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Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants (Review)

Balain M, Oddie SJ, McGuire W

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[Intervention Review]

Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants

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ABSTRACT

Background

Central venous catheter-related bloodstream infection is an important cause of mortality and morbidity in newborn infants cared for in neonatal units. Potential strategies to prevent these infections include the use of central venous catheters impregnated with antimicrobial agents.

Objectives

To determine the effect of antimicrobial-impregnated central venous catheters in preventing catheter-related bloodstream infection in newborn infants.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 8), MEDLINE (1966 to September 2015), EMBASE (1980 to September 2015), CINAHL (1982 to September 2015), conference proceedings and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials comparing central venous catheters impregnated or coated with any antibiotic or antiseptic versus central venous catheters without antibiotic or antiseptic coating or impregnation in newborn infants.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Neonatal Group, with independent evaluation of risk of bias and data extraction by two review authors.

Main results

We found only one small trial (N = 98). This trial found that silver zeolite-impregnated umbilical venous catheters reduced the incidence of bloodstream infection in very preterm infants (risk ratio 0.11, 95% confidence interval 0.01 to 0.87; risk difference -0.17, 95% CI -0.30 to -0.04; number needed to treat for benefit 6, 95% CI 3 to 25].

Authors' conclusions

Although the data from one small trial indicates that antimicrobial-impregnated central venous catheters might prevent catheter-related bloodstream infection in newborn infants, the available evidence is insufficient to guide clinical practice. A large, simple and pragmatic randomised controlled trial is needed to resolve on-going uncertainty.

PLAIN LANGUAGE SUMMARY

Antimicrobial-impregnated central venous catheters to prevent bloodstream infection in newborn infants

Review question: In newborn infants requiring a central venous catheter (CVC), are antimicrobial-impregnated CVCs compared to standard CVCs effective in preventing acquired bloodstream infection?

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 vessel). While the catheter may provide a secure route for delivering drugs and nutrition, it may also be a locus for infecting organisms to grow and cause long-term or more severe infection. One potential method of reducing this serious complication is to use central venous catheters that contain antiseptics or antibiotics to stop organisms from sticking to or growing on the catheter.

Study characteristics: We found only one small randomised controlled trial (with 98 very preterm infants participating) that addressed this question.

Key results: This trial showed that central venous catheters containing antiseptics or antibiotics to stop organisms from sticking to or growing on the catheter could reduce the chance of infants developing a bloodstream infection by about 90%. Becasue the trial was small, however, this finding is not certain.

Conclusions: The trial did provide some evidence that antimicrobial-impregnated central venous catheters can prevent bloodstream infection in newborn infants, but further, large trials are needed to resolve this question fully.

BACKGROUND

Description of the condition

Bloodstream infection is the most common serious complication associated with the use of central venous catheters (CVCs). The most commonly used CVCs in neonatal practice are umbilical venous catheters or peripherally-inserted percutaneous CVCs; these are used to deliver drugs, fluids or parenteral nutrition for newborn infants. Micro-organisms can gain access through the CVC entry site or, less commonly, via the catheter hub into the lumen or the tract of the CVC (Salzman 1995). Microbial pathogens adhere to the material of the CVC and secrete a protective intraluminal or extraluminal biofilm of extracellular polymeric substances (Machado 2009). Bacteria or fungi proliferating within the biofilm are relatively protected from circulating antimicrobial agents, enabling sustained colonisation (Ramirez de Arellano 1994; Stewart 2001). CVC-associated thrombosis can act as an additional nidus for infection (Thornburg 2008). It is often necessary to remove the CVC in order to clear the infection (Benjamin 2001).

The reported incidence of CVC-related bloodstream infection ranges from about 5% to 30%, depending on the precise diagnostic criteria used and the demographics of the population (Trotter 1996a; Trotter 1996b; Cartwright 2004; Van der Zwet 2005; Garland 2008; Hoang 2008; Ohki 2008; Olsen 2009; O'Grady 2011). Very preterm (less than 32 weeks gestation) infants are at the highest risk, but inter-unit variation in the incidence of CVC-associated bloodstream infection is not fully explained by case mix, and may relate to care or infection control practices (Wong 2012). Other putative risk factors include prolonged use of parenteral nutrition and insertion of the CVC after the first postnatal week (Mahieu 2001c; Mahieu 2001d).

The most common causes of CVC-related bloodstream infections in newborn infants are coagulase-negative staphylococci, Gram-negative bacilli (mainly enteric bacilli), Gram-positive cocci (Staphylococcus aureus (*S. aureus*), enterococci), and fungi (predominantly Candida species) (Makhoul 2002; O'Grady 2002; Stoll 2002; Isaacs 2003; Isaacs 2004; Gordon 2006; De Brito 2010). Newborn infants, particularly very preterm infants, with acquired bloodstream infection have a higher risk of mortality and a range of important morbidities that require intensive care and mechanical ventilation: bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, hepatic dysfunction and prolonged hospitalisation (Saint 2000; Mahieu 2001a; Mahieu 2001b; Chapman 2003; Payne 2004; Adams-Chapman 2006; Hermans 2007; Lahra 2009). Bloodstream infection is also associated with higher rates of several adverse neurodevelopmental outcomes, long-term disability, vision and hearing impairment, and cerebral palsy (Stoll 2004; Shah 2008; Bassler 2009).

Various strategies to reduce and prevent CVC-related bloodstream infections have been introduced, often as care bundles. These include strict aseptic precautions when inserting and accessing the CVC, use of needleless intravascular catheter systems and prompt removal when the CVC is no longer needed (O'Grady 2002; Yébenes 2004; Pronovost 2006; Miller 2010; Sannoh 2010; Vanholder 2010; Wirtschafter 2010; Kaplan 2011; O'Grady 2011; Schulman 2011). Care bundles have been shown to reduce bloodstream infection rates in adult, paediatric and neonatal intensive care studies (Pronovost 2006; Miller 2010; Wirtschafter 2010; Kaplan 2011; Schulman 2011). However, despite these strategies, CVC-related infections remain a major cause of morbidity and mortality in newborn infants and other interventions are required to reduce the infection rates further.

Description of the intervention

CVCs are vascular cannulae terminating in a large (central) vein. In neonatal practice, the most commonly used CVCs are umbilical venous catheters (usually inserted within the first postnatal day), and peripherally-inserted percutaneous CVCs (inserted via a peripheral vein). Other CVCs that are commonly used in caring for older children or adults, such as those inserted directly via a central vein (typically the femoral or subclavian vein) and subcutaneously "tunnelled" catheters (usually requiring a surgical procedure to insert), are much less commonly used in neonatal care.

Most commercially available CVCs are made of a silicone or polyurethane (polytetrafluoroethylene) based material. The intervention under study here is the use of CVCs coated with, or manufactured from, materials impregnated with antibiotic or antiseptic agents. Such catheters have been available in adult practice for several years, and emerging evidence supports their clinical and cost-effectiveness in preventing bloodstream infection (Alonso-Echanove 2003; Eggimann 2003; Shorr 2003; Casey 2008; Gilbert 2008; Hockenhull 2008; Halton 2009; Walz 2010; Lambert 2012). A US Centre for Disease Control (CDC) expert consensus statement recommends the "use of a chlorhexidine/silver sulphadiazine or minocycline/rifampicin-impregnated CVCs in [paediatric and adult] patients whose catheter is expected to remain in place for more than 5 days if, after successful implementation of a comprehensive strategy to reduce rates of [CVC-related bloodstream infection], the [CVC-related bloodstream infection] rate is not decreasing" (O'Grady 2011).

How the intervention might work

Use of antimicrobial-impregnated or coated CVCs might reduce micro-organism adhesion and survival, thus inhibiting intraluminal or extraluminal biofilm formation. Inhibited or abolished biofilm formation would be expected to reduce the incidence of bloodstream infection, reduce the need for CVC removal, and reduce infection-associated mortality and morbidity (Cicalini 2004).

In vitro studies suggest that antiseptic- and antibiotic-impregnated CVCs are equally effective at inhibiting microbial adherence and colonisation (Sampath 2001), but a systematic review of trials with mainly adult participants, found that antibiotic-impregnated (minocycline/rifampicin) CVCs were more effective than antiseptic-impregnated (chlorhexidine/silver sulphadiazine) CVCs at preventing catheter-related bloodstream infections (Casey 2008). Although there is the possibility that prolonged use of antibiotic-impregnated CVCs might select for antibiotic-resistant micro-organisms, evidence exists that if bacteria, including methicillin-resistant *Staphylococcus aureus* (*S. aureus*) and vancomycin-resistant enterococci, are exposed to antibiotic combinations (rather than a single agent) they are less likely to develop antibiotic resistance (Tambe 2001; Munson 2004; Aslam 2007).

Why it is important to do this review

There are important differences between adults and infants that mean that antimicrobial-impregnated CVCs might work differently. Firstly, infants' veins are much smaller and so CVCs need to be narrower, with associated higher flow rates per unit of cross-sectional area. Secondly, CVCs are often kept in place for much longer in infants and the risk of infection may increase over the time a CVC is in place (Schelonka 2006). Thirdly, there is a higher incidence of infection in newborn infants, especially in very preterm and very low birth weight infants, as their immature immune systems and thin, immature skin increase susceptibility (Borghesi 2008). Finally, the consequences of infection in newborn infants are different and more serious than in older children and adults.

Given the potential for the use of antimicrobial-impregnated CVCs to affect important outcomes for newborn infants, we will undertake a systematic review to identify, appraise and synthesise the available evidence from randomised controlled trials.

OBJECTIVES

To determine the effectiveness of antimicrobial-impregnated CVCs compared to standard CVCs in preventing acquired bloodstream infection in newborn infants.

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 who are to have a CVC placed.

Types of interventions

1. Intervention: CVCs impregnated or coated with any antibiotic or antiseptic agent.
2. Control: any other CVC without antibiotic or antiseptic coating or impregnation.

Trials which assess the effect of antibiotic-impregnated CVCs as part of a package of infection control measures (care bundle) were eligible for inclusion, but we planned to analyse these separately from trials of discreet interventions.

Types of outcome measures

Primary outcomes

1. Incidence (and rates per 1000 catheter-days) of laboratory-confirmed bloodstream infection, where the CVC was in place on the day or the day before the blood sample for microbial culture was obtained. If the CVC was placed on the first postnatal day, then it must have been in place for more than two calendar days on the day that the blood sample for microbial culture was obtained.

Secondary outcomes

1. Mortality due to all causes prior to hospital discharge and at one year corrected age.
2. Neurodevelopmental outcomes assessed after 12 months corrected 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 quotient more than two standard deviations below the population mean; and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).
3. Death or neurological impairment assessed after 12 months corrected age.
4. Other morbidity developing after enrolment in trial until discharge from hospital:
   - bronchopulmonary dysplasia (oxygen supplementation at 36 weeks postmenstrual age);
   - necrotising enterocolitis (Bell stage 2 or 3);
   - retinopathy of prematurity, requiring treatment (medical or surgical).
5. Length of index CVC use (days).
6. Incidence of CVC removal for suspected or confirmed CVC infection.
7. Length of stay in the neonatal intensive care and overall hospital stay (days).
8. Proportion of catheters colonised with antibiotic-resistant organisms at removal.

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* (2015, issue 8), MEDLINE (1966 to September 2015), EMBASE (1980 to September 2015), and CINAHL (1982 to September 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 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 OR antibiotic impregnat* OR antimicrobial impregnat* OR antibacterial impregnate* OR antiseptic impregnat* OR antibiotic coat* OR antimicrobial coat* OR antibacterial coat* OR antiseptic coat*]

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 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 2014), 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 2014), 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 used the standard methods of the Cochrane Neonatal Group.

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy; two review authors independently assessed the full articles for all potentially relevant trials. We excluded those studies that did not meet all of the inclusion criteria and stated the reason for exclusion. We discussed any disagreements until consensus was achieved.

Data extraction and management

Two authors independently extracted data using a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We discussed any disagreements until we reached consensus. If data from the trial reports were insufficient, we contacted the trialists for further information.

Assessment of risk of bias in included studies

We used the criteria and standard methods of the Cochrane Neonatal Group to assess the methodological quality of any included trials. Two authors conducted the assessment of risk of bias. We resolved 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 evaluated the following issues in the 'Risk of bias' tables:

Random sequence generation - we categorised the method used to generate the allocation sequence as:

- 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 - we categorised the method used to conceal the allocation sequence as:

- 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 - we assessed blinding of participants, clinicians and caregivers, and outcome assessors separately for different outcomes and categorised the methods as:

- low risk;
- high risk; and
- unclear.

Incomplete outcome data - we described the completeness of data, including attrition and exclusions from the analysis, for each outcome and any reasons for attrition or exclusion, where reported. We assessed whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to reinstate missing data in the analyses. We categorised completeness as:

- low risk - up to and including10% missing data;
- high risk - more than 10% missing data; and
- unclear risk - no or unclear information provided.

Overall risk of bias - we made explicit judgements about whether studies were at high risk of bias, according to the criteria suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the likely magnitude and direction of the bias and whether we considered it likely to impact the findings. We planned to explore the impact of the level of bias in sensitivity analyses.

Measures of treatment effect

We analysed the treatment effects in the trial using Review Manager 5.2 (RevMan 2012) and reported risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis was the participating infant in individually randomised trials. An infant was considered only once in an analysis. We planned to exclude infants with multiple enrolments unless we obtained data from the report or investigators relating to the first episode of randomisation. If we could not separate data from the first randomisation, we planned to exclude the study as we would not be able to address the unit of analysis issues that arise from multiple enrolments of the same infant.

We intended to conduct intention-to-treat analyses. However, if the allocated CVC placement was unsuccessful, the primary outcome (bloodstream infection when the CVC is in place) for that infant may not have been possible to evaluate.

The participating neonatal unit or section of a neonatal unit was the unit of analysis in cluster randomised trials. We planned to analyse these using an estimate of the intra-cluster correlation coefficient derived from the trial (if possible), or from another source as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

If we identified both cluster randomised trials and individually randomised trials, we planned to only combine the results from both if there was little heterogeneity between the study designs,

and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Dealing with missing data

We requested additional data from the trial investigators if data on important outcomes were missing or reported unclearly. Where data were still missing, we examined the impact on effect size estimates in sensitivity analyses.

Assessment of heterogeneity

As only one study was included in any analysis tests for heterogeneity were not applicable.

Assessment of reporting biases

Where we suspected reporting bias, we contacted trial investigators asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such trials in the overall assessment of results in a sensitivity analysis.

Data synthesis

We planned to use the fixed-effect model in Review Manager 5.2 (RevMan 2012) for meta-analyses (as per Cochrane Neonatal Group recommendations). Where substantial heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Very preterm (less than 32 weeks) infants (versus infants born at or later than 32 weeks).
- Type of CVC (umbilical venous catheters versus peripherally-inserted CVCs versus surgically-placed or tunnelled central lines, and antimicrobial versus antiseptic impregnation or coating).

Sensitivity analysis

We planned sensitivity analyses to determine if findings were affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and up to and including a 10% loss to follow-up.

RESULTS

Description of studies

See the Characteristics of included studies and Characteristics of excluded studies sections.

Characteristics of ongoing studies: PREVAIL

Results of the search

We identified 31 records, for four of which we assessed full-text articles for eligibility. Only one trial met all of our inclusion criteria (Bertini 2013).

Included studies

We identified one randomised controlled trial (N = 98) that met the inclusion criteria (Bertini 2013).

Excluded studies

We excluded three reports (see Characteristics of excluded studies).

Risk of bias in included studies

We included only one trial (Bertini 2013).

Allocation

The report states that allocation was contained in sealed opaque envelopes.

Blinding

The trial was unblinded.

Incomplete outcome data

Of the 98 infants who were randomised, 12 died within the first week. These 12 infants were not included in the mortality analysis in the primary report.

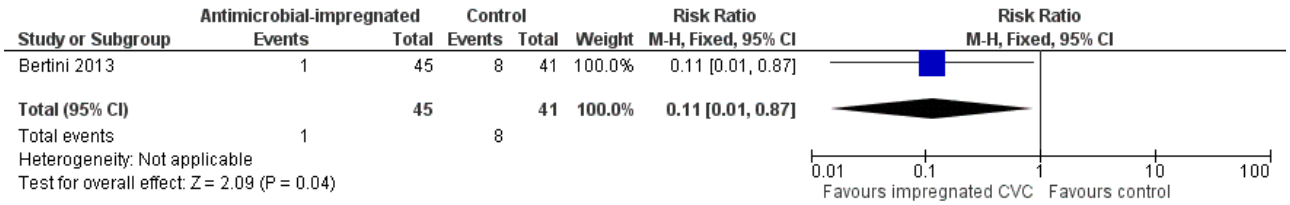
Effects of interventions

Antimicrobial-impregnated bloodstream infection (Comparison 1)

Primary outcomes

1. Catheter-related bloodstream infection (Analysis 1.1):Bertini 2013 found that a statistically significant reduced incidence in infants allocated to the intervention (RR 0.11, 95% CI 0.01 to 0.87; RD -0.17, 95% CI -0.30 to -0.04; NNTB 6, 95% CI 3 to 25; Figure 1).

Figure 1. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.1 Catheter-related bloodstream infection.



Secondary outcomes

1. Mortality due to all causes prior to hospital discharge (Analysis 1.2)**:**Bertini 2013 did not find a statistically significant difference (RR 0.73, 95% CI 0.21 to 2.53; RD -0.03, 95% CI -0.16 to 0.10; Figure 2).
2. Neurodevelopmental outcomes: Not reported.
3. Death or neurological impairment assessed after 12 months corrected age: Not reported.
4. Other morbidity developing after enrolment in trial until discharge from hospital:
   a. Bronchopulmonary dysplasia (oxygen supplementation at 36 weeks postmenstrual age; Analysis 1.3): Bertini 2013 did not find a statistically significant difference (RR 0.80, 95% CI 0.45 to 1.42; RD -0.08, 95% CI -0.28 to 0.12; Figure 3).
   b. Necrotising enterocolitis (Bell stage 2 or 3; Analysis 1.4): Bertini 2013 reported the incidence of "necrotising enterocolitis [defined] by Bell's criteria" and did not find a statistically significant difference (RR 0.46, 95% CI 0.04 to 4.84; RD -0.03, 95% CI -0.11 to 0.05; Figure 4). It is unclear if this analysis included infants with Bell stage 1 disease (as well as Bell stage 2 or 3).
   c. Retinopathy of prematurity, requiring treatment (medical or surgical; Analysis 1.5): Bertini 2013 reported the incidence of retinopathy of prematurity as not statistically significantly different (RR 0.46, 95% CI 0.12 to 1.70; RD -0.08, 95% CI -0.21 to 0.05; Figure 5). It is unclear if this analysis included infants with retinopathy that did not require treatment (as well as those who did).
5. Length of index CVC use (days; Analysis 1.6)**:**Bertini 2013 found that a statistically significant increase in duration of UVC (days) in infants allocated to the intervention (MD 2.3, 95% CI 0.38 to 4.22; Figure 6).
6. Incidence of CVC removal for suspected or confirmed CVC infection: Not reported.
7. Length of stay in the neonatal intensive care and overall hospital stay (Analysis 1.7)**:**Bertini 2013 did not report data on length of stay in neonatal intensive care. Bertini 2013 found a statistically significant shorter duration of stay in hospital for infants allocated to the intervention (MD -15.00 days, 95% CI -29.41 to -0.59; Figure 7).
8. Proportion of catheters colonised with antibiotic-resistant organisms at removal: Stated as "similar" between groups but data not presented.

Figure 2. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.2 Mortality prior to hospital discharge.

Figure 3. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.3 Bronchopulmonary dysplasia.

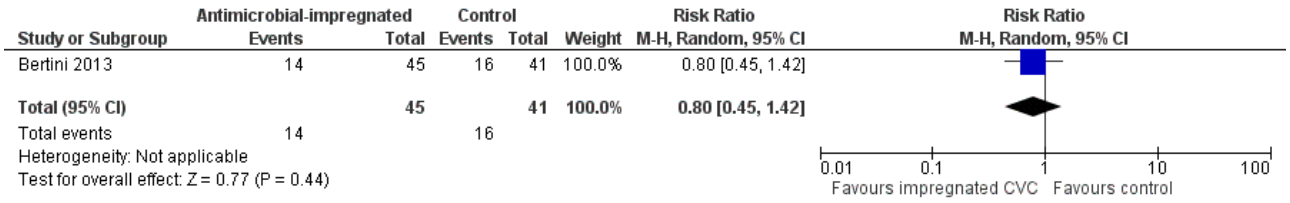


Figure 4. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.4 Necrotising enterocolitis.

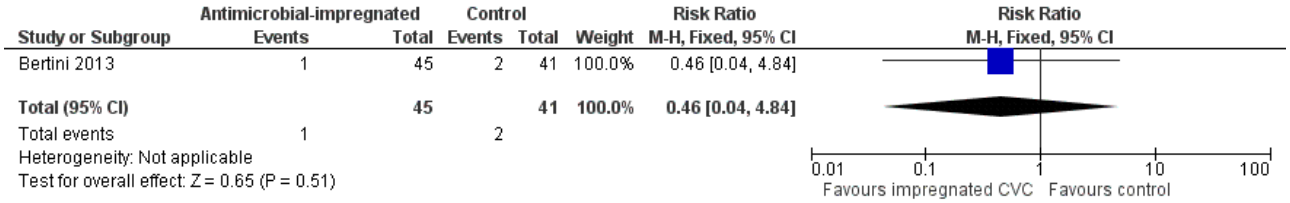


Figure 5. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.5 Retinopathy of prematurity.

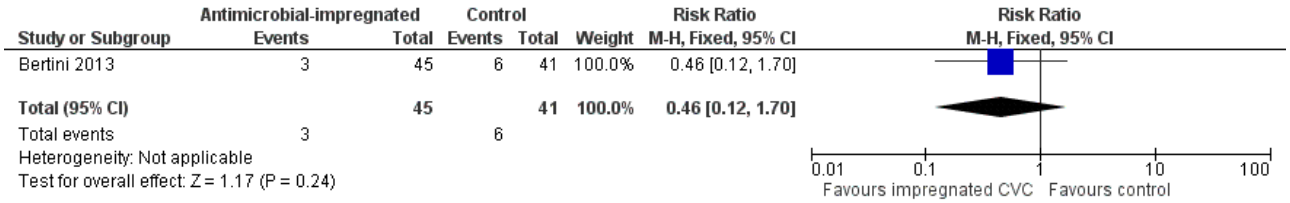


Figure 6. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.6 Length of index CVC use.

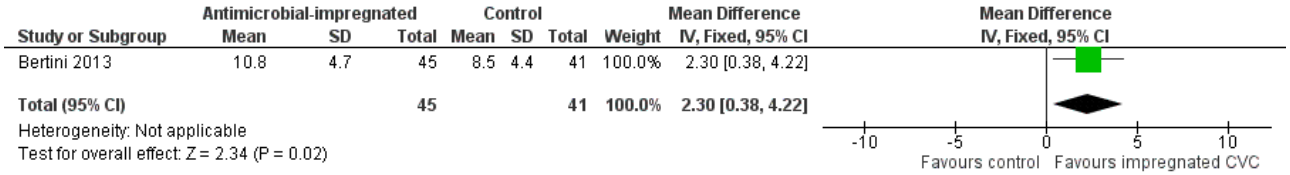
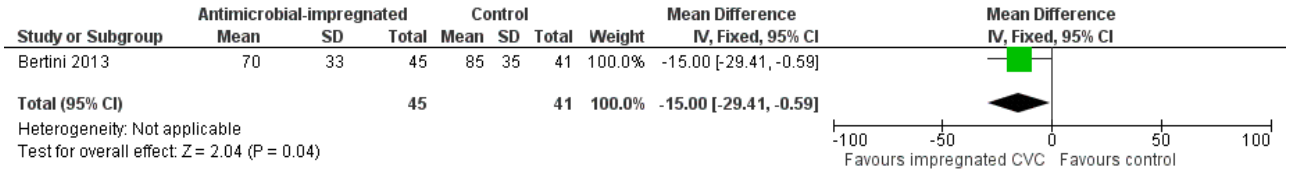


Figure 7. Forest plot of comparison: 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, outcome: 1.7 Length of hospital stay.



Subgroup analyses

- Very preterm (less than 32 weeks) infants (versus infants born at or later than 32 weeks): All participants were less than 31 weeks' gestation at birth.
- Type of CVC (umbilical venous catheters versus peripherally-inserted CVCs versus surgically-placed or tunnelled central lines, and antibiotic- versus antiseptic-impregnation or coating): Bertini 2013 only assessed silver zeolite-impregnated umbilical venous catheters.

DISCUSSION

Summary of main results

We found only one trial for inclusion in this review. This trial had various methodological limitations, including lack of blinding and incomplete inclusion of all randomised participants. The trial reported a statistically significant reduction in the incidence of catheter-related bloodstream infection, a statistically significant increase in the length of duration of use of the CVC, and a borderline statistically significant reduction in total length of stay in hospital. There was no evidence of an effect on mortality.

Overall completeness and applicability of evidence

We identified only one small trial (N = 98) for inclusion in this review. This trial provided some evidence that use of antiseptic-impregnated umbilical venous catheters reduced the risk of bloodstream infection in very preterm infants. The control events rate (20% incidence of catheter-related bloodstream infection) is comparable to other published studies and the findings are likely to be generally applicable to healthcare settings in high-income and middle-income countries with similar populations and care practices (Van der Zwet 2005; Olsen 2009; Wong 2012).

The available data are insufficient to exclude plausible and important effects on important secondary outcomes. For example, for mortality, wide 95% confidence interval bounds included a five-fold reduced risk and a more than two-fold increased risk. Long-term (post discharge) data have not been reported in this trial.

Quality of the evidence

Although allocation was concealed, the trial intervention was not blinded to caregivers and investigators, and surveillance bias may have influenced the assessment of some outcomes, including bloodstream infection. Clinicians' subjective assessment of when to investigate for infection may have been affected by the perceived clinical efficacy of antimicrobial impregnated CVCs. The unblinded design may also have influenced care practices. For example, a perception that antimicrobial-impregnated CVCs prevent infection may influence healthcare staff's adherence to other infection control practices. Lack of blinding may also influence the timing of the decision to remove the CVC, which may be reflected in the longer duration of use of antibiotic-impregnated CVCs reported in the trial.

Intention-to-treat analysis for mortality

Of the 98 infants who were randomised, 12 died within the first week. These infants were not included in the mortality analysis in the primary report. The reason for exclusion from analysis after randomisation is not clear. We have contacted the principal investigator seeking these data (not yet obtained) which can be included in an intention-to-treat re-analysis in an update of this review.

Potential biases in the review process

We found only one trial for inclusion in this review. Although we conducted a comprehensive search, including conference proceedings, we cannot exclude fully the possibility of publication bias since do not know whether other published (but not indexed) or unpublished trials exist.

Definition of catheter-related bloodstream infection

Our protocol defined catheter-related bloodstream infection as culture of a micro-organism from blood obtained when the "CVC was in place on the day or the day before the blood sample for microbial culture was obtained". The included trial's protocol defined catheter-related bloodstream infection as culture of a micro-organism from blood "concordant with organism colonising the UVC tip" obtained "when the UVC is in place or within 48 hours of central line removal". We made a post hoc, pragmatic, consensus decision to accept this definition of the primary outcome since (i) it was very similar to our a priori definition (allowing a 48 hours rather than 24 hours window post CVC removal for obtaining blood cultures), and (ii) it was unlikely to be possible to obtain trial data revised to fit our review definition.

Agreements and disagreements with other studies or reviews

The current evidence from studies in which adults participated suggests that antimicrobial-impregnated CVCs are clinically effective and cost-effective in preventing bloodstream infection (Alonso-Echanove 2003; Eggimann 2003; Shorr 2003; Casey 2008; Gilbert 2008; Hockenhull 2008; Halton 2009; Walz 2010; Lambert 2012). In the paediatric population, there are more limited and inconsistent data available (Lenz 2010, Weber 2012).

Other antimicrobial-impregnated or coated devices for newborn infants, including ventriculoperitoneal shunts, external ventricular drain catheters, and tympanostomy tubes, have been studied and assessed in randomised controlled trials. The limited data currently available do not provide consistent or definite evidence of benefit or harm (Licameli 2008; Muttaiyah 2010; Demetriades 2011; Kandasamy 2011; Thomas 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The available data from one, methodologically-weak trial, although indicating that antimicrobial-impregnated umbilical venous catheters might reduce the incidence of bloodstream infections in very preterm infants, are insufficient to guide clinical practice.

Implications for research

Further trials are required to assess the effectiveness of antimicrobial-impregnated CVCs for preventing bloodstream infections in newborn infants. The trials should be large, simple and pragmatic, and ideally should blind caregivers and investigators to the intervention to avoid introducing bias. Trials might compare either antibiotic- or antiseptic-impregnated CVCs with non-impregnated standard CVCs. Participants may include any newborn infants cared for in neonatal care centres who require CVC placement, or may be restricted to infants who are at a very high risk of catheter-related bloodstream infection, such as very, or extremely, preterm infants. As well as assessing the impact on the incidence of bloodstream infection and mortality, trials should be powered to detect plausible effects on important secondary outcomes, including acute neonatal morbidity, duration of hospital admission, and neurodevelopmental outcomes. There are theoretical concerns about potential harm due to emergence of resistant strains of bacteria and drug toxicity, which could be assessed within and between trials. Given the costs associated with this intervention, it is also important to embed a health economics assessment within any trial design.

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REFERENCES

References to studies included in this review

Bertini 2013 *{published data only}*

Bertini G, Elia S, Ceciarini F, Dani C. Reduction of catheter-related bloodstream infections in preterm infants by the use of catheters with the AgION antimicrobial system. *Early Human Development* 2013;**89**(1):21-5. [PUBMED: 22841551]

References to studies excluded from this review

Seidler 2006 *{published data only}*

Seidler M, Salvenmoser S, Muller FM. In vitro effects of micafungin against Candida biofilms on polystyrene and central venous catheter sections. *International Journal of Antimicrobial Agents* 2006;**28**(6):568-73. [PUBMED: 17101265]

Stevens 2011 *{published data only}*

Stevens KN, Croes S, Boersma RS, Stobberingh EE, van der Marel C, van der Veen FH, et al. Hydrophilic surface coatings with embedded biocidal silver nanoparticles and sodium heparin for central venous catheters. *Biomaterials* 2011;**32**(5):1264-9. [PUBMED: 21093906]

Venkatesh 2009 *{published data only}*

Venkatesh M, Rong L, Raad I, Versalovic J. Novel synergistic antibiofilm combinations for salvage of infected catheters. *Journal of Medical Microbiology* 2009;**58**(Pt 7):936-44. [PUBMED: 19502361]

References to ongoing studies

PREVAIL *{published data only}*

PREVAIL. Ongoing study June 2015.

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**(3):290-7. [PUBMED: 16645492]

Alonso-Echanove 2003

Alonso-Echanove J, Edwards JR, Richards MJ, Brennan P, Venezia RA, Keen J, et al. Effect of nurse staffing and antimicrobial-impregnated central venous catheters on the risk for bloodstream infections in intensive care units. *Infection Control and Hospital Epidemiology* 2003;**24**(12):916-25. [PUBMED: 14700407]

Aslam 2007

Aslam S, Darouiche RO. Prolonged bacterial exposure to minocycline/rifampicin-impregnated vascular catheters does not affect antimicrobial activity of catheters. *The Journal of Antimicrobial Chemotherapy* 2007;**60**(1):148-51. [PUBMED: 17525051]

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**(1):313-8. [PUBMED: 19117897]

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**(6):1272-6. [PUBMED: 11389242]

Borghesi 2008

Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. *The Journal of Hospital Infection* 2008;**68**(4):293-300. [PUBMED: 18329134]

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**(6):F504-8. [PUBMED: 15499142]

Casey 2008

Casey AL, Mermel LA, Nightingale P, Elliott TS. Antimicrobial central venous catheters in adults: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2008;**8**(12):763-76. [PUBMED: 19022192]

Chapman 2003

Chapman RL, Faix RG. Persistent bacteremia and outcome in late onset infection among infants in a neonatal intensive care unit. *The Pediatric Infectious Disease Journal* 2003;**22**(1):17-21. [PUBMED: 12544403]

Cicalini 2004

Cicalini S, Palmieri F, Petrosillo N. Clinical review: new technologies for prevention of intravascular catheter-related infections. *Critical Care* 2004;**8**(3):157-62. [PUBMED: 15153233]

De Brito 2010

de Brito CS, de Brito DV, Abdallah VO, Gontijo Filho PP. Occurrence of bloodstream infection with different types of central catheter in critically neonates. *The Journal of Infection* 2010;**60**(2):128-32. [PUBMED: 19944717]

Demetriades 2011

Demetriades AK, Bassi S. Antibiotic resistant infections with antibiotic-impregnated Bactiseal catheters for ventriculoperitoneal shunts. *The British Journal of Neurosurgery* 2011;**25**(6):671-3. [PUBMED: 21707238]

Eggimann 2003

Eggimann P, Pittet D. Pathophysiology and prevention of intravascular catheter-related infection [Physiopathologie et prevention des infections liees aux acces vasculaires]. *Medecine et Maladies Infectieuses* 2003;**33**(11):554-63.

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**(3):243-9. [PUBMED: 18220483]

Gilbert 2008

Gilbert RE, Harden M. Effectiveness of impregnated central venous catheters for catheter related blood stream infection: a systematic review. *Current Opinion in Infectious Diseases* 2008;**21**(3):235-45. [PUBMED: 18448967]

Gordon 2006

Gordon A, Isaacs D. Late onset neonatal Gram-negative bacillary infection in Australia and New Zealand: 1992-2002. *The Pediatric Infectious Disease Journal* 2006;**25**(1):25-9. [PUBMED: 16395098]

Halton 2009

Halton KA, Cook DA, Whitby M, Paterson DL, Graves N. Cost effectiveness of antimicrobial catheters in the intensive care unit: addressing uncertainty in the decision. *Critical Care* 2009;**13**(2):R35. [PUBMED: 19284570]

Hermans 2007

Hermans D, Talbotec C, Lacaille F, Goulet O, Ricour C, Colomb V. Early central catheter infections may contribute to hepatic fibrosis in children receiving long-term parenteral nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2007;**44**(4):459-63. [PUBMED: 17414144]

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: complication rates related to upper versus lower extremity insertion. *Pediatrics* 2008;**121**(5):e1152-9. [PUBMED: 18390957]

Hockenhull 2008

Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dündar Y, et al. The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation. *Health Technology Assessment* 2008;**12**(12):iii-iv, xi-xii, 1-154. [PUBMED: 18405471]

Isaacs 2003

Isaacs D, The 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**(2):F89–93. [PUBMED: 12598493]

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;**89**(4):F331-5. [PUBMED: 15210669]

Kandasamy 2011

Kandasamy J, Dwan K, Hartley JC, Jenkinson MD, Hayhurst C, Gatscher S, et al. Antibiotic-impregnated ventriculoperitoneal shunts--a multi-centre British paediatric neurosurgery group (BPNG) study using historical controls. *Child's Nervous System* 2011;**27**:575-81. [PUBMED: 20953871]

Kaplan 2011

Kaplan HC, Lannon C, Walsh MC, Donovan EF, Ohio Perinatal Quality Collaborative. Ohio statewide quality-improvement collaborative to reduce late onset sepsis in preterm infants. *Pediatrics* 2011;**127**(3):427-35. [PUBMED: 21339274]

Lahra 2009

Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. *Pediatrics* 2009;**123**(5):1314-9. [PUBMED: 19403497]

Lambert 2012

Lambert A, Lemarignier-Nueffer C, Iooss P, Roncalez D. Anti-infective-treated central venous catheters clinical effectiveness and safety [Evaluation de l'interet clinique et de la tolerance des catheters veineux centraux impregnes d'antimicrobiens]. *Journal de Pharmacie Clinique* 2012;**31**(2):73-87.

Lenz 2010

Lenz AM, Vassallo JC, Moreno GE, Althabe M, Gómez S, Magliola R, et al. Prevention of catheter-related infection: usefulness and cost-effectiveness of antiseptic catheters in children. *Archivos Argentinos Pediatria* 2010;**108**(3):209-15. [PUBMED: 20544135]

Licameli 2008

Licameli G, Johnston P, Luz J, Daley J, Kenna M. Phosphorylcholine-coated antibiotic tympanostomy tubes: are post-tube placement complications reduced?. *International Journal of Pediatric Otorhinolaryngology* 2008;**72**(9):1323-8. [PUBMED: 18635268]

Machado 2009

Machado JD, Suen VM, Figueiredo JF, Marchini JS. Biofilms, infection, and parenteral nutrition therapy. *Journal of Parenteral and Enteral Nutrition* 2009;**33**(4):397–403. [PUBMED: 19401480]

Mahieu 2001a

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**(6):357-62. [PUBMED: 11519913]

Mahieu 2001b

Mahieu LM, Buitenweg N, Beutels P, De Dooy JJ. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. *The Journal of Hospital Infection* 2001;**47**(3):223-9. [PUBMED: 11247683]

Mahieu 2001c

Mahieu LM, De Muynck AO, Ieven MM, De Dooy JJ, Goossens HJ, Van Reempts PJ. Risk factors for central vascular catheter-associated bloodstream infections among patients in a neonatal intensive care unit. *The Journal of Hospital Infection* 2001;**48**(2):108-16. [PUBMED: 11428877]

Mahieu 2001d

Mahieu LM, De Dooy JJ, Lenaerts AE, Ieven MM, De Muynck AO. Catheter manipulations and the risk of catheter-associated bloodstream infection in neonatal intensive care unit patients. *The Journal of Hospital Infection* 2001;**48**(1):20-6. [PUBMED: 11358467]

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**(1):34-9. [PUBMED: 11773539]

Miller 2010

Miller MR, Griswold M, Harris JM 2nd, Yenokyan G, Huskins WC, Moss M, et al. Decreasing PICU catheter-associated bloodstream infections: NACHRI's quality transformation efforts. *Pediatrics* 2010;**125**(2):206-13. [PUBMED: 20064860]

Munson 2004

Munson EL, Heard SO, Doern GV. In vitro exposure of bacteria to antimicrobial impregnated-central venous catheters does not directly lead to the emergence of antimicrobial resistance. *Chest* 2004;**126**(5):1628-35. [PUBMED: 15539737]

Muttaiyah 2010

Muttaiyah S, Ritchie S, John S, Mee E, Roberts S. Efficacy of antibiotic-impregnated external ventricular drain catheters. *Journal of Clinical Neuroscience* 2010;**17**(3):286-8. [PUBMED: 20074964]

O'Grady 2002

O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, et al. Guidelines for the prevention of intravascular catheter-related infections. *Infection Control and Hospital Epidemiology* 2002;**23**(12):759-69. [PUBMED: 12517020]

O'Grady 2011

O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. *American Journal of Infection Control* 2011;**39**(4 Suppl 1):S1-34. [PUBMED: 21511081]

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**(5):636-9. [PUBMED: 19261110]

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**(8):1294-9. [PUBMED: 19438843]

Payne 2004

Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocom surviving very low birth weight infants. *Pediatrics* 2004;**114**(2):348-55. [PUBMED: 15286215]

Pronovost 2006

Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine* 2006;**355**(26):2725-32. [PUBMED: 17192537]

Ramirez de Arellano 1994

Ramirez de Arellano E, Pascual A, Martinez-Martinez L, Perea EJ. Activity of eight antibacterial agents on staphylococcus epidermidis attached to Teflon catheters. *Journal of Medical Microbiology* 1994;**40**(1):43-7. [PUBMED: 8289214]

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Saint 2000

Saint S, Veenstra DL, Lipsky BA. The clinical and economic consequences of nosocomial central venous catheter-related infection: are antimicrobial catheters useful?. *Infection Control and Hospital Epidemiology* 2000;**21**(6):375-80. [PUBMED: 10879567]

Salzman 1995

Salzman MB, Rubin LG. Intravenous catheter-related infections. *Advances in Pediatric Infectious Diseases* 1995;**10**:337-68. [PUBMED: 7718211]

Sampath 2001

Sampath LA, Tambe SM, Modak SM. In vitro and in vivo efficacy of catheters impregnated with antiseptics or antibiotics: evaluation of the risk of bacterial resistance to the antimicrobials in the catheters. *Infection Control and Hospital Epidemiology* 2001;**22**(10):640-6. [PUBMED: 11776351]

Sannoh 2010

Sannoh S, Clones B, Munoz J, Montecalvo M, Parvez B. A multimodal approach to central venous catheter hub care can decrease catheter-related bloodstream infection. *American Journal of Infection Control* 2010;**38**(6):424-9. [PUBMED: 20137829]

Schelonka 2006

Schelonka RL, Scruggs S, Nichols K, Dimmitt RA, Carlo WA. Sustained reductions in neonatal nosocomial infection rates

following a comprehensive infection control intervention. *Journal of Perinatology* 2006;**26**(3):176-9. [PUBMED: 16341027]

Schulman 2011

Schulman J, Stricof R, Stevens TP, Horgan M, Gase K, Holzman IR, et al. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. *Pediatrics* 2011;**127**(3):436-44. [PUBMED: 21339265]

Shah 2008

Shah DK, Doyle LW, Anderson PJ, Bear M, Daley AJ, Hunt RW, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *The Journal of Pediatrics* 2008;**153**(2):170-5. [PUBMED: 18534228]

Shorr 2003

Shorr AF, Humphreys CW, Helman DL. New choices for central venous catheters: potential financial implications. *Chest* 2003;**124**(1):275-84. [PUBMED: 12853534]

Stewart 2001

Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *The Lancet* 2001;**358**(9276):135-8. [PUBMED: 11463434]

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**(2 Pt 1):285-91. [PUBMED: 12165580]

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**(19):2357-65. [PUBMED: 15547163]

Tambe 2001

Tambe SM, Sampath L, Modak SM. In vitro evaluation of the risk of developing bacterial resistance to antiseptics and antibiotics used in medical devices. *The Journal of Antimicrobial Chemotherapy* 2001;**47**(5):589-98. [PUBMED: 11328769]

Thomas 2012

Thomas R, Lee S, Patole S, Rao S. Antibiotic-impregnated catheters for the prevention of CSF shunt infections: a systematic review and meta-analysis. *British Journal of Neurosurgery* 2012;**26**(2):175-84. [PUBMED: 21973061]

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**(6):782-5. [PUBMED: 17997477]

Trotter 1996a

Trotter CW. Percutaneous central venous catheter-related sepsis in the neonate: an analysis of the literature from 1990 to 1994. *Neonatal Network* 1996;**15**(3):15-28. [PUBMED: 8715646]

Trotter 1996b

Trotter CW. Percutaneous central venous catheters in neonates: a descriptive analysis and evaluation of predictors for sepsis. *The Journal of Perinatal & Neonatal Nursing* 1996;**10**(2):56-71. [PUBMED: 8868627]

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. *The Journal of Hospital Infection* 2005;**61**(4):300-11. [PUBMED: 16221510]

Vanholder 2010

Vanholder R, Canaud B, Fluck R, Jadoul M, Labriola L, Marti-Monros, A, et al. Catheter-related blood stream infections (CRBSI): a European view. *Nephrology, Dialysis, Transplantation* 2010;**25**(6):1753–6. [PUBMED: 20466662]

Walz 2010

Walz JM, Memtsoudis SG, Heard SO. Prevention of central venous catheter bloodstream infections. *Journal of Intensive Care Medicine* 2010;**25**(3):131-8. [PUBMED: 20089527]

Weber 2012

Weber JM, Sheridan RL, Fagan S, Ryan CM, Pasternack MS, Tompkins RG. Incidence of catheter-associated bloodstream infection after introduction of minocycline and rifampin antimicrobial-coated catheters in a pediatric burn population. *Journal of Burn Care & Research* 2012;**33**(4):539-43. [PUBMED: 22210071]

Wirtschafter 2010

Wirtschafter DD, Pettit J, Kurtin P, Dalsey M, Chance K, Morrow HW, et al. A state wide quality improvement collaborative to reduce neonatal central line-associated blood stream infections. *Journal of Perinatology* 2010;**30**(3):170–81. [PUBMED: 19940855]

Wong 2012

Wong J, Dow K, Shah PS, Andrews W, Lee S. Percutaneously placed central venous catheter-related sepsis in Canadian neonatal intensive care units. *American Journal of Perinatology* 2012;**29**(8):629-34. [PUBMED: 22566117]

Yébenes 2004

Yébenes JC, Vidaur L, Serra-Prat M, Sirvent JM, Batlle J, Motje M, et al. Prevention of catheter related blood stream infection in critically ill patients using a disinfectable, needle free connector: a randomised controlled trial. *American Journal of Infection Control* 2004;**32**(5):291-5. [PUBMED: 15292895]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bertini 2013

Methods	Randomised controlled trial
Participants	Preterm newborn infants (< 31 weeks' gestation) who needed an umbilical venous catheter (UVC) for parenteral nutrition, therapy, or both during the first week after birth.
Interventions	1. Silver zeolite-impregnated UVC (Vygon Lifecath PICC Expert™), 4 to 5 French gauge (Fr). 2. Another polyurethane UVC (Argyle™), 3.5 to 5 Fr.
Outcomes	Incidence of "definite" catheter-related bloodstream infection: micro-organism grown on peripheral, percutaneously-obtained blood culture concordant with organism colonising the UVC tip in infants with clinical manifestation of infection, with a UVC in place or within 48 hours of central line removal, and without other apparent sources of bloodstream infection.
Notes	Location: Tertiary Neonatal Unit, Florence, Italy (2007 to 2009).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Allocation contained in sealed opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 98 infants who were randomised, 12 died within the first week. These 12 infants were not included in the mortality analysis in the primary report - we have sought (but not yet obtained) this information from the investigators (email to cdani@unifi.it on 07/05/14)

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Seidler 2006	In vitro study.
Stevens 2011	In vitro study.
Venkatesh 2009	Study of catheter-lock solutions.

Characteristics of ongoing studies *[ordered by study ID]*

PREVAIL

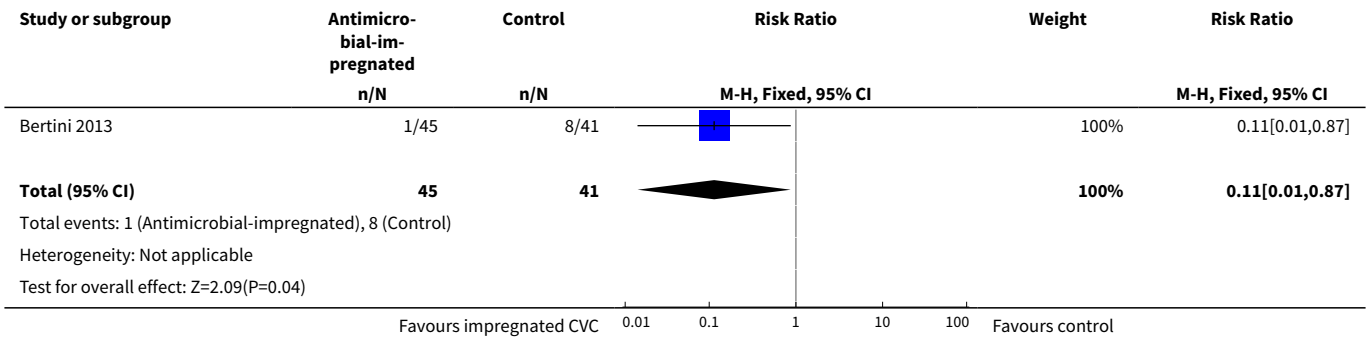
Trial name or title	PREVAIL
Methods	Randomised controlled trial
Participants	Infants in neonatal units for whom placement of a 1 French percutaneously-inserted CVC is planned
Interventions	CVC with rifampicin and miconazole coating or identical catheter without antimicrobial coating
Outcomes	Time to first positive blood culture taken 24 after randomisation and up to 48 hours after CVC removal
Starting date	June 2015
Contact information	sam.oddie@bthft.nhs.uk
Notes	

DATA AND ANALYSES

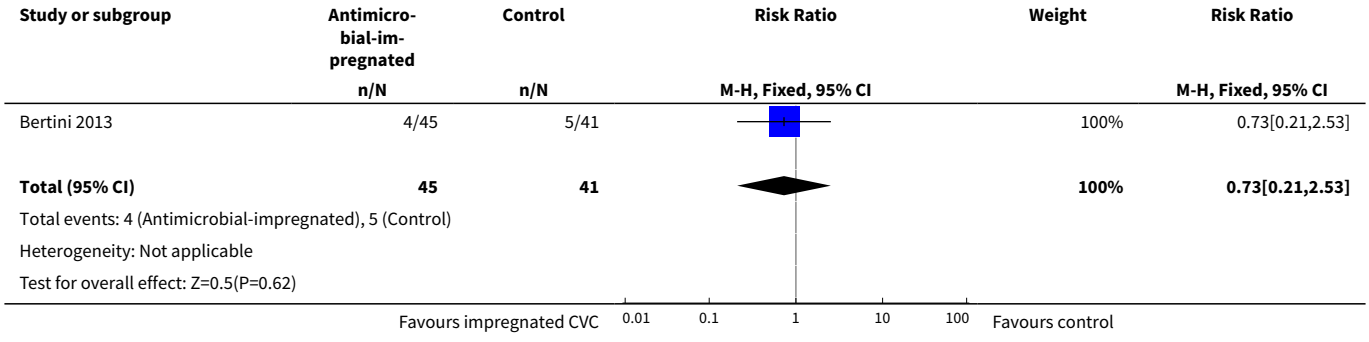
Comparison 1. Antimicrobial-impregnated CVC vs. non-impregnated CVC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related bloodstream infection	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.87]
2 Mortality prior to hospital discharge	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.21, 2.53]
3 Bronchopulmonary dysplasia	1	86	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.45, 1.42]
4 Necrotising enterocolitis	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.84]
5 Retinopathy of prematurity	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.12, 1.70]
6 Length of index CVC use	1	86	Mean Difference (IV, Fixed, 95% CI)	2.30 [0.38, 4.22]
7 Length of hospital stay	1	86	Mean Difference (IV, Fixed, 95% CI)	-13.00 [-29.41, -0.59]

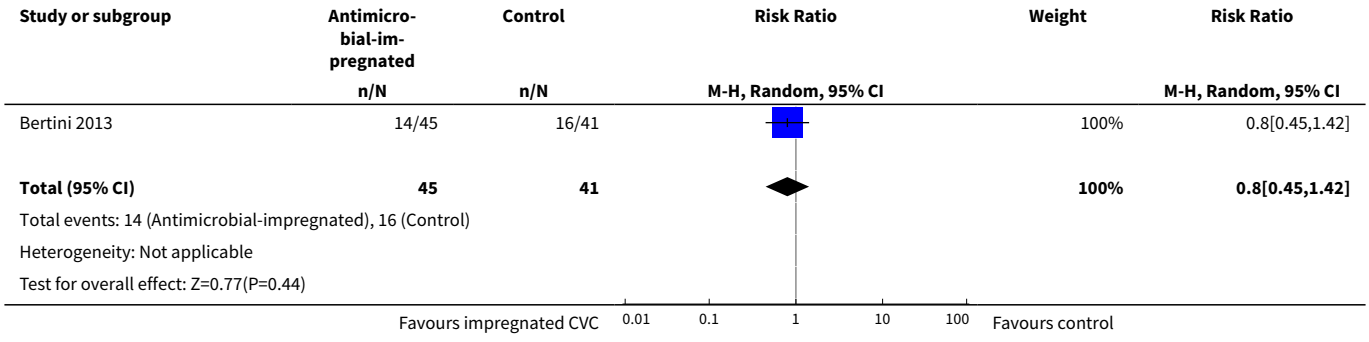
Analysis 1.1. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 1 Catheter-related bloodstream infection.



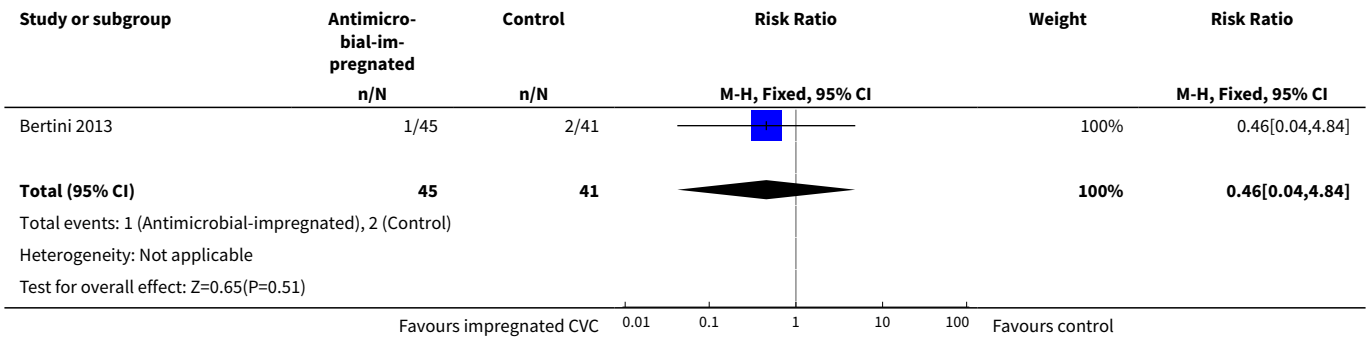
Analysis 1.2. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 2 Mortality prior to hospital discharge.



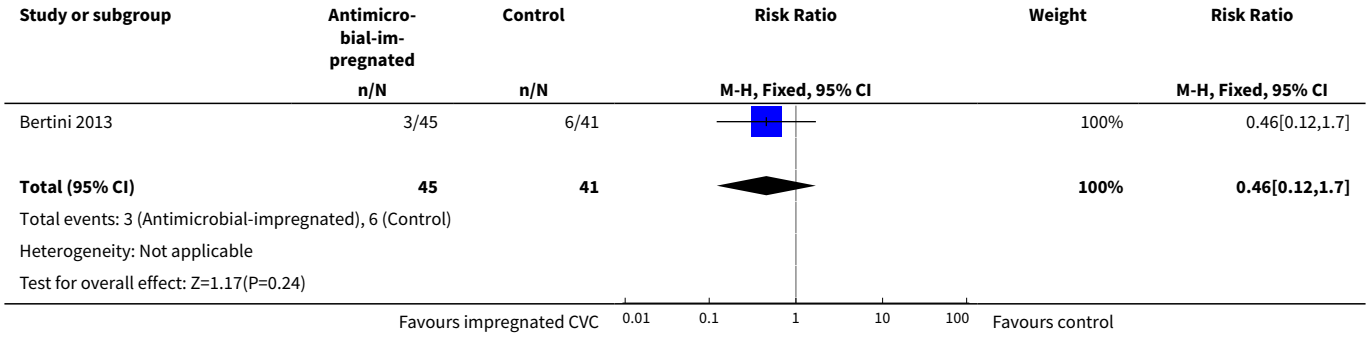
Analysis 1.3. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 3 Bronchopulmonary dysplasia.



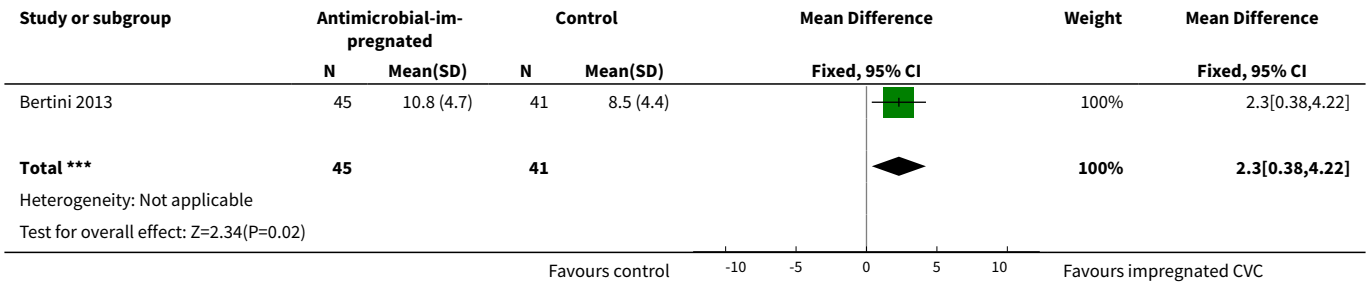
Analysis 1.4. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 4 Necrotising enterocolitis.



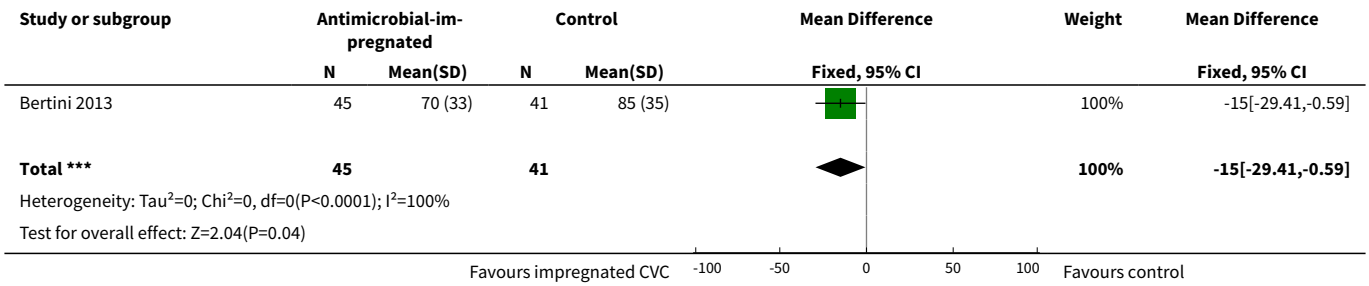
Analysis 1.5. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 5 Retinopathy of prematurity.



Analysis 1.6. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 6 Length of index CVC use.



Analysis 1.7. Comparison 1 Antimicrobial-impregnated CVC vs. non-impregnated CVC, Outcome 7 Length of hospital stay.



CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the protocol and production of the review..

DECLARATIONS OF INTEREST

Drs Sam Oddie and William McGuire are co-investigators in a UK multi-centre trial of antimicrobial-impregnated CVC in preterm infants (PREVAIL).

Dr Munisha Balain does not have any conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Definition of catheter-related bloodstream infection

Our protocol defined catheter-related bloodstream infection as culture of a micro-organism from blood obtained when the "CVC was in place on the day or the day before the blood sample for microbial culture was obtained". The included trial's protocol defined catheter-related bloodstream infection as culture of a micro-organism from blood "concordant with organism colonising the UVC tip" obtained "when the UVC is in place or within 48 hours of central line removal". We made a post hoc, pragmatic, consensus decision to accept this definition of the primary outcome since (i) it was very similar to our a priori definition (allowing a 48 hours rather than 24 hours window post CVC removal for obtaining blood cultures), and (ii) it was unlikely to be possible to obtain trial data revised to fit out review definition.

INDEX TERMS

Medical Subject Headings (MeSH)

*Central Venous Catheters; Anti-Infective Agents [*administration & dosage]; Catheter-Related Infections [*prevention & control]; Silver Compounds [*administration & dosage]; Umbilical Veins; Zeolites [*administration & dosage]

MeSH check words

Humans; Infant, Newborn