernes, 2007; Wongworawat, 2007; Trick, 2003). All studies except one, Wongworawat (2007), showed that hand hygiene, irrespective of ring wearing or procedure used, did not totally eliminate transient and or pathological organisms. In this study there was no significant difference in the bacterial count between hands with and hands without rings for the groups that used alcohol wash or alcohol chlorhexidine lotion. In participants who used povidone-iodine, the number of bacteria on hands with rings was greater than the number on hands without rings (p<0.05). Yildirim (2008) showed a significantly greater bacterial colonisation when wearing rings (p=0.001) but type of ring (plain vs stoned) did not increase the risk of colonisation. Fagernes (2007) found no difference in overall bacterial counts between those with and those without rings but there was a significant difference in Gram negative organism count; ring wearers more likely to have Enterobacteriaceae (p=0.006). Trick (2003) found that ring wearing was associated with an increased frequency of carriage of Staphylococcus aureus, Gram negative bacilli and Candida.

Apart from hand contamination, ring wearing has been reported to cause tears in gloves thereby diminishing the protective nature they afford (Larsen 1989; Nicolai, 1997). The general recommendation is that it is acceptable to wear plain bands, for example wedding bands, however, these must be moved or removed when hand hygiene is performed in order to reach the bacteria which may harbour underneath them (Health Protection Scotland, 2007).

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<tr>
<th><strong>Key points</strong></th>
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<tr>
<td>Hand colonisation occurs following routine care activities</td>
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<tr>
<td>Hand colonisation with Gram positive organisms is associated with an increased incidence of catheter related BSI</td>
<td>B</td>
</tr>
<tr>
<td>Gram negative catheter related BSI is not associated with hand colonisation.</td>
<td>B</td>
</tr>
<tr>
<td>Thorough hand hygiene is important in the prevention and control of infection control.</td>
<td>B</td>
</tr>
<tr>
<td>Jewellery may impede the process of effective hand hygiene.</td>
<td>B</td>
</tr>
<tr>
<td>The wearing of artificial nails is associated with colonisation and infection.</td>
<td>C</td>
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Barrier precautions

As CVCs carry a substantially greater risk for infection than peripheral cannulae, experts recommend the use of maximal sterile barriers that includes the use of a head cap, facemask, sterile body gown, sterile gloves and full size sterile drape, during insertion of the CVC (O’Grady, 2002). Whilst the benefits of using maximal sterile barriers have been demonstrated with significantly fewer episodes of catheter colonisation and catheter related sepsis in trials with adult subjects (Yilmaz, 2007; Hu, 2004; Raad, 1994; Mermel, 1991), there are no data about its effectiveness in the newborn population. Many newborn infants are managed in an incubator, which in itself presents a barrier but on the other hand, manipulation of equipment and the infant through small portholes and within the incubator, makes it is easier for the gloves, drapes, or catheter to be contaminated. Compliance with educational programmes on maximal sterile barriers has also been shown to reduce catheter related BSI (Sherertz, 2000).

Gloves

The wearing of gloves is highly protective with respect to hand contamination but does not fully eliminate contamination (Hayden, 2008; Pessoa-Silva, 2004; Tenorio, 2001; Pittet, 1999). Ng et al (2004) reviewed how changing the hand washing protocol in their neonatal unit would alter the incidence of late onset infection. Conventional hand washing was compared with using 1 % chlorhexidine in isopropyl and ethyl alcohol rub before and after the application of non-sterile gloves. The two hand hygiene protocols were consecutively assessed over 72 months. Data from 337 very low birth weight infants were collected. The introduction of their new protocol was associated with a 2.8 fold reduction in the incidence of late onset infection rate in the NICU setting.

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<th>Key points</th>
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<tr>
<td>Use of maximal sterile barriers during the insertion of central venous catheters reduces colonisation of the catheter.</td>
<td>A</td>
</tr>
<tr>
<td>Staff knowledge about the importance of maximal sterile barriers and aseptic technique can decrease the incidence of bloodstream infection.</td>
<td>B</td>
</tr>
<tr>
<td>Wearing gloves reduces hand contamination</td>
<td>B</td>
</tr>
<tr>
<td>The combined use of alcohol and gloves reduces the incidence of late-onset infection.</td>
<td>B</td>
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Skin antisepsis

Skin disinfection prior to the insertion of a CVC is one of the most important measures for reducing catheter related infection. It is thought that bacteria resident on the skin firmly attach to the catheter’s external surface. As the catheter passes through the skin the bacteria are transported into the infant. These microflora adhere to the catheter and form a polysaccharide film to protect themselves. This layer is referred to as a ‘biofilm’. Within this film, microorganisms can survive (Hadaway, 2003). A variety of solutions are used to disinfect the skin; their performance depends on a number of factors: presence of proteinaceous material, initial bioburden, contact time, concentration, pH and temperature.

Historically 10% povidone-iodine has been used to disinfect the skin of infants. However prematurely born infants experience transient hypothyroidism in early postnatal life (Williams, 2006; Biswas, 2002; Reuss 1997; Van Wassenaar, 1997) and exposure to iodine from the use of contrast media and or 10% povidone-iodine as a skin disinfectant may further compromise thyroid function (Yilmaz, 2003; Brown, 1997; Reuss 1997; Parravicini, 1996; Gordon, 1995; Lin, 1994). This is of concern as congenital hypothyroidism adversely affects neurodevelopmental outcome and it may be that exposure to additional iodine has an additive effect on the neurodevelopmental impairment associated with prematurity. It is recommended that povidone-iodine is not used in infants <32 weeks gestational age or 1500 grams (BNF for Children, 2007). There are a number of studies comparing povidone-iodine and various chlorhexidine solutions/interventions. Those involving adults with central venous and arterial catheters, show chlorhexidine to be superior to povidone-iodine in reducing colonisation rate and in some of these, there is a concomitant reduction in catheter related BSI (Mimoz, 2007; Vallés, 2007; Chaiyakunapruk, 2002). Studies involving infants have shown no clear benefit of chlorhexidine over povidone-iodine (Linder, 2004; Garland, 2001).

Linder (2004) studied sepsis rates when 10% povidone-iodine or 0.5% chlorhexidine gluconate solution in 70% isopropanol was used as a skin antiseptic prior to any invasive procedure in infants admitted to the neonatal unit over two time points. Methods of disinfection, staff education and hand washing protocol were identical over the two time scales. A total of 1146 infants were included in the study. They concluded that no differences were found in the effectiveness of the disinfectant or the rate of true infections when using either the chlorhexidine gluconate or the povidone-iodine. An earlier RCT carried out by Garland (2001) compared the efficacy of a specific catheter site antisepsis regime on BSI in 705 preterm infants. The regimen consisted of cleaning the CVC insertion site with 10% povidone-iodine or with a 70% alcohol scrub followed by the placement of a chlorhexidine impregnated disk. In both groups the insertion site was covered by a transparent polyurethane dressing. They concluded that whilst the chlorhexidine patch reduced the rate of catheter tip colonisation there were no differences
between the two site regimens in rates of BSI. A consequence of the alcohol/chlorhexidine procedure was that 5.9% (n=7/118) of infants in this group suffered a severe localised contact dermatitis under the chlorhexidine patch and 2 other neonates developed areas of pressure necrosis. All adverse events occurred in infants < 27 weeks gestation. Because of these events the protocol was altered so that infants <26 weeks gestation were only enrolled if the CVC was inserted after the first week of life. After this change there were a further 5.5% (n=12/217) episodes of contact dermatitis reported. In total 15% of infants (n=15/98) <1000gms and 1.5% of infants ≥ 1000gms (n=4/237) randomised to the antisepsis dressing developed dermatitis (p=0.0001).

In 2002 the CDC published their recommendation that chlorhexidine should not be used on infants aged less than 2 months (O’Grady, 2002). Since then there have been other accounts of severe skin burn occurring after the use of chlorhexidine in alcohol (Mannan, 2007; Upadhyayula, 2007; Reynolds, 2005). Because of the growing evidence of skin trauma in ELBW infants following the use of chlorhexidine in alcohol, the efficacy of aqueous chlorhexidine has been investigated (Lilley, 2006; Anderson, 2005). Lilley et al (2007) randomised 85 newborn infants to receive 0.5% or 0.05% aqueous chlorhexidine as a skin antiseptic prior to the insertion of a venous or arterial cannula. Skin surface swabs taken before and after skin cleaning showed 0.5% aqueous chlorhexidine gave significantly better total clearance of bacteria than 0.05% chlorhexidine (92% v 38%, p = 0.002; OR 19.2; 95% CI 3.71 to 99.45). The study by Anderson et al (2005) considered the effect of a multi-factorial strategy on nosocomial infection in the newborn. As part of this strategy, povidone-iodine was changed for 2% aqueous chlorhexidine; they found that nosocomial BSI rate was reduced from 21% to 9% (p=0.05; CI 0.19–1.0). A CVC was present in 63% of BSI and although there was a significant reduction in catheter colonisation (p=0.001), the same level of reduction was not seen in catheter related BSI. It was also reported that 11% (n=4/36) of infants with a birth weight <1000 g and who were <48 hours of age developed severe skin irritation from 2% aqueous chlorhexidine. In 1 of these infants this progressed to skin breakdown and exudation.

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>In some studies povidone iodine has been shown to cause transient hypothyroidism in infants.</td>
<td>B</td>
</tr>
<tr>
<td>There is no clear benefit of chlorhexidine over povidone-iodine in infants.</td>
<td>A</td>
</tr>
<tr>
<td>Chlorhexidine has been associated with severe contact dermatitis and is not recommended for use in infants &lt; 26 weeks gestation in the first two weeks of life.</td>
<td>A</td>
</tr>
<tr>
<td>In infants, 0.5% aqueous chlorhexidine eliminates skin bacteria more effectively than 0.05% aqueous chlorhexidine</td>
<td>A</td>
</tr>
<tr>
<td>Aqueous and alcoholic chlorhexidine are more effective than povidone iodine at reducing catheter colonisation and sepsis in adult patients.</td>
<td>A</td>
</tr>
</tbody>
</table>
Type of catheter, site of insertion and duration of use

The risk of acquiring a blood stream infection may be associated with the type of CVC used, duration of usage and site of catheter insertion. Decision on choice of catheter is influenced by venous access in the individual infant, anticipated function of the catheter and expected duration of use.

The risks of BSI associated with various types of CVC in the newborn have been described: 3.8 to 7.2/1000 umbilical venous catheter days, 4.7 to 13.1/1000 peripherally inserted central catheter days and 8.1 to 12.1/1000 surgically placed central venous catheter days (Chien, 2002; Mahieu, 2001a).

The site at which the catheter is placed influences the subsequent risk for catheter-related infection due to the density of skin flora at the insertion site (Hadaway, 2003). It has been estimated that skin preparation procedures leave approximately 20% of skin flora behind (Hadaway, 2005).

In a retrospective observational study by Hoang (2008) with 396 infants, comparing PICC site (upper or lower extremity insertion) and BSI, there was no difference in overall rate of catheter related BSI and site of catheter insertion (7.1 infections/1000 catheter days vs 4.8 infections/1000 catheter days respectively). In sub-group analysis by organism type, BSI with coagulase negative Staphylococcus was significantly greater in the upper extremity site (n=37/43 PICCs [86%]) as compared to the lower extremity site (n=5/10 PICCs [50%]), p=0.05. In an earlier study by Fallat (1998) of 268 CVCs inserted, [antecubitaly (n = 95) or via subclavian (n = 88), sapheno-femoral (n = 23), facial (n = 3), axillary (n = 17) or jugular (n = 40) veins] in 157 infants, there was a catheter related BSI rate of 24% (12.5 episodes/1000 catheter days). Type of catheter or location of site were not associated with an increased risk of BSI.

When long term intravenous nutrition and/or treatment is required, a percutaneous or tunnelled central catheter is inserted. The choice of site is influenced by ease of access and subsequent risk of complications e.g. infection, pneumothorax, haematoma. Vegunta et al (2005) carried out a retrospective analysis of all the tunnelled CVCs inserted at a children’s hospital over a 5-year period. Eighty-eight neck lines and 49 groin lines were placed (n=137). Even though the infants in the groin line group were significantly more immature than the infants in the neck group (30.1 vs 32.2 weeks gestational age, p=0.03), complication rates in the neck placement group were higher (29.5% [13.7/1000 catheter days] vs 8.2% [2.67/1000 catheter days], p=0.005) as were catheter-related sepsis rates (12.5% [5.8/1000 catheter days] vs 2% [0.7/1000 catheter days], p=0.032). The authors conclude that the fewer number of complications associated with femoral insertions were possibly due to local practice in the NICU where handling was more frequent around the neck than around the groin. A second study involving 60 infants compared 47 femoral venous catheter
insertions and 64 jugular venous catheter insertions (Murai, 2002). There were 2.32 infections/1000 catheter days in the jugular insertion group and 2.48 infections/1000 catheter days in the femoral group despite the catheter use being significantly longer in the femoral group (median of 24 vs 17 days, \( p=0.021 \)). There were no significant differences in other complications such as thrombosis and catheter dislodgement. However the femoral vein was the preferential insertion site as the catheter was easier to insert and there was a decreased need to induce muscle relaxation in the patient.

Benjamin (2001) evaluated the consequences of CVC retention in bacteraemic low birth weight infants. Of the 153 episodes of bacteraemia, no relationship was noted between type of catheter and complicated bacteraemia \( (p=0.89) \). Complicated bacteraemia was seen in 44% \( (n=36/82) \) of PICC lines, 43% \( (n=13/30) \) of Broviac lines, 38% \( (n=3/8) \) of femoral lines and 21% \( (n=7/33) \) umbilical lines.

The effect of having more than one lumen has also been examined. It is postulated that having an increased number leads to a greater likelihood of multiple manipulations and that the larger intraluminal surface of the multi-lumen as compared with single-lumen catheter may lead to increased bacterial growth and subsequently to an increased risk of bacterial infection (Zurcher, 2004; Dobbins 2003). The review by Zurcher (2004) of 5 randomized trials involving adults with data on 530 multi and single lumen CVCs, found no difference in colonisation rates but BSI occurred in 8.4% of multi-lumen and 3.1% single-lumen catheters \( (OR, 2.58; 95\% CI, 1.24-5.37; NNT, 19; 95\% CI, 11-75) \). However, other studies have shown no association between the number of lumina and infection (Kabra, 2005; Farkas, 1992). Kabra (2005) carried out a systematic review of 3 studies with 186 infants on the effectiveness and safety of multiple versus single lumen umbilical venous catheters in term and preterm infants. In the first week of life there were fewer peripheral cannulae placed in the multi-lumen group than in the single-lumen group \( (WMD -1.42, 95\% CI: -1.74 to -1.10, p<0.0001) \) but there was also an increase in catheter malfunction in the multi-lumen group \( (typical RR 3.69 (95\% CI 0.99, 13.81), p=0.05; RD 0.15, 95\% CI: 0.03 to 0.27, p=0.01). Clinical sepsis, catheter related BSI, catheter associated thrombosis, complications related to catheter malposition, necrotising enterocolitis (NEC) and early neonatal mortality were not significantly different in the two groups. However the authors comment that the quality of included randomized studies is poor and the estimates of clinically important complications imprecise.

In considering the possible increased risk of BSI when multiple-lumen catheters are used, Murai (1996) compared complication rates in 60 newborns with the use of a single-lumen tunnelled catheter \( (23 \text { infants with 23 catheters}) \) verses the simultaneous use of multiple single-lumen tunnelled catheters \( (37 \text { infants with 84 multiple concurrent catheters}) \). He showed no difference in complication rate and suggested that an additional potential advantage of multiple catheters is that the individual catheter
can be removed separately for complications such as catheter leaks, thrombosis or infection without possible loss of all vascular access.

The risk of catheter related BSI and duration of catheter use has been investigated by several groups. Fallat et al’s (1998) retrospective cohort study showed that the duration of use of non-umbilical CVCs was associated with an increased risk of catheter related BSI (OR 1.03, p=0.029). Butler-O’Hara (2006) randomly assigned 210 infants <1250 grams to UVC use for long term (up to 28 days) or short term use (up to 10 days) and then if central venous access was still required, the UVC was replaced by a percutaneous CVC. There was no difference in catheter related BSI (7.4 infections/1000 catheter days in the short-term and 11.5 infections/1000 catheter days in the long-term group), time to full enteral feeding, NEC or death.

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<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>There is no difference in the incidence of sepsis between peripheral intravenous catheters and PICCs</td>
<td>B</td>
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<tr>
<td>Infection risk with the use of an umbilical venous catheter is not associated with the duration of catheter use.</td>
<td>A</td>
</tr>
<tr>
<td>Infection risk with the use of non-umbilical venous catheter is associated with the duration of catheter use.</td>
<td>C</td>
</tr>
<tr>
<td>There is no difference in BSI when using tunnelled or non-tunnelled catheters.</td>
<td>B</td>
</tr>
<tr>
<td>There is no relationship between type of catheter and complicated bacteraemia</td>
<td>B</td>
</tr>
<tr>
<td>There is an increase risk of catheter malfunction in the multi-lumen UVCs as compared to single lumen UVCs.</td>
<td>B</td>
</tr>
<tr>
<td>Data on number of lumen/catheter and risk of BSI is inconsistent</td>
<td>B</td>
</tr>
<tr>
<td>Data on placement of CVC (femoral vs jugular) and subsequent risk of BSI is inconsistent.</td>
<td>C</td>
</tr>
<tr>
<td>Tunnelled femoral venous catheters are easier to insert than jugular catheters.</td>
<td>C</td>
</tr>
</tbody>
</table>
In-line filters, manipulations and connectors

In-line filters are recommended when administering intravenous fluids through peripheral and central lines to prevent contaminants i.e. particles and microorganisms from migrating into the infant (Bethune, 2001). However, guidance in Epic2: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infection (Pratt, 2007) and the Centers for Disease Control and Prevention guidelines for the prevention of catheter related infections (O’Grady, 2002) documents indicate that in-line filters play no role in the prevention of catheter related infection but for other reasons may be important for the administration of TPN. Both of these papers report that infusate-related blood stream infection is incredibly rare and conclude that filtration of medications and infusate in the pharmacy is a more practical and less costly way to remove the majority of particulates.

The use of in-line filters versus no filter for preventing morbidity and mortality in term and preterm neonates has been reported in a recent Cochrane Collaboration review (Foster, 2006). Three published studies met the inclusion criteria giving a total of 262 neonates. In all studies a 0.2micron filter was used; administration sets were changed 24 or 96 hourly. In one study CVCs were used to deliver IV fluids and in the other two studies peripheral catheters were used. Collectively the studies reported a number of outcomes including mortality, proven and suspected sepsis, phlebitis, thrombosis and suspected NEC. There was no difference between the use or non-use of filters on the outcome measures. However, the authors commented that all of the studies lacked the required power to confidently make a recommendation about in-line filter use. In a subsequent randomised controlled study of infants with CVCs (umbilical, peripheral, percutaneous and tunnelled), clear fluids and lipid emulsions were administered with a filter on 228 occasions and without a filter on 214 occasions (Van den Hoogen, 2006). In the filter group the lines were changed 96 hourly and non-filter group 24 hourly. There were no differences in the clinical characteristics of the infants, CVC use or catheter days. Sepsis rates were similar in the 2 groups: filter group - 16.2% infants (24/1000 catheter days) and no filter group - 16.4% infants (28/1000 catheter days).

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<td>In-line filters reduce the incidence of particulate infusion.</td>
<td>D</td>
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<tr>
<td>In lines changed 24 hourly, the use of in-line filters has no effect on BSI.</td>
<td>A</td>
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</table>
Catheter manipulations and connectors

Catheter manipulation includes the number of times the line system is interrupted for changing fluids and for sampling and therefore also includes studies on hubs and needleless connectors. Needleless connectors were introduced to reduce the incidence of needlestick injury; because they maintain a closed system, a secondary effect of reducing CVC colonisation has been investigated. The catheter hub is defined as the female end of a central venous catheter to which the tubing of an infusion connects (Salzman, 1997).

Colonisation of the catheter hub is considered to be one of the risk factors contributing to the increasing infection rate associated with CVC use (Segura, 1996). Organisms colonizing the hub can gain access to the bloodstream through migration along the internal surface of the catheter. When increasing the frequency that the catheter, and in particular the hub is manipulated, the likelihood of introducing pathogenic microorganisms also increases. Salzman et al (1993) studied catheter hub contamination and its relation to sepsis in a NICU population. Catheter hubs were prospectively cultured three times a week in all infants who had long-term CVCs. A total of 113 catheters were placed in 88 infants; contamination of the catheter hub was common with 402 (45%) of the 900 hub cultures taken showing organisms, these being predominately coagulase negative Staphylococcus. Contamination of the catheter hub was often transient, with subsequent cultures showing no growth or a different microorganism. Overall there were 35 cases of sepsis of which 28 (80%) were identified as being catheter related. In 36% (10/28) of these episodes the same organism was cultured from the hub 1 or 2 days prior to the peripheral blood culture being taken.

In a prospective cohort study, Mathieu et al (2001a) identified major risk factors for catheter related BSI: of the patient factors, infant weight <1000 grams at time of catheter insertion was an independent risk factor for BSI (OR 5.13, 95% CI 2.1-12.5, p<0.001) and of the catheter characteristics, catheter hub colonisation was the strongest risk factor for BSI (OR 44.1, 05% CI 14.5-134.4, p<0.001). In a sub-group of this cohort, Mahieu et al (2001b) considered the relationship between catheter manipulations and hub colonisation and the subsequent risk of bloodstream infection. Over a 12-month period 223 neonates had 357 CVCs inserted; 10960 catheter manipulations occurred. The median number of manipulations per catheter was greatest in infants <1000 grams (p=0.001). There were 17 episodes of catheter related BSI giving an incidence density of 4.9 infections/1000 catheter days. Catheterisation duration (OR 1.04, 95% CI 0.94-1.14) and the cumulative number of catheter manipulations (OR 1, 95% CI 0.97-1.03) were not independent risk factors for BSI. Hub colonisation was associated with blood drawing through the central line and the number of TPN line changes (OR 1.3, 95% CI 1.1-1.5, p=0.005 and OR 1.3, 95% CI 1.2-1.5, p<0.001 respectively) whereas the number of heparin flushes was protective (OR 0.8, 95% CI 0.7-0.9, p= 0.005).
Kellerman et al (1996) studied 243 CVCs that were placed in 182 children who were receiving home health care. Over the course of the study period the total number of bloodstream infections rose from 0.8 to 1.4 /1000 catheter days (RR 1.8; 95% CI 1.12-2.89, p=0.02). The rise coincided with the introduction of needleless access devices. As this change in rate was detected in the home care setting, the investigators thought it likely that discrepancies and misunderstandings in teaching methods and standards of needleless device management may have led to the increase in infection rate. Other studies have shown no change or a decrease in colonisation rates. Two studies have found that using a needleless access device reduced the colonisation rate of CVCs (Bouza, 2003, Casey, 2003). Bouza et al (2003) recruited 352 adult patients who were undergoing heart surgery. One hundred and seventy-eight patients received the needleless connector and 174 patients used conventional open systems. Catheter hub colonisation was 4.3% in the needleless device as opposed to 14.2% in the control group. The colonisation of catheter tips was also reduced in the closed access device (10.9% vs 17.2%). Episodes of bloodstream infection were 3.4% and 6.3% respectively. They concluded that the needleless closed connector offered considerable protection from catheter hub and tip colonisation.

Casey et al (2003) compared colonisation rates of needleless connectors with standard Luer caps and also the most efficient way to disinfect connectors. Seventy-seven adult patients who were undergoing cardiac surgery were recruited into the study; 38 patients used the needleless access device and 39 the Luer caps. Five hundred and eighty devices were analysed. In addition, each patient was randomly allocated either chlorhexidine gluconate 0.5% in industrial methylated spirit BP 70% spray, isopropyl alcohol 70% spray or 10% aqueous povidone-iodine for catheter insertion skin preparation and disinfection of all intravenous connections. Entry ports with the needleless access device had a lower colonisation rate compared with those that had standard Luer caps (6.6% vs 18%, p<0.0001). When using a needleless connector, disinfection with either chlorhexidine or povidone-iodine showed a significantly reduced colonisation rate than when compared with isopropyl alcohol (p<0.0001). When using the standard Luer caps, there was no difference detected among the 3 different methods of disinfection. None of the patients who were recruited into this trial showed any clinical signs of a catheter related infection. Whilst this study demonstrates less colonisation with needleless connectors, others have shown no microbiological disadvantage or advantage either (Seymour, 2000; Luebke, 1998). Seymour et al (2000) compared needleless connectors with conventional 3-way taps that were connected to the hubs of CVCs. Seventy-seven adult surgical patients were recruited to the study. One hundred and seventy three needleless devices were measured against 132 standard 3-way taps. Prior to manipulation the needleless devices were swabbed with 70% isopropanol and the standard caps sprayed with 70% isopropanol; new caps were placed on the 3-way taps after manipulation. There was no significant difference in the numbers of colonised access ports between the two groups (17.1% of needleless access devices vs 14.4% of 3-way taps, p>0.1).
Several studies in adults have examined the effect of specific hub protection devices (León, 2003; Lucet, 2000). In the study by León et al (2003) adult patients requiring the insertion of a non-tunneled CVC for ≥6 days were randomized at the time of catheter insertion to receive catheters with standard Luer-lock connector (control group, n = 114) or catheters with the new hub model (an antiseptic chamber filled with 3% iodinated alcohol; n = 116). Colonisation of catheter hubs was higher in the control group (14.4% vs. 4.3%, p < 0.001) as was BSI (7% vs. 1.7%, RR 4.14, 95% CI 0.8–19, p=0.049). Lucet et al (2000) looked at colonisation of CVCs and CVC hubs when hub protection boxes or needleless connectors were in situ. Group 1 (37 patients with 216 hubs from 67 catheters) were randomised to use the hub protection box; this was impregnated twice daily with antiseptics. Group 2 (40 patients with 235 hubs from 70 catheters) were randomised to the needleless connectors. The hubs were changed every 3 days, insertion and maintenance followed the CDC recommendations. In group 1, 7% (15/216) of catheter hubs were colonised and in group 2, 9% (21/235) were colonised (p=0.36). Overall 30 catheters were colonised; 19% in group 1 and 24% in group 2 (13/67 and 17/70 respectively, p= 0.5). Two catheter-related bacteraemias were found, one in each group. The authors concluded that catheter hubs are frequently colonised but are rarely responsible for actual catheter colonisation or infection.

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<th>Key points</th>
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<tr>
<td>Increasing the frequency of catheter hub manipulations does not increase the likelihood of introducing pathogenic organisms.</td>
<td>B</td>
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<tr>
<td>Blood sampling through a central venous catheter is a risk factor for hub colonisation.</td>
<td>B</td>
</tr>
<tr>
<td>Catheter hub colonisation infrequently leads to bloodstream infection.</td>
<td>A</td>
</tr>
<tr>
<td>Needleless connectors are more efficiently decontaminated than standard Luer caps</td>
<td>A</td>
</tr>
<tr>
<td>Entry ports with needleless connectors attached have lower colonisation rates.</td>
<td>A</td>
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</table>
Dressing type and frequency of change

The purpose of a dressing is to protect the insertion site and to assist in securing the catheter. It also has a function to facilitate the visualisation of the site for signs of infection. Dressings that are used for central venous catheter sites include: transparent, gauze, occlusive and hydrocolloids. There are few published data on type of dressing to secure CVC in newborn infants.

Transparent dressings are permeable to water vapour and impermeable to micro-organisms, they reliably secure a CVC and permit continuous visual inspection of the catheter site. Sterile gauze secured with tape is an absorbent dressing but is not waterproof. It also restricts visualisation of the CVC entry site. An occlusive dressing is an air and water tight dressing. It is generally made with a waxy coating providing a total seal and as a result does not have the absorbent properties of sterile gauze pads. Hydrocolloids are a type of dressing containing gel-forming agents. In many products these are combined with elastomers and adhesives and applied to a carrier. This is usually a polyurethane foam or film and forms an absorbent, self adhesive, waterproof wafer. In the presence of wound exudate, hydrocolloids absorb liquid and form a gel.

A prospective randomised controlled trial involving children and neonates (0-18 yrs) compared transparent polyurethane dressings on catheter sites with chlorhexidine gluconate impregnated sponges followed by a covering of transparent polyurethane dressing (Levy, 2005). One hundred and forty five children were included, 71 in the transparent dressing group and 74 in the sponge dressing group. CVC colonisation was significantly reduced among the children in the chlorhexidine group (RR 0.61, 95% CI 0.3716-1.023, p=0.04) but with no difference in catheter related BSI (4.2% in the transparent dressing group compared with 5.4% in the chlorhexidine sponge group). No significant adverse effects were associated with the use of the device in the study population but 5.4% of participants encountered dermatitis with the chlorhexidine patch; these patients were neonates.

Trials comparing gauze and tape with transparent polyurethane dressings are reported in a Cochrane Collaboration review (Gillies, 2008). In this review of 6 studies with 331 subjects (age>2 years), there was insufficient data to confirm whether one of the dressings was associated with any more risk of infection than the other.

A randomized controlled trial in 204 adult patients compared the use of transparent polyurethane and hydrocolloid dressings with CVCs; cultures were obtained from 125 skin insertion sites, 141 catheter hubs, 128 catheter tips and blood samples from 132 patients (Nikoletti, 1999). Results showed that the group of patients using hydrocolloid dressings had an increased risk of catheter colonisation compared to the polyurethane group (p=0.048). However, 38.3% of the catheters were excluded from
the results of this trial due to missing data, making interpretation of the findings difficult.

The optimal frequency for changing dressing has not been investigated.

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<tr>
<td>There are insufficient data to indicate type of dressing and risk of infection.</td>
<td>A</td>
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</table>
Total Parenteral Nutrition

Several studies have indicated that the use of TPN is an independent risk factor for catheter related bloodstream infections (Holmes, 2008; Perlman, 2007; Kawagoe, 2001; Mahieu, 2001a; Yeung, 1998). Holmes (2008) investigated BSI in 1367 admissions to a neonatal unit; in these infants there were 124 episodes of BSI. On univariate regression the highest incidence rate ratios were found for TPN (16.5), birthweight <700 g (10.6), gestational age <26 weeks (6.4) and CVC (5.8). Multiple regression analysis identified only TPN, whether administered centrally or peripherally (IRR: 14.2; 95% CI 8.8-22.9; p< 0.001), and gestational age <26 weeks (IRR: 2.5; 95% CI 1.7-3.8; p< 0.001) as significant independent risk factors. Perlman (2007) as part of a larger study looking at antiseptic hand hygiene products, examined risk factors for late-onset bloodstream infections within two neonatal units. Of the 2935 infants included in the study, 1132 had at least 1 CVC inserted during their stay; 16% (n=182) of these infants developed a bloodstream infection. In the logistic regression model of risk factors, the neonates with a CVC who received TPN were 4.7 times more likely to have a bloodstream infection than those without TPN (95% CI 2.22-9.87). In a prospective cohort study of 1544 eligible infants admitted to a neonatal unit, Kawagoe (2001) identified 10 risk factors associated with nosocomial infection. Of these, 5 were independent (prolonged rupture of membranes, maternal disease, mechanical ventilation, CVC use and TPN) with TPN showing the strongest association (HR 4.04 [95% CI 2.61-6.25]).

In considering the effect of each component of TPN (dextrose, amino acids and electrolytes solution and lipid emulsion) on BSI, the administration of lipids is an important risk factor in the development of sepsis (Avila-Figueroa, 1998; Freeman, 1990). In the study by Avila-Figueroa (1998), of the 590 consecutively admitted newborns with birth weight<1500 grams, 83 cases (14.1%) of BSI were identified. A sample of 74 of these infants were matched on birth weight and length of stay with 2 control infants; data were missing or controls not found for 9 infants. When adjusting for indicators of severity of illness, two procedures were independently associated with subsequent risk of coagulase negative Staphylococcal bacteraemia at any time during hospitalisation: IV lipids, OR = 9.4 [95% CI 1.2 - 74.2] and any surgical or percutaneously placed CVC, OR = 2.0 (95% CI 1.1 - 3.9). The authors conclude that exposure to lipids is the largest risk factor for coagulase negative Staphylococcus (CoNS) bacteraemia (OR 9.4). In the earlier case-control study by Freeman (1990) investigating the risk factors associated with CoNS, patients with CoNS were 5.8 times more likely to have received lipid infusion (CI 4.1-8.3) and 3.5 times more likely to have had a PICC in-situ (CI 1.4-8.3).

Two prospective randomised studies have reported contamination rates associated with changing TPN administration sets at 24, 48, and 72 hours in newborn infants. Matlow et al (1999) randomly assigned 1189
infants to 72 or 24 hour intravenous tubing set changes in a 3:1 ratio. In the initial randomisation there were no differences in the demographic characteristics of the 2 groups but when considering only those infants whose infusate was sampled, [54.1% (n=691/1278) of those randomised], the infants in the 72 hour group were smaller (birth weight 1958 grams vs 2223 grams, p=0.003) and received TPN for longer (17.06 days vs 14.67 days, p=0.001) than those infants in the 24 hour group. Microbial contamination rates were significantly higher in the 72 hour group than the 24 hour group for lipid infusions (39/1101 sets [3.54%] vs 15/1112 sets [1.35%]; p=0.001) but not for amino acid infusions (1.10% sets [12/1093] vs 0.36% sets [4/1103]; p=0.076). When controlling for birth weight, gestational age, and type of venous access, only the tubing change interval was significantly associated with lipid set contaminations (OR, 2.69; p=0.001). Fox et al (1999) randomised 166 infants to have TPN infusate changed either every 24 hours or every 48 hours; samples of the infusate were cultured from 148 of these infants (97 infants in the 24 hour group and 51 infants in the 48 hour group). There were no significant differences in bacterial contamination for either amino acid solution or lipid emulsion from the 2 groups. Fungal contamination of the lipid emulsion was significantly greater in the 24 hour group compared to the 48 hour group (p=0.01).

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<tr>
<td>The use of TPN and in particular lipid emulsion predisposes an infant to the risk of catheter related BSI.</td>
<td>B</td>
</tr>
<tr>
<td>There is no difference in infusate bacterial contamination rate in lines changed 24 hourly or 48 hourly.</td>
<td>A</td>
</tr>
<tr>
<td>There is no difference in amino acid contamination rate in lines changed 24 hourly or 72 hourly but lipid emulsion is more likely to become contaminated by 72 hours.</td>
<td>A</td>
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</table>
Staff numbers, knowledge, skill and compliance

Understaffing and the use of temporary staff are significant risk factors for infectious outbreaks (Cimiotti, 2006; Alonso-Echanove, 2003; Harbarth, 1999; Fridkin, 1996). Cimiotti et al (2006) considered the association between registered nurse staffing numbers, use of temporary/pool nurses and nosocomial bloodstream infections in 2 neonatal intensive care units over a 2-year period. In one of the units, an increase in the number of permanent staff was significantly associated with a decrease in bloodstream infection (hazard ratio 0.21; 95% CI 0.06-0.79). The authors attributed these findings to lapses in aseptic technique by those unfamiliar with the routine care policies of the unit. In another study, neonatal unit overcrowding and understaffing also resulted in less optimal infection-control measures. Here, adherence to hand-hygiene practices before CVC contact was only 25% during the workload peak, but later increased to 70% when occupancy and staffing levels were appropriate for unit size and workload (Harbarth, 1999).

The belief that catheter management by staff unfamiliar with processes may contribute to sepsis is further supported by work on the introduction of dedicated catheter teams (Brunelle, 2003; Golombek, 2002; Meier, 1998). Golombek (2002) introduced “proactive” management of PICCs in their extremely low birth weight population with the establishment of a specific PICC maintenance team who were involved in the daily monitoring of central lines and authority for the removal or replacement of catheters. This study of 97 infants, consisted of a prospective collection and analysis of catheter-related sepsis data over a 15-month period. The introduction of the PICC team showed a reduction of 17.9% in bloodstream infections (from 15.8/1000 catheter days to 5.1/1000 catheter days, p<0.05). The authors concluded that this was achieved through the optimisation of aseptic technique used for catheter placements and dressing changes. However Abi-Said et al (1999) report a retrospective cohort study on the risk of CVC infection if ward nurses or a dedicated CVC team carries out the CVC dressings. They found no difference in catheter related infection or catheter site infection between the 2 groups and concluded that adherence to strict aseptic procedures during catheter insertion and subsequent changes of dressings may lead to a decrease in BSI irrespective of staff group carrying out the procedures.

The effect of knowledge and compliance with processes is reflected in several other studies. Pre and post observational studies with different staff groups and educational packages specific to CVC insertion and management have shown a positive effect on the risk of infection associated with vascular catheters (Warren, 2004; Coopersmith, 2004; Coopersmith, 2002; Sherrertz, 2000). In these studies, the reported baseline catheter related bacteraemia ranged from 3.4 to 10.8 infections/1000 catheter days; following the education packages it fell to between 2.8
and 5.5 infections/1000 catheter days. This decrease was significant in all but one study where the baseline was lowest of all reported at 3.4 infections/1000 catheter days and fell to 2.8/1000 catheter days. However whether the educational programme or better compliance with evidence based guidelines brought about the decrease is unknown.

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<td>Familiarity and compliance with local procedures and protocols reduces nosocomial infections.</td>
<td>B</td>
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<tr>
<td>Staff knowledgeable in the correct insertion and maintenance techniques reduces the incidence of bloodstream infection.</td>
<td>B</td>
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</table>
**Administration of prophylactic antibiotics**

Routine use of low dose vancomycin prophylaxis has been shown to reduce the incidence of sepsis in preterm infants with percutaneous central venous catheters. In the study by Ocete et al (1998), bacteraemia in infants with a CVC were examined over 2 time points. During the first period, the control group (n=61) received no antibiotics through the CVC; in the second period, prophylactic vancomycin (25mg/ml) was infused via the central line. The rate of catheter related bacteraemia was significantly less in the intervention group: CoNS (control 34% vs intervention 22%, p<0.05); other Gram positive organisms (control 43% vs intervention 31%, p<0.05). There were no significant differences between the two groups in terms of Gram negative or fungal infections.

A review by Jardine (2007) considered the effect of prophylactic antibiotics on mortality and morbidity in neonates with central venous catheters. Three randomised controlled trials with 271 infants were included; 2 studies using vancomycin and 1 using amoxicillin. Overall there was no significant difference in mortality (n=9/137 intervention group vs 13/134 control group; typical RR 0.68, 95% CI 0.31, 1.51). Proven or suspected bacterial septicaemia occurred in 9% (n=9/102) of the intervention group vs 22% (n=22/99) of the control group (typical RR 0.40, 95% CI 0.20, 0.78, typical RD -0.13, NNT 7.5). The authors conclude that there is some evidence to suggest that prophylactic systemic antibiotics in neonates with CVCs can reduce the rates of septicaemia. However, given that there was no significant reduction in overall mortality and outcome data on long-term neurodevelopment, the importance of using prophylactic antibiotic is questioned. Furthermore, there is a lack of information of such an approach on the emergence of resistant organisms which are becoming increasingly prevalent (Siegel, 2006).

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<tr>
<td>CoNS is the most common organism responsible for nosocomial bacteraemia within the neonatal population</td>
<td>B</td>
</tr>
<tr>
<td>Vancomycin has been found to decrease the rate of nosocomial infections but not necessarily mortality rates in the neonatal population</td>
<td>B</td>
</tr>
<tr>
<td>There is a risk of vancomycin resistant microorganisms emerging.</td>
<td>C</td>
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Therapeutic treatment versus removal of line

The need to remove a CVC in the event of a BSI is uncertain. Oppenheim (2000) reviewed the published data on management of CVC related infection in children and adults and concluded that the evidence was poor; however it was suggested “that for the majority of infections it is safe to attempt to conserve the catheter” (p 29). A number of authors have attempted to address the issue of CVC removal versus treatment without removal in the newborn population (Nazemi, 2003; Karlowicz, 2002; Benjamin, 2001; Karlowicz, 2000). In these retrospective cohort studies the decision to remove or maintain the catheter is dependant on the organism causing the BSI and the effectiveness of the antibiotic treatment.

Benjamin (2001) evaluated the consequences of CVC retention in bacteraemic low birth weight infants. Sterilisation of catheter was attempted in 128 episodes of bacteraemia; of these 42% (n=54/128) of lines were retained without complications. Where Staphylococcus aureus or non-enteric Gram negative organisms were present, complicated bacteraemia developed in 93% (n=14/15; including 5 deaths) of episodes (p=0.04); where enteric Gram negative or Enterococcus organisms were present, complicated bacteraemia developed in 63%(n=19/40; including 1 death) of episodes (p=0.07) and where CoNS was present, complicated bacteraemia developed in 49% (n=35/72) of episodes. From this data the authors recommend that CVCs are removed immediately when Staphylococcus aureus or non-enteric Gram negative organisms are detected. As the success rate in the presence of enteric Gram negative or Enterococcus organisms was <50%, the authors consider that the catheters should probably be removed. In respect to CoNS, if there is >1 positive blood culture, then the line should be removed.

The papers by Karlowicz et al (2000, 2002) report the outcome of Candida bacteraemia and CoNS bacteraemia when CVCs are either removed within 3 days (ER-CVC) of a positive culture being obtained or left in-situ (LR-CVC). During a 5 year period 2952 infants were admitted to the NNU; 50 infants had ER-CVC and 54 infants LR-CVC. In infants who survived there was a significantly shorter duration of candidaemia in the ER-CVC as compared to the LR-CVC (median 3 vs 6 days [range 1-14 vs 1-24 days] respectively; p=0.0002) although there were no differences in length of treatment or stay. However mortality attributable to candidaemia was significantly more likely in the LR-CVC than the ER-CVC infants (19% vs 2%; OR 11.1, 95% CI 1.4-90.6, p=0.008 respectively). From the same original cohort of infants, there were 119 episodes of CoNS; 56 in the ER-CVC group and 63 in the LR-CVC group. There were no differences in length of stay, recurrence of bacteraemia or mortality between the 2 groups. However CoNS bacteraemia lasting >3 days was significantly more likely in the LR-CVC group than the ER-CVC group (43% vs 13%; RR 3.4, 95% CI 1.6-7.2, p=0.0003 respectively).
<table>
<thead>
<tr>
<th>Key points</th>
<th>Grade of evidence</th>
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<tr>
<td>There is a high mortality rate associated with Candida bacteraemia and continuing use of a CVC</td>
<td>B</td>
</tr>
<tr>
<td>Irrespective of organism, if there is continuing bacteraemia (&gt;1 positive blood culture) whilst on treatment, it is unlikely that the line will be sterilised.</td>
<td>B</td>
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Conclusion

Nosocomial infection, and in particular blood stream infection, contributes significantly to the morbidity and mortality seen in newborn infants in the NICU. Various maternal and infant risk factors are associated with BSI with the most important being: extreme immaturity and low birth weight, use of TPN, use of central vascular devices and ventilatory support. Quality improvement initiatives suggest that ‘bundles of care’ result in significant and sustained decreases in catheter related BSI (Costello, 2008; Institute of Healthcare Improvement, 2006; Pronovost, 2006). A ‘bundle of care’ is a set of interventions that are individually effective but when applied together result in a substantially better outcome; each is based on evidence which is unequivocal and accepted. Implementing the bundle requires compliance with each step and this being documented by the use of a checklist.

It is however difficult to make firm recommendations for a ‘bundle of care’ about clinical practice in the NICU to reduce catheter related BSI because of the methodological and clinical heterogeneity in reported studies. The use of retrospective cohort studies where individual clinician judgement guides practice, the variable case definitions of BSI which are adopted, the way in which rates of infection are reported and the range of neonate/infant investigated diminishes the strength and acceptance of the available evidence. Given these limitations the following strategies are suggested: educational programmes and competency assessment on insertion and maintenance of catheters; appropriate hand hygiene and use of aseptic technique for catheter insertion and manipulation and daily assessment of infant nutritional state and catheter need. In addition continuous monitoring using an unambiguous standardised case-definition of catheter related BSI will aid in the surveillance of CVC related infection (Modi, 2008).
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