Article:
Vasudevan, Chakrapani, Oddie, Sam J and McGuire, William (2016) Early removal versus expectant management of central venous catheters in neonates with bloodstream infection. Cochrane Database of Systematic Reviews. CD008436. ISSN: 1469-493X

https://doi.org/10.1002/14651858.CD008436.pub3

Cochrane Library

Cochrane Database of Systematic Reviews

Early removal versus expectant management of central venous catheters in neonates with bloodstream infection (Review)

Vasudevan C, Oddie SJ, McGuire W

Vasudevan C, Oddie SJ, McGuire W.
Early removal versus expectant management of central venous catheters in neonates with bloodstream infection.
Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD008436.
DOI: 10.1002/14651858.CD008436.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Early removal versus expectant management of central venous catheters in neonates with bloodstream infection

Chakrapani Vasudevan[1], Sam J Oddie[2], William McGuire[3]

[1]University of Leeds, Leeds, UK. [2]Bradford Royal Infirmary, Bradford, UK. [3]Hull York Medical School & Centre for Reviews and Dissemination, University of York, York, UK

Contact address: William McGuire, Hull York Medical School & Centre for Reviews and Dissemination, University of York, York, Y010 5DD, UK. William.McGuire@hyms.ac.uk.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2016.
Review content assessed as up-to-date: 11 November 2015.

Citation: Vasudevan C, Oddie SJ, McGuire W. Early removal versus expectant management of central venous catheters in neonates with bloodstream infection. *Cochrane Database of Systematic Reviews* 2016, Issue 4. Art. No.: CD008436. DOI: 10.1002/14651858.CD008436.pub3.

ABSTRACT

Background

Uncertainty exists regarding the management of newborn infants with a bloodstream infection and a central venous catheter in place. The central venous catheter may act as a nidus for infecting organisms and observational studies have suggested that early removal of the catheter is associated with a lower incidence of persistent or complicated infection. However, since central venous catheters provide secure vascular access to deliver nutrition and medications, the possible harms of early removal versus expectant management also need to be considered.

Objectives

To determine the effect of early removal versus expectant management of central venous catheters on morbidity and mortality in newborn infants with bloodstream infections.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 11), MEDLINE (1966 to October 2015), EMBASE (1980 to October 2015), CINAHL (1982 to October 2015), conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised controlled trials that compared early removal versus expectant management of central venous catheters in neonates with bloodstream infections.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Main results

We did not identify any eligible randomised controlled trials.

Authors' conclusions

There are no trial data to guide practice regarding early removal versus expectant management of central venous catheters in newborn infants with bloodstream infections. A simple and pragmatic randomised controlled trial is needed to resolve the uncertainty about optimal management in this common and important clinical scenario.

PLAIN LANGUAGE SUMMARY

Early removal versus expectant management of central venous catheters in newborn infants with bloodstream infection

Review question: In newborn infants with a bloodstream infection who have a central venous catheter in place, does early removal of the catheter reduce the risk of complications, including death and long-term disability?

Background: Infection in the bloodstream is a frequent and harmful complication for newborn infants who have a central venous catheter (a cannula that extends several centimetres into the infant's blood vessels). Bloodstream infection may cause death and disability. When infants develop a bloodstream infection, clinicians need to decide whether or not to remove the catheter. While the catheter may provide a secure route for delivering drugs and nutrition, it may also be a place for infecting organisms to grow and cause long-term or more severe infection.

Study characteristics/key results: We did not find any randomised controlled trials that addressed this question.

Conclusions: There are no trial data available to help clinicians to address this common clinical dilemma. Due to the potential for benefit and harm, such a trial is warranted.

BACKGROUND

Description of the condition

Bloodstream infection is the most common serious complication associated with the use of central venous catheters (CVCs) including peripherally inserted percutaneous CVCs, umbilical catheters and subcutaneously tunnelled CVCs in newborn infants. Between 5% to 30% of neonates with a CVC *in situ* develop a bloodstream infection (Mahieu 2001; Cartwright 2004; van der Zwet 2005; Garland 2008; Hoang 2008; Ohki 2008; Olsen 2009; O'Grady 2011). The reported incidence varies with the case definition and with the demographic characteristics of the populations studied. The incidence of bloodstream infection is higher in very preterm and very low birth weight (VLBW) infants, reflecting their level and duration of exposure to invasive procedures and intensive care (Makhoul 2002; Stoll 2002; Stoll 2003; Shane 2013). Nosocomial (acquired in hospital) bloodstream infection is more strongly associated with the use of peripherally inserted percutaneous CVCs and subcutaneously tunnelled catheters than with the use of umbilical catheters even after accounting for infant characteristics and illness severity (Chien 2002). However, it is not certain to what extent CVC use is an independent risk factor for a bloodstream infection or whether an association exists because infants who are smaller, less mature, sicker and receiving more intensive and invasive support are also more likely to have a CVC *in situ*. A Cochrane review of randomised controlled trials of peripherally inserted percutaneous CVCs versus peripheral cannulae for delivering parenteral nutrition to neonates did not find any evidence of an effect on invasive infection rates (Ainsworth 2007).

Coagulase-negative staphylococci cause about half of all CVC-related bloodstream infections in neonates (Isaacs 2003). Other pathogens include Gram-negative bacilli (mainly enteric bacilli), Gram-positive cocci (*Staphylococcus aureus*, enterococci) and fungi (predominantly *Candida* species) (Stoll 2002; Isaacs 2004; Gordon 2006). Neonates, particularly VLBW infants, with bloodstream infections have a higher risk of mortality and a range of important morbidities, including the need for intensive care and mechanical ventilation, bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity and prolonged hospitalisation (Stoll 2002; Chapman 2003; Adams-Chapman 2006; Bassler 2009). These higher rates of mortality and serious morbidity are usually associated with Gram-negative enteric bacillus or fungal infection. Coagulase-negative staphylococcal infection, although common, is associated with a more benign clinical course. Meningitis and other deep-seated involvement is rare and attributable

mortality is much lower than with infection from other organisms. However, even 'low-grade' coagulase-negative staphylococcal bloodstream infections may generate inflammatory cascades associated with both acute morbidity (e.g. metabolic, respiratory or thermal instability, thrombocytopenia) and long-term white matter and other brain damage that may result in neurodevelopmental disability (Stoll 2004; Khashu 2006).

Description of the intervention

A clinical management dilemma exists when a neonate with a CVC *in situ* develops signs consistent with a bloodstream infection. There is substantial uncertainty among clinicians about whether early CVC removal versus retention and expectant management is the better option (Karlowicz 2002; Rubin 2002). The CVC provides secure vascular access that allows continued provision of fluids, nutrition and medications, including anti-infective agents. If the CVC is removed then an alternative route for drug and fluid administration, either a peripheral cannula or a new CVC, may be required. However, the CVC, or an associated thrombus, may act as a harbour for micro-organisms thus decreasing the effectiveness of anti-infective agents and perpetuating the invasive infection, inflammatory cascades and end-organ damage (Thornburg 2008). The decision whether to retain or to remove the CVC depends on the perceived balance between these potential benefits and risks and may be affected by additional factors including the infant's clinical status, the level of need for continued vascular access and the ease with which replacement vascular access can be secured.

Surveys of practice suggest that clinicians generally elect to retain an existing CVC*in situ* in neonates with 'suspected' bloodstream infection; that is, a possible infection treated empirically with antibiotics but not yet confirmed by microbiological culture from blood (Benjamin 2001; Rubin 2002). Furthermore, many clinicians opt for expectant CVC management in neonates and young infants with a confirmed bloodstream infection due to coagulase-negative staphylococci. However, some clinicians elect to remove the CVC at an early stage whenever infection is suspected because the early clinical features of a bloodstream infection due to Gram-negative bacilli or fungi can be similar to those due to a coagulase-negative staphylococcal infection (Benjamin 2000).

Several additional factors need to be considered when deciding whether to remove or retain a CVC in neonates with bloodstream infections. Clinical signs of bloodstream infections in neonates, especially very preterm and VLBW infants, are generally non-specific. Similarly, laboratory measures (biomarkers) have low predictive value for bloodstream infections (Fowlie 1998; Malik 2003). Most neonates who have a suspected bloodstream infection and who undergo 'sepsis evaluation' do not have the infection confirmed subsequently (Buttery 2002). Since clinical signs and laboratory markers are generally unreliable predictors of a true bloodstream infection, a policy of early CVC removal when the infection is suspected would inevitably result in many unnecessary interventions. Even in situations where an infection has been confirmed by microbiological culture from blood this may represent contamination from skin commensals, particularly coagulase-negative staphylococci (Isaacs 2003). Conversely, culture of blood samples that are of insufficient volume may give falsely reassuring negative results (Jawaheer 1997; Connell 2007).

How the intervention might work

Early removal of a CVC in neonates with nosocomial bloodstream infections may hasten microbiological clearance and thereby reduce the incidence of end-organ involvement and damage including that due to inflammatory cascades (Chapman 2003). Observational studies have provided some evidence that prompt CVC removal following a confirmed bloodstream infection due to *Staphylococcus aureus*, enterococci, Gram-negative bacilli or *Candida* species reduces the likelihood of persistent or complicated bacteraemia or fungaemia with end-organ involvement (Eppes 1989; Karlowicz 2000; Benjamin 2001; Nazemi 2003). Data from retrospective cohort studies also suggest that early CVC removal in neonates with a confirmed coagulase-negative staphylococcal infection is associated with a reduced risk of persistent bacteraemia and end-organ involvement and that infants with persistent coagulase-negative staphylococcal bacteraemia only achieve microbiological cure when the CVC is removed (Benjamin 2001; Karlowicz 2002). However, these observational studies need to be interpreted cautiously since their findings may be due to confounding factors such as clinicians electing to delay CVC removal in smaller, less mature or sicker infants.

Why it is important to do this review

Uncertainty exists about the balance between the putative benefits and harms associated with early removal versus expectant management of CVC in neonates with bloodstream infections. This intervention has the potential to affect several major outcomes for this population. Observational data may be subject to various biases that limit validity and utility to inform practice, therefore an attempt to detect, appraise and synthesise evidence from randomised controlled trials is needed.

Related Cochrane reviews

Other Cochrane reviews assess the effects of strategies to prevent CVC-related infection in newborn infants including antimicrobial impregnation or antibiotic locks (Balain 2015; Taylor 2015). Two other reviews will evaluate the evidence for short- versus longer-term CVC use for newborn infants (Gordon 2016a; Gordon 2016b).

OBJECTIVES

To determine the effect of early removal versus expectant management of central venous catheters on morbidity and mortality in newborn infants with bloodstream infections.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials including cluster-randomised trials.

Types of participants

Newborn infants (including preterm infants up to 44 weeks postmenstrual age) with suspected or confirmed bloodstream infections who have a CVC *in situ*.

- 'Suspected' bloodstream infection: any clinical or laboratory (or both) criteria that trigger clinicians to undertake a 'sepsis' evaluation that includes a blood culture.
- 'Confirmed' bloodstream infection: determined by microbiological culture from blood. Blood samples may have been obtained from peripheral sites or from an indwelling CVC.

Types of interventions

- Interventions: removal of CVC within 24 hours of (i) evaluation of a suspected infection or (ii) microbiological confirmation of a bloodstream infection. Options for maintaining nutrient and drug delivery may have included some or all of: replacement CVC, peripheral (short) catheter, subcutaneous infusion (for fluids), intramuscular injection (for medications), enteral administration.
- Control: expectant management; intended retention of CVC during (i) evaluation and treatment of a suspected bloodstream infection or (ii) at least 24 hours after microbiological confirmation of a bloodstream infection. Indications for later selective catheter removal may be determined by primary investigators.

Since infants may experience more than one episode of a bloodstream infection, eligible trials should have enrolled participants on one occasion only, with management of subsequent infections determined by clinician preference.

Types of outcome measures

Primary outcomes

- Mortality from study entry (due to all causes):
  - before 28 days after birth;
  - up to 44 weeks postmenstrual age; until one year corrected for preterm gestation;
  - at latest follow-up assessment.
- Neurodevelopmental outcomes assessed after 12 months postmenstrual age using validated tools: neurological evaluations, developmental scores and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient > two standard deviations below population mean), blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).

Secondary outcomes

- Persistent or recurrent infection; proportion of neonates with:
  - positive blood cultures > 48 hours after starting antimicrobial therapy;
  - positive blood cultures < one week after stopping antimicrobial therapy;
  - deep-seated infection (meningitis, osteomyelitis, endocarditis, peritonitis) diagnosed > 48 hours after starting antimicrobial therapy and < one week after stopping antimicrobial therapy.
- Other morbidity developing after enrolment in trial:
  - receipt of mechanical ventilation;
  - duration of mechanical ventilation (days);
  - receipt of inotrope support;
  - receipt of blood product transfusion (erythrocytes, platelets, coagulation factors) reported either as a dichotomous (any transfusion or none) or continuous outcome (number of transfusions the infants received) as defined by primary investigators;
  - incidence of bronchopulmonary dysplasia (oxygen supplementation at 36 weeks postmenstrual age);
  - incidence of necrotising enterocolitis (Bell stage 2 or 3);
  - incidence of retinopathy of prematurity: a) any stage; b) requiring treatment;
  - duration of intensive care unit or hospital admission (days).
- Parenteral nutrient input from trial enrolment until establishment of full enteral feeding:
  - average daily input of calories (kcal/kg/day) and protein (g/kg/day);

- average daily proportion of prescribed calories and protein that were actually delivered.

- Number of cannulae/catheters per infant during trial period.
- Growth from trial enrolment until establishment of full enteral feeding:
  - weight gain (g/day or g/kg/day);
  - linear growth (mm/week);
  - head growth (mm/week);
  - skinfold thickness growth (mm/week).

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 11), MEDLINE (1966 to October 2015), EMBASE (1980 to October 2015) and CINAHL (1982 to October 2015) using a combination of the following text words and MeSH terms:

[Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR infan* OR neonat*] AND [Catheters, Indwelling/ adverse effects OR Catheterization, Central Venous OR central near3 cathet* OR central near3 cannul* OR central near3 line OR CVC OR CVL OR PCVC OR PICC OR Umbilical, Veins OR UVC OR UAC OR umbilical near3 cathet* OR umbilical near3 cannul* OR umbilical near3 line OR Broviac OR Hickman].

We limited the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any language restrictions.

We searched ClinicalTrials.gov and Current Controlled Trials for completed or ongoing trials.

Searching other resources

We examined the references in studies identified as potentially relevant.

We examined reference lists in previous reviews and included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to 2015), the European Society for Pediatric Research (1995 to 2015), the Royal College of Paediatrics and Child Health (2000 to 2015), the Perinatal Society of Australia and New Zealand (2000 to 2015), the European Society for Paediatric Infectious Diseases (2005 to 2015) and the Infectious Diseases Society of America (2003 to 2014). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We planned to use the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

Two authors planned to screen independently the title and abstract of all studies identified by the above search strategy and assess the full articles for all potentially relevant trials. We planned to exclude any studies that did not meet all of the inclusion criteria and to state the reason for exclusion. We intended to discuss any disagreements until we reached a consensus.

Data extraction and management

If we had identified any eligible studies, we planned to use a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We intended to discuss any disagreements until we reached a consensus. If data from the trial reports were insufficient, we planned to contact the trialists for further information.

Assessment of risk of bias in included studies

We planned to use the criteria and standard methods of the Cochrane Neonatal Group to assess the methodological quality of any included trials. Two authors should conduct the assessment of risk of bias and resolve disagreements in consultation with a third author. We planned to request additional information from the trial authors to clarify methodology and results if necessary.

We planned to evaluate the following issues in the 'Risk of bias' tables:

Random sequence generation - the method used to generate the allocation sequence:

- low risk - any truly random process, e.g. random number table; computer random number generator;
- high risk - any non-random process, e.g. odd or even date of birth; hospital or clinic record number; and
- unclear risk - no or unclear information provided.

Allocation concealment - the method used to conceal the allocation sequence:

- low risk - e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes;
- high risk - open random allocation, e.g. unsealed or non-opaque envelopes, alternation; date of birth; and
- unclear - no or unclear information provided.

Blinding - the methods used to blind participants, clinicians and caregivers, and outcome assessors for different outcomes:

- low risk;
- high risk; and

- unclear.

Incomplete outcome data - the completeness of data, including attrition and exclusions from the analysis, for each outcome and any reasons for attrition or exclusion, where reported:

- low risk: ≤ 10% missing data;
- high risk: > 10% missing data; and
- unclear risk: no or unclear information provided.

Measures of treatment effect

We planned to calculate risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CI). We planned to determine the number needed to treat to benefit (NNTB) or to harm (NNTH) for a statistically significant reduction in the RD.

Unit of analysis issues

We planned that the unit of analysis would be the participating infant in individually randomised trials and the neonatal unit (or sub-unit) for cluster-randomised trials.

More than one episode of a bloodstream infection can occur in the same infant with a CVC. We planned to include only one episode per infant to avoid a unit of analysis problem.

Assessment of heterogeneity

We planned to examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We planned to calculate the I^2 statistic for each analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error.

Assessment of reporting biases

If there were data from more than 10 trials included in a meta-analysis, we intended to conduct a funnel plot analysis.

Data synthesis

We planned to perform meta-analyses using the fixed-effect model.

Quality of evidence

Two authors planned to assess independently the quality of the evidence found for outcomes identified as critical or important for clinical decision-making (mortality) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence as one of four grades (Schünemann 2013):

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We planned to consider evidence from randomised controlled trials as high quality, but they could be downgraded based on consideration of any of five areas:

- design and risk of bias (Guyatt 2011b);
- consistency across studies (Guyatt 2011c);
- precision of estimates (Guyatt 2011d);
- directness of the evidence (Guyatt 2011e);
- presence of publication bias.

In cases where we considered the risk of bias arising from inadequate concealment of allocation, randomised assignment, complete follow-up or blinded outcome assessment to reduce our confidence in the effect estimates, we planned to downgrade the quality of evidence accordingly (Guyatt 2011b). We planned to evaluate consistency by examining similarity of point estimates, extent of overlap of confidence intervals and by using statistical tests of heterogeneity (I^2). The quality of evidence would be downgraded when large and unexplained inconsistency across studies results was present (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation) (Guyatt 2011c). We planned to assess precision according to the 95% confidence interval (CI) around the pooled estimate of effect (Guyatt 2011d). When trials were conducted in populations other than the target population, we planned to downgrade the quality of evidence because of indirectness (Guyatt 2011e).

We planned to enter the data (pooled estimates of the effects and corresponding 95% CI) and make explicit judgements for each of the above aspects in the Guideline Development Tool, the software used to create Summary of Findings (SoF) tables (GRADEpro 2008). We planned to explain judgements involving the assessment of the study characteristics in footnotes or comments in the SoF table.

Subgroup analysis and investigation of heterogeneity

We pre-specified separate comparisons for infants with:

- suspected infection;
- confirmed infection.

For confirmed infection, we planned to perform subgroup analyses by infecting organism:

- coagulase-negative staphylococci;

- other Gram-positive cocci;
- Gram-negative bacillus;
- fungi.

If sufficient data were available, we would have performed further subgroup analyses by:

- birth weight and gestational age: VLBW infants (< 1500 g) and very preterm infants (< 32 weeks gestation at birth);
- CVC type: peripherally inserted percutaneous CVCs; subcutaneously tunnelled catheters; umbilical catheters.

If substantial heterogeneity had been detected (I^2 > 50%), we planned to explore the possible causes (for example, differences in study design, participants, interventions or completeness of outcome assessments) in sensitivity analyses.

RESULTS

Description of studies

We did not identify any studies or ongoing trials that met our inclusion criteria.

Results of the search

We did not identify any eligible trials.

Risk of bias in included studies

We did not identify any eligible trials.

Effects of interventions

We did not identify any eligible trials.

DISCUSSION

Given that nosocomial bloodstream infection in neonates with a central venous catheter (CVC) in place is a common and important clinical problem and that substantial uncertainty and variation in practice exists with regard to early CVC removal versus expectant management, it is surprising that this question has not yet been addressed in any randomised controlled trials. This may in part be due to historical differences and inconsistencies in defining CVC-associated bloodstream infections. Over the past 20 years, consensus definitions of nosocomial infections have become accepted more widely in practice, for example in neonatal network benchmarking and audit process where infection incidence is an established key quality indicator (Stoll 2002; Lee 2009). The availability of validated definitions should help in planning future trials and facilitate synthesis of data from individual trials that adhere to broadly consistent definitions (Modi 2009).

In the absence of trial data, decisions regarding the timing of removal of CVCs in infants with bloodstream infections continue to rely on the findings of observational studies. Some retrospective cohort studies have indicated that bloodstream infections progress to persistent bacteraemia or fungaemia with end-organ damage if the CVC is not removed promptly (Eppes 1989; Karlowicz 2000; Benjamin 2001; Nazemi 2003; Tsai 2012). However, these studies have inherent methodological weaknesses with potential for bias and should be interpreted with caution since their findings may be due to confounding factors such as clinicians electing to delay CVC removal in smaller, less mature or sicker infants. The variation in policy and practice between neonatal centres and clinicians reflects the ongoing uncertainty with which the available observational data are viewed (Karlowicz 2002; Rubin 2002).

Similarly, there appear to be limited data to inform decisions about CVC removal in other populations of patients with bloodstream infections (Rijnders 2004; O'Grady 2011; Deliberato 2012; Lorente 2014). Practice guidelines published by the European Society for Clinical Nutrition and Metabolism and the Infectious Diseases Society of America recommend that peripherally inserted percutaneous CVCs should be removed in patients with a bloodstream infection. However, the level of evidence to support these statements is acknowledged to be low, being based largely on data from retrospective cohort studies (Mermel 2009; Pittiruti 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials to inform practice. Retrospective cohort studies suggest that early central venous catheter (CVC) removal is associated with a lower risk of persistent infection but these findings were not systematically reviewed and should be interpreted with caution because of biases inherent in the study design.

Implications for research

Given the potential for benefit and harm to be associated with the timing of removal of the CVC in a neonate with a bloodstream infection, a pragmatic randomised controlled trial of early removal versus expectant management seems warranted. Such a trial might first address this issue in infants with confirmed bloodstream infections (defined using established and validated criteria) and should ideally be powered to allow pre-specified subgroup analyses based on the infecting organism.

REFERENCES

Additional references

Adams-Chapman 2006

Adams-Chapman I, Stoll BJ. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. *Current Opinion in Infectious Diseases* 2006;**19**:290–7.

Ainsworth 2007

Ainsworth SB, Clerihew L, McGuire W. Percutaneous central venous catheters versus peripheral cannulae for delivery of parenteral nutrition in neonates. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD004219.pub3]

Balain 2015

Balain M, Oddie SJ, McGuire W. Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD011078.pub2]

Bassler 2009

Bassler D, Stoll BJ, Schmidt B, Asztalos EV, Roberts RS, Robertson CM, et al. Using a count of neonatal morbidities to predict poor outcome in extremely low birth weight infants: added role of neonatal infection. *Pediatrics* 2009; **123**:313–8.

Benjamin 2000

Benjamin DK Jr, Ross K, McKinney RE Jr, Benjamin DK, Auten R, Fisher RG. When to suspect fungal infection in neonates: a clinical comparison of Candida albicans and Candida parapsilosis fungemia with coagulase-negative staphylococcal bacteremia. *Pediatrics* 2000;**106**:712–8.

Benjamin 2001

Benjamin DK Jr, Miller W, Garges H, Benjamin DK, McKinney RE Jr, Cotton M, et al. Bacteremia, central catheters, and neonates: when to pull the line. *Pediatrics* 2001;**107**:1272–6.

Buttery 2002

Buttery JP. Blood cultures in newborns and children: optimising an everyday test. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2002;**87**:F25–8.

Cartwright 2004

Cartwright DW. Central venous lines in neonates: a study of 2186 catheters. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**:F504–8.

Chapman 2003

Chapman RL, Faix RG. Persistent bacteremia and outcome in late onset infection among infants in a neonatal intensive care unit. *Pediatric Infectious Disease Journal* 2003;**22**: 17–21.

Chien 2002

Chien LY, Macnab Y, Aziz K, Andrews W, McMillan DD, Lee SK, Canadian Neonatal Network. Variations in central venous catheter-related infection risks among Canadian neonatal intensive care units. *Pediatric Infectious Disease Journal* 2002;**21**:505–11.

Connell 2007

Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics* 2007;**119**:891–6.

Deliberato 2012

Deliberato RO, Marra AR, Correa TD, Martino MD, Correa L, Dos Santos OF, et al. Catheter related bloodstream infection (CR-BSI) in ICU patients: making the decision to remove or not to remove the central venous catheter. *PloS One* 2012;**7**(3):e32687. [PUBMED: 22403696]

Eppes 1989

Eppes SC, Troutman JL, Gutman LT. Outcome of treatment of candidemia in children whose central catheters were removed or retained. *Pediatric Infectious Disease Journal* 1989;**8**:99–104.

Fowlie 1998

Fowlie PW, Schmidt B. Diagnostic tests for bacterial infection from birth to 90 days--a systematic review. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 1998;**78**:F92–8. [PUBMED: 9577277]

Garland 2008

Garland JS, Alex CP, Sevallius JM, Murphy DM, Good MJ, Volberding AM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. *Infection Control and Hospital Epidemiology* 2008;**29**:243–9.

Gordon 2006

Gordon A, Isaacs D. Late onset neonatal Gram-negative bacillary infection in Australia and New Zealand: 1992-2002. *Pediatric Infectious Disease Journal* 2006;**25**:25–9.

Gordon 2016a

Gordon A, Greenhalgh M, McGuire W. Early planned removal versus expectant management of peripherally-inserted central catheters to prevent infection in newborn infants. *Cochrane Database of Systematic Reviews* 2016.

Gordon 2016b

Gordon A, Greenhalgh M, McGuire W. Early planned removal of umbilical venous catheters to prevent infection in newborn infants. *Cochrane Database of Systematic Reviews* 2016.

GRADEpro 2008 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro [Version 3.2 for Windows]. The GRADE Working Group, 2008.

Guyatt 2011a
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94. [PUBMED: 21195583]

Guyatt 2011b
Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15. [PUBMED: 21247734]

Guyatt 2011c
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302. [PUBMED: 21803546]

Guyatt 2011d
Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93. [PUBMED: 21839614]

Guyatt 2011e
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10. [PUBMED: 21802903]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoang 2008
Hoang V, Sills J, Chandler M, Busalani E, Clifton-Koeppel R, Modanlou HD. Percutaneously inserted central catheter for total parenteral nutrition in neonates: complications rates related to upper versus lower extremity insertion. *Pediatrics* 2008;**121**:e1152–9.

Isaacs 2003
Isaacs D, Australasian Study Group for Neonatal Infections. A ten year, multicentre study of coagulase negative staphylococcal infections in Australasian neonatal units. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2003;**88**:F89–93.

Isaacs 2004
Isaacs D, Fraser S, Hogg G, Li HY. Staphylococcus aureus infections in Australasian neonatal nurseries. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**4**: F331–5.

Jawaheer 1997
Jawaheer G, Neal TJ, Shaw NJ. Blood culture volume and detection of coagulase negative staphylococcal septicaemia in neonates. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 1997;**76**:F57–8.

Karlowicz 2000
Karlowicz MG, Hashimoto LN, Kelly RE Jr, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates?. *Pediatrics* 2000;**106**: E63.

Karlowicz 2002
Karlowicz MG, Furigay PJ, Croitoru DP, Buescher ES. Central venous catheter removal versus in situ treatment in neonates with coagulase-negative staphylococcal bacteremia. *Pediatric Infectious Disease Journal* 2002;**21**:22–7.

Khashu 2006
Khashu M, Osiovich H, Henry D, Al Khotani A, Solimano A, Speert DP. Persistent bacteremia and severe thrombocytopenia caused by coagulase-negative Staphylococcus in a neonatal intensive care unit. *Pediatrics* 2006;**117**:340–8.

Lee 2009
Lee SK, Aziz K, Singhal N, Cronin CM, James A, Lee DS, et al. Improving the quality of care for infants: a cluster randomized controlled trial. *CMAJ* 2009;**181**:469–76. [PUBMED: 19667033]

Lorente 2014
Lorente L, Martin MM, Vidal P, Rebollo S, Ostabal MI, Sole-Violan J. Should central venous catheter be systematically removed in patients with suspected catheter related infection?. *Critical Care* 2014;**18**(5):564. [PUBMED: 25514404]

Mahieu 2001
Mahieu LM, De Dooy JJ, De Muynck AO, Van Melckebeke G, Ieven MM, Van Reempts PJ. Microbiology and risk factors for catheter exit-site and -hub colonization in neonatal intensive care unit patients. *Infection Control and Hospital Epidemiology* 2001;**22**:357–62.

Makhoul 2002
Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B. Epidemiological, clinical, and microbiological characteristics of late-onset sepsis among very low birth weight infants in Israel: a national survey. *Pediatrics* 2002;**109**:34–9.

Malik 2003
Malik A, Hui CP, Pennie RA, Kirpalani H. Beyond the complete blood cell count and C-reactive protein: a systematic review of modern diagnostic tests for neonatal sepsis. *Archives of Pediatrics & Adolescent Medicine* 2003; **157**:511–6. [PUBMED: 12796229]

Mermel 2009
Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2009;**49**:1–45. [PUBMED: 19489710]

Modi 2009
Modi N, Dore CJ, Saraswatula A, Richards M, Bamford KB, Coello R, et al. A case definition for national and international neonatal bloodstream infection surveillance. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2009;**94**:F8–12. [PUBMED: 18499771]

Nazemi 2003
Nazemi KJ, Buescher ES, Kelly RE Jr, Karlowicz MG. Central venous catheter removal versus in situ treatment in neonates with enterobacteriaceae bacteremia. *Pediatrics* 2003;**111**:e269–74.

O'Grady 2011
O'Grady NP, Chertow DS. Managing bloodstream infections in patients who have short-term central venous catheters. *Cleveland Clinic Journal of Medicine* 2011;**78**: 10–7. [PUBMED: 21199902]

Ohki 2008
Ohki Y, Yoshizawa Y, Watanabe M, Kuwashima M, Morikawa A. Complications of percutaneously inserted central venous catheters in Japanese neonates. *Pediatrics International* 2008;**50**:636–9.

Olsen 2009
Olsen AL, Reinholdt J, Jensen AM, Andersen LP, Jensen ET. Nosocomial infection in a Danish Neonatal Intensive Care Unit: a prospective study. *Acta Paediatrica* 2009;**98**: 1294–9.

Pittiruti 2009
Pittiruti M, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clinical Nutrition* 2009;**28**:365–77. [PUBMED: 19464090]

Rijnders 2004
Rijnders BJ, Peetermans WE, Verwaest C, Wilmer A, Van Wijngaerden E. Watchful waiting versus immediate catheter removal in ICU patients with suspected catheter-related infection: a randomized trial. *Intensive Care Medicine* 2004; **30**:1073–80. [PUBMED: 14999442]

Rubin 2002
Rubin LG, Sanchez PJ, Siegel J, Levine G, Saiman L, Jarvis WR, Pediatric Prevention Network. Evaluation and treatment of neonates with suspected late-onset sepsis: a survey of neonatologists' practices. *Pediatrics* 2002;**110**:e42.

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GWG. GRADE handbook for grading quality of evidence and strength of recommendations. Available from www.guidelinedevelopment.org/handbook Updated October 2013.

Shane 2013
Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *American Journal of Perinatology* 2013;**30**(2):131–41. [PUBMED: 23297182]

Stoll 2002
Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002;**110**:285–91.

Stoll 2003
Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. *Seminars in Perinatology* 2003;**27**:293–301.

Stoll 2004
Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;**292**:2357–65.

Taylor 2015
Taylor JE, Tan K, Lai NM, McDonald SJ. Antibiotic lock for the prevention of catheter-related infection in neonates. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD010336.pub2]

Thornburg 2008
Thornburg CD, Smith PB, Smithwick ML, Cotten CM, Benjamin DK, Jr. Association between thrombosis and bloodstream infection in neonates with peripherally inserted catheters. *Thrombosis Research* 2008;**122**:782–5.

Tsai 2012
Tsai MH, Hsu JF, Lien R, Huang HR, Chiang CC, Chu SM, et al. Catheter management in neonates with bloodstream infection and a percutaneously inserted central venous catheter in situ: removal or not?. *American Journal of Infection Control* 2012;**40**(1):59–64. [PUBMED: 21839544]

van der Zwet 2005
van der Zwet WC, Kaiser AM, van Elburg RM, Berkhof J, Fetter WP, Parlevliet GA, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. *Journal of Hospital Infection* 2005;**61**:300–11.

References to other published versions of this review

Vasudevan 2011
Vasudevan C, McGuire W. Early removal versus expectant management of central venous catheters in neonates with bloodstream infection. *Cochrane Database of Systematic Reviews* 2011, Issue 8. [DOI: 10.1002/14651858.CD008436.pub2]

* *Indicates the major publication for the study*

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 11 November 2015.

Date	Event	Description
14 March 2016	New citation required but conclusions have not changed	No studies identified.
17 November 2015	New search has been performed	No studies identified.

CONTRIBUTIONS OF AUTHORS

Chakrapani Vasudevan, Sam Oddie and William McGuire undertook the search, assessed the studies and updated the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Centre for Reviews and Dissemination, Hull York Medical School, University of York, UK.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C

- National Institute for Health Research, UK.

This report is independent research funded by a UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the UK Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Bacteremia; *Watchful Waiting; Catheter-Related Infections [*blood; prevention & control]; Catheterization, Central Venous [*instrumentation]; Catheters, Indwelling [*adverse effects]; Device Removal [*standards]; Time Factors

MeSH check words

Humans; Infant, Newborn