Cochrane
Library

Cochrane Database of Systematic Reviews

Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters (Review)

Lai NM, Taylor JE, Tan K, Choo YM, Ahmad Kamar A, Muhamad NA

Lai NM, Taylor JE, Tan K, Choo YM, Ahmad Kamar A, Muhamad NA.

Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters.

Cochrane Database of Systematic Reviews 2016, Issue 3. Art. No.: CD011082.

DOI: [10.1002/14651858.CD011082.pub2](https://doi.org/10.1002/14651858.CD011082.pub2).

www.cochranelibrary.com

Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	8
OBJECTIVES	9
METHODS	9
Figure 1.	13
Figure 2.	14
RESULTS	16
Figure 3.	17
Figure 4.	19
Figure 5.	20
Figure 6.	20
DISCUSSION	21
AUTHORS' CONCLUSIONS	22
ACKNOWLEDGEMENTS	22
REFERENCES	23
CHARACTERISTICS OF STUDIES	28
DATA AND ANALYSES	34
Analysis 1.1. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 1 CRBSI.	35
Analysis 1.2. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 2 Sepsis without a source.	35
Analysis 1.3. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 3 Catheter colonisation.	35
Analysis 1.4. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 4 Adverse effects: contact dermatitis.	36
Analysis 1.5. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 5 Adverse effects: pressure necrosis.	36
Analysis 2.1. Comparison 2 Silver-Alginate dressing versus control, Outcome 1 CRBSI.	37
Analysis 2.2. Comparison 2 Silver-Alginate dressing versus control, Outcome 2 Mortality.	37
Analysis 2.3. Comparison 2 Silver-Alginate dressing versus control, Outcome 3 Adverse effects: contact dermatitis.	37
APPENDICES	38
WHAT'S NEW	41
CONTRIBUTIONS OF AUTHORS	41
DECLARATIONS OF INTEREST	41
SOURCES OF SUPPORT	41
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	42
INDEX TERMS	42

[Intervention Review]

Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters

Nai Ming Lai¹, Jacqueline E Taylor², Kenneth Tan³, Yao Mun Choo⁴, Azanna Ahmad Kamar⁴, Nor Asiah Muhamad⁵

¹School of Medicine, Taylor's University, Subang Jaya, Malaysia. ²Monash Newborn, Monash Medical Centre/Monash University, Clayton, Australia. ³Department of Paediatrics, Monash University, Melbourne, Australia. ⁴Department of Paediatrics, University of Malaya, Kuala Lumpur, Malaysia. ⁵Disease Control Division, Ministry of Health Malaysia, Putrajaya, Malaysia

Contact address: Kenneth Tan, Department of Paediatrics, Monash University, 246 Clayton Road, Clayton, Melbourne, Victoria, VIC 3168, Australia. kenneth.tan@monash.edu, kenneth.tan@monashhealth.org.

Editorial group: Cochrane Neonatal Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2017.

Citation: Lai NM, Taylor JE, Tan K, Choo YM, Ahmad Kamar A, Muhamad NA. Antimicrobial dressings for the prevention of catheter-related infections in newborn infants with central venous catheters. *Cochrane Database of Systematic Reviews* 2016, Issue 3. Art. No.: CD011082. DOI: [10.1002/14651858.CD011082.pub2](https://doi.org/10.1002/14651858.CD011082.pub2).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Central venous catheters (CVCs) provide secured venous access in neonates. Antimicrobial dressings applied over the CVC sites have been proposed to reduce catheter-related blood stream infection (CRBSI) by decreasing colonisation. However, there may be concerns on the local and systemic adverse effects of these dressings in neonates.

Objectives

We assessed the effectiveness and safety of antimicrobial (antiseptic or antibiotic) dressings in reducing CVC-related infections in newborn infants. Had there been relevant data, we would have evaluated the effects of antimicrobial dressings in different subgroups, including infants who received different types of CVCs, infants who required CVC for different durations, infants with CVCs with and without other antimicrobial modifications, and infants who received an antimicrobial dressing with and without a clearly defined co-intervention.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group (CNRG). We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2015, Issue 9), MEDLINE (PubMed), EMBASE (EBHOST), CINAHL and references cited in our short-listed articles using keywords and MeSH headings, up to September 2015.

Selection criteria

We included randomised controlled trials that compared an antimicrobial CVC dressing against no dressing or another dressing in newborn infants.

Data collection and analysis

We extracted data using the standard methods of the CNRG. Two review authors independently assessed the eligibility and risk of bias of the retrieved records. We expressed our results using risk difference (RD) and risk ratio (RR) with 95% confidence intervals (CIs).

Main results

Out of 173 articles screened, three studies were included. There were two comparisons: chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following povidone-iodine cleansing (one study); and silver-alginate patch versus control (two studies). A total of 855 infants from level III neonatal intensive care units (NICUs) were evaluated, 705 of whom were from a single study. All studies

were at high risk of bias for blinding of care personnel or unclear risk of bias for blinding of outcome assessors. There was moderate-quality evidence for all major outcomes.

The single study comparing chlorhexidine dressing/alcohol cleansing against polyurethane dressing/povidone-iodine cleansing showed no significant difference in the risk of CRBSI (RR 1.18, 95% CI 0.53 to 2.65; RD 0.01, 95% CI -0.02 to 0.03; 655 infants, moderate-quality evidence) and sepsis without a source (RR 1.06, 95% CI 0.75 to 1.52; RD 0.01, 95% CI -0.04 to 0.06; 705 infants, moderate-quality evidence). There was a significant reduction in the risk of catheter colonisation favouring chlorhexidine dressing/alcohol cleansing group (RR 0.62, 95% CI 0.45 to 0.86; RD -0.09, 95% CI -0.15 to -0.03; number needed to treat for an additional beneficial outcome (NNTB) 11, 95% CI 7 to 33; 655 infants, moderate-quality evidence). However, infants in the chlorhexidine dressing/alcohol cleansing group were significantly more likely to develop contact dermatitis, with 19 infants in the chlorhexidine dressing/alcohol cleansing group having developed contact dermatitis compared to none in the polyurethane dressing/povidone-iodine cleansing group (RR 43.06, 95% CI 2.61 to 710.44; RD 0.06, 95% CI 0.03 to 0.08; number needed to treat for an additional harmful outcome (NNTH) 17, 95% CI 13 to 33; 705 infants, moderate-quality evidence). The roles of chlorhexidine dressing in the outcomes reported were unclear, as the two assigned groups received different co-interventions in the form of different skin cleansing agents prior to catheter insertion and during each dressing change.

In the other comparison, silver-alginate patch versus control, the data for CRBSI were analysed separately in two subgroups as the two included studies reported the outcome using different denominators: one using infants and another using catheters. There were no significant differences between infants who received silver-alginate patch against infants who received standard line dressing in CRBSI, whether expressed as the number of infants (RR 0.50, 95% CI 0.14 to 1.78; RD -0.12, 95% CI -0.33 to 0.09; 1 study, 50 participants, moderate-quality evidence) or as the number of catheters (RR 0.72, 95% CI 0.27 to 1.89; RD -0.05, 95% CI -0.20 to 0.10; 1 study, 118 participants, moderate-quality evidence). There was also no significant difference between the two groups in mortality (RR 0.55, 95% CI 0.15 to 2.05; RD -0.04, 95% CI -0.13 to 0.05; two studies, 150 infants, $I^2 = 0\%$, moderate-quality evidence). No adverse skin reaction was recorded in either group.

Authors' conclusions

Based on moderate-quality evidence, chlorhexidine dressing/alcohol skin cleansing reduced catheter colonisation, but made no significant difference in major outcomes like sepsis and CRBSI compared to polyurethane dressing/povidone-iodine cleansing. Chlorhexidine dressing/alcohol cleansing posed a substantial risk of contact dermatitis in preterm infants, although it was unclear whether this was contributed mainly by the dressing material or the cleansing agent. While silver-alginate patch appeared safe, evidence is still insufficient for a recommendation in practice. Future research that evaluates antimicrobial dressing should ensure blinding of caregivers and outcome assessors and ensure that all participants receive the same co-interventions, such as the skin cleansing agent. Major outcomes like sepsis, CRBSI and mortality should be assessed in infants of different gestation and birth weight.

PLAIN LANGUAGE SUMMARY

Antimicrobial dressings attached to the central venous catheters in reducing catheter-related infections in newborn infants

Review question: In newborn infants who require a central venous catheter, does the use of antiseptic or antibiotic catheter dressing, compared to no dressing, reduce catheter-related infections?

Background: Central venous catheters (CVCs) are small tubes inserted into the vein to give fluids, medication and intravenous nutrition to sick patients. The risks of CVCs are well-known, and can cause infections, which may result in death or serious illnesses. Newborn infants are vulnerable, as they on the one hand require the CVCs to sustain life, and on the other hand are at high risks of the complications, due to their thin skin and poorly-developed immune system.

Several measures have been developed to reduce infections in newborn infants. These include hand hygiene for caregivers, skin cleaning for the infants, antibiotics and modification of the catheters including the use of antiseptic or antibiotic-coated catheter dressing or patch that could be placed on the skin at the CVC insertion site. While promising, these measures need on-going evaluation. In this review, we synthesized up-to-date evidence on the effectiveness and safety of antiseptic or antibiotic dressing as a part of CVC care in sick newborn infants.

Search date: We performed a search in multiple medical databases in September 2015.

Study characteristics: Three studies (total participants: 855) fit our inclusion criteria. There were two main comparisons: i) chlorhexidine dressing and alcohol skin cleansing against standard polyurethane dressing and povidone-iodine skin cleansing (from one large study), and ii) silver-alginate patch against a control group without patch (from two smaller studies). The quality of the included studies are high, except that the people closely involved in the trials such as the care personnel were not masked from knowing whether or not the infants in the study were given antiseptic or antibiotic dressing, which might have affected their recording or interpretation of the results.

Study funding sources: One of the studies was funded in part by Johnson and Johnson Medical; Children's Foundation; Children's Hospital, Milwaukee and National Institutes of Health. Another study was funded by the Vanderbilt NICU Research Fund. Funding source was not stated in the third study.

Key results: In our main findings, chlorhexidine dressing/alcohol skin cleansing made no difference to catheter-related blood stream infection (CRBSI) and blood stream infection ("sepsis") without an identifiable source, although it significantly reduced the chance of micro-organisms lodging in the CVCs ("catheter colonisation"), with an average of 9% reduction in risk among newborn infants with a baseline risk of 24% (1 study, 655 infants). However, infants who received chlorhexidine dressing/alcohol skin cleansing were more likely to develop skin irritation ("contact dermatitis"), as 19 out of 335 infants (5.7%) in the chlorhexidine group developed this complication compared to none in the group that received standard dressing/povidone-iodine cleansing. However, it was unclear whether the dressing or the alcohol solution was mainly responsible for the skin irritation, as the other group did not use alcohol solution for skin cleansing. In the other comparison, silver-alginate patch made no overall differences in CRBSI and mortality compared to no dressing, neither did it cause any adverse reaction.

Quality of the evidence: There was moderate-quality evidence for all the major outcomes. The major factor that affected the quality of evidence was the lack of precision in the result estimates, as the calculated plausible range of the effects (the 95% confidence intervals) were wide.

Conclusions: Chlorhexidine CVC dressing with alcohol skin cleansing posed a high risk of skin irritation against a modest reduction in catheter colonisation. For silver-alginate patch, evidence is still insufficient for a clear picture of benefit an harm. We have made recommendations for future research that evaluate these interventions.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Chlorhexidine dressing following alcohol cleansing compared to polyurethane dressing following aqueous povidone-iodine cleansing for the prevention of catheter-related infections in newborn infants with central venous catheters

Chlorhexidine dressing/alcohol cleansing compared to polyurethane dressing/povidone-iodine cleansing for the prevention of catheter-related infections in newborn infants with central venous catheters

Patient or population: newborn infants with central venous catheters

Settings: neonatal intensive care units

Intervention: chlorhexidine dressing/alcohol cleansing

Comparison: polyurethane dressing/povidone-iodine cleansing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	polyurethane dressing following aqueous povidone-iodine cleansing	Chlorhexidine dressing following alcohol cleansing				
Sepsis without a source	Study population		RR 1.06 (0.75 to 1.52)	705 (1 RCT)	⊕⊕⊕⊖ MODERATE ¹	
	143 per 1000	152 per 1000 (107 to 218)				
	Moderate					
	143 per 1000	152 per 1000 (107 to 218)				
Catheter-related blood stream infection	Study population		RR 1.18 (0.53 to 2.65)	655 (1 RCT)	⊕⊕⊕⊖ MODERATE ¹	
	32 per 1000	38 per 1000 (17 to 85)				
	Moderate					
	32 per 1000	38 per 1000 (17 to 86)				
Catheter colonisation	Study population		RR 0.62 (0.45 to 0.86)	655 (1 RCT)	⊕⊕⊕⊖ MODERATE ²	
	240 per 1000	149 per 1000				

	(108 to 207)				
	Moderate				
	241 per 1000	149 per 1000 (108 to 207)			
Adverse effects: contact dermatitis	Study population		RR 43.06 (2.61 to 710.44)	670 (1 RCT)	⊕⊕⊕⊖ MODERATE ¹
	57 per 1000	2442 per 1000 (148 to 40294)			
	Moderate				
	0 per 1000	0 per 1000 (0 to 0)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹95% confidence interval is wide

²Catheter colonisation might not be strongly correlated with major clinical outcomes such as CRBSI and mortality

Summary of findings 2. Silver-alginate dressing versus control for the prevention of catheter-related infections in newborn infants with central venous catheters

Silver-alginate patch compared to standard dressing for the prevention of catheter-related infections in newborn infants with central venous catheters

Patient or population: newborn infants with central venous catheters

Settings: neonatal intensive care units

Intervention: silver-Alginate patch

Comparison: standard dressing

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
----------	--	-----------------------------	---------------------------------	---------------------------------------	----------

	Assumed risk	Corresponding risk			
	Control	Silver-Alginate dressing versus control			
CRBSI - Unit of analysis: infants Clinical and microbiological methods	Study population		RR 0.5 (0.14 to 1.78)	50 (1 study)	⊕⊕⊕⊖ moderate ¹
	240 per 1000	120 per 1000 (34 to 427)			
	Moderate				
	240 per 1000	120 per 1000 (34 to 427)			
CRBSI - Unit of analysis: catheters Clinical and microbiological methods	Study population		RR 0.72 (0.27 to 1.89)	118 (1 study)	⊕⊕⊕⊖ moderate ¹
	172 per 1000	124 per 1000 (47 to 326)			
	Moderate				
	172 per 1000	124 per 1000 (46 to 325)			
Mortality Clinical assessment	Study population		RR 0.55 (0.15 to 2.05)	150 (2)	⊕⊕⊕⊖ moderate ¹
	100 per 1000	55 per 1000 (15 to 205)			
	Moderate				
	100 per 1000	55 per 1000 (15 to 205)			
Adverse effects: contact dermatitis	See comment	See comment	Not estimable	150 (2)	See comment

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

¹ 95 % CI was wide and covered substantial benefits on one end and substantial harm on the other.

BACKGROUND

Description of the condition

Central venous catheters (CVCs) are essential devices in the care of sick individuals. A CVC provides a relatively secure access for administering intravenous medications, fluids and parenteral nutrition. It is estimated that, annually, five million and 200,000 CVCs are used in the USA and UK, respectively (Worthington 2005). One of the major problems associated with the use of CVCs is catheter-related infections, which have been shown to cause significant morbidity and mortality associated with considerable costs to the healthcare system (CDC 2011; Cicalini 2004). It is estimated that in the USA approximately 80,000 cases of CVC-associated blood stream infections (BSIs) occur in intensive care units (ICUs) every year, with a mortality rate of up to 35% and estimated associated healthcare costs ranging from USD 296 million to USD 2.3 billion (CDC 2011). These estimates, however, are based mainly on adult data.

CVCs are frequently placed in newborn infants in the neonatal intensive care unit (NICU). Infants in the NICU represent a distinct group of individuals who are particularly at risk of infections due to their compromised skin barrier and immature immune system (Ygberg 2012). The presence of a CVC represents a significant risk factor for catheter-related infection in newborn infants, in particular catheter-related blood stream infection (CRBSI) (Chien 2002; Couto 2006; Olsen 2009). The reported baseline rates of CVC-associated blood stream infection (BSI) in NICUs in different parts of the world range from approximately 4 to over 21 per 1000 CVC-days (Fisher 2013; Jaggi 2013; Rosenthal 2013). The daily increase in the risk of CRBSI in neonates in the first few weeks of NICU stay varies from a 2% increase per day of catheter use in one report (Wong 2012) to a 14% increase in another report (Sengupta 2010). An episode of CRBSI in a neonate increases hospital stay by four to seven days and increases the overall cost of care by up to USD 6000 (Payne 2004). Multifaceted quality improvement approaches, which include staff education, strict daily monitoring by dedicated line maintenance teams and catheter-specific strategies, have been shown consistently to reduce CRBSI in adult as well as neonatal ICU settings around the world, with a two- to seven-fold reduction in CRBSI reported (Bizzarro 2010; Costello 2008; Jaggi 2013; Rosenthal 2013).

Description of the intervention

Several catheter-specific strategies that aim to reduce catheter-related infections are implemented during the insertion and in-dwelling time of a catheter. These include skin antisepsis, prophylactic antibiotics, antimicrobial catheters, implementation of catheter care bundles and the specialised addition of antimicrobials to the catheter in the form of antimicrobial locks or dressings.

An antimicrobial is generally an agent that kills or stops the growth of bacteria, fungi, viruses or parasites (CDC 2011). There are two major types of antimicrobial: antiseptic and antibiotic. Antiseptics, such as hand washes or surgical scrubs, destroy a range of micro-organisms on a surface or in living tissues, whereas antibiotics are administered in relatively small amounts with the aim of selective targeting of micro-organisms, especially bacteria (McDonnell 1999).

A catheter dressing refers to a protective material applied to the site of catheter insertion with the major aim of securing the CVC in place and includes, for instance, gauze with tape or transparent dressing. More recently, the use of catheter dressings that incorporate antiseptics or antibiotics has been introduced; these are produced commercially but can be improvised by the hospital. A CVC dressing is usually applied during insertion of the CVC at the insertion site, and is either changed regularly, with recommendations ranging from every two to seven days depending on the catheter material, or kept in place until catheter removal, unless the dressing is damp, loosened or visibly soiled (CDC 2011).

How the intervention might work

Insertion of a CVC, a foreign body, puts an individual at risk of catheter microbial colonisation. Catheter colonisation, in turn, has been postulated to lead to CRBSI, as micro-organisms gain entry to the individual's circulation via the external and intraluminal surfaces of the catheter (Linares 2007). It has been shown that catheter colonisation correlates strongly with CRBSI (Maki 1977; Rijnders 2002), with intraluminal and extraluminal routes of bacterial migration accounting for 67% and 20%, respectively, of CRBSI in neonates according to a cohort study (Garland 2008). The use of a catheter dressing may further increase the risks, as the dressing represents another foreign material in close proximity to the catheter and insertion site – the point at which the skin barrier is breached (Webster 2011). Although skin antisepsis using an antiseptic solution has been recommended as one of the most important measures to prevent CVC-related infections (Pratt 2007), skin antisepsis alone does not eliminate all micro-organisms on the skin surface, due to problems in the permeability of the antiseptic and the presence of micro-organisms that reside in deeper layers of the skin (Bashir 2012; Brown 1989; Karpanen 2009; Leeming 1984). Residual micro-organisms on the skin may act as a nidus for the colonisation of any device such as a CVC (Karpanen 2011). Antiseptics or antibiotics that are incorporated into the catheter dressing aim to provide another means of protection against infections by enabling the steady release of the antimicrobial to kill or stop the growth of micro-organisms that may be present on the dressing before they multiply in sufficient numbers to cause catheter colonisation and infection (Cicalini 2004).

Why it is important to do this review

The benefits and harms of catheter-related interventions have been subjected to ongoing assessment, due to the dynamic relationship between micro-organisms and hosts, the changing susceptibility of micro-organisms to antibiotics over time (Raad 2002), and advances in catheter-based technologies (Cicalini 2004), as well as infection control measures in general (CDC 2011), which may lead to the changing contribution of each intervention in influencing the overall rate of catheter-related infections. This is reflected in the number of Cochrane systematic reviews in this area that have either been published or are in development (Arora 2010; Foster 2006; Gavin 2011; Ge 2012; Inglis 2005; Jardine 2008; Kabra 2005; Lai 2012; Lai 2013; Schoot 2011; Shah 2007; Taylor 2013; Ullman 2013; Vasudevan 2011; Webster 2011). There are currently uncertainties in recommending the use of antimicrobial dressings, as reflected in the most recent Centers for Disease Control and Prevention (CDC) guidelines, which state there is low- to very low quality evidence to support the recommendation regarding the use of chlorhexidine-based dressings and give no recommendations for other types of dressing (CDC 2011). The question of whether

the use of antimicrobial dressings adds significantly to the other measures used to reduce catheter-related infections in newborn infants warrants ongoing evaluation in the form of a systematic review. The relative effectiveness of one antimicrobial dressing versus another should be assessed, together with the adverse effects of the antimicrobial agent and the dressing itself (most notably any possible adverse effect on the highly vulnerable skin of the infant ([Afsar 2009](#))), as well as the risk of antibiotic resistance.

OBJECTIVES

We assessed the effectiveness and safety of antimicrobial (antiseptic or antibiotic) dressings in reducing CVC-related infections in newborn infants. Had there been relevant data, we would have evaluated the effects of antimicrobial dressings in different subgroups, including infants who received different types of CVCs, infants who required CVC for different durations, infants with CVCs with and without other antimicrobial modifications, and infants who received an antimicrobial dressing with and without a clearly defined co-intervention.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT), quasi-RCT and cluster-RCT comparing any antimicrobial dressing (single or in combination) against no dressing, or one type of antimicrobial dressing against another, in neonates with a CVC in place.

We included the following types of CVCs in our consideration in this review:

1. umbilical venous catheters (UVCs);
2. percutaneously inserted CVCs (long line);
3. other types of double- or triple-lumen CVCs, such as tunnelled catheters and femoral lines that are inserted to any length beyond that of a typical intravenous cannula.

We accepted studies assessing any catheter material, including standard or impregnated catheters.

Types of participants

Newborn infants of any postmenstrual age cared for in an NICU with a CVC in place. Each infant should have only one CVC at any time during the study, although we accepted studies in which the same infant received more than one CVC sequentially. We have described how we planned to handle studies that report outcome data using catheters rather than infants as the unit of analysis in the section [Unit of analysis issues](#).

There were no studies that evaluated UVC dressing in infants with or without a concurrent umbilical arterial catheter. We would have included such studies if they met the inclusion criteria in terms of population, intervention and outcome.

Types of interventions

Intervention

- The use of any antimicrobial dressing for CVC, either alone or in combination.

The antimicrobial dressings that we assessed included dressings that contain chlorhexidine gluconate, povidone-iodine or specific antibiotics.

Comparison

- The use of placebo, no dressing or another antimicrobial dressing for CVC, either alone or in combination.

The dressing should be applied during the insertion of the catheter, and changed either regularly or only when the dressing is damp, loosened or visibly soiled. The selection, insertion, use, maintenance and removal of CVCs as well as the dressing in both the intervention and comparison groups must follow the standard protocol as specified in the study. There should be no difference in the catheter material, including the presence or absence of antimicrobial impregnation or other catheter-related antimicrobial technologies, intended in-dwelling period and concurrent infection control measures, in the intervention and comparison groups.

We did not place any limits on the minimum and maximum duration of the follow-up period for each study.

Types of outcome measures

Primary outcomes

1. Proven CRBSI: expressed by the authors of the individual studies as absolute rates or episodes per 1000 catheter-days, or both. Episodes per 1000 catheter-days were calculated as follows: absolute rate divided by the total catheter-days (the sum of the in-dwelling time for all catheters in the assigned group) multiplied by 1000. We used a broad definition of CRBSI based on CDC criteria ([CDC 2011](#); [CDC 2014](#)). We have provided a detailed description of these criteria below. We planned to include studies that define CVC-related and CVC-associated infections using criteria that are not covered by the CDC definitions, provided the authors justified their definitions with valid sources;
2. Clinically diagnosed sepsis (with or without concurrent microbiological evidence of a CRBSI), expressed as absolute rates or episodes per 1000 catheter-days, or both, if data are available;
3. All-cause mortality, assessed throughout the hospital stay of the participants.

Definition of sepsis related to an intravascular device (CDC 2011; CDC 2014)

CRBSI

Bacteraemia or fungaemia in an individual with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infections (i.e. fever, chills, hypotension or a combination) and no apparent source for the BSI except the catheter. This definition applies in general to all age groups although some clinical features may not apply to the neonatal population.

Additionally, one of the following should be present:

1. A positive semiquantitative (15 colony-forming units (CFU)/catheter segment) or quantitative (10^3 CFU/catheter segment) culture whereby the same organism is isolated from the catheter segment and peripheral blood;

2. Differential period of CVC culture versus peripheral blood culture positivity of two hours;
3. In cases of a neonatal death, positive bacterial culture at normally sterile sites (e.g. liver, spleen, meninges, lung) at autopsy.

Clinical sepsis

All of the following criteria should be fulfilled:

1. Infants should demonstrate at least one of the following clinical features:
 - a. fever (more than 38 °C core temperature);
 - b. hypothermia (less than 36 °C core temperature);
 - c. apnoea or bradycardia.
2. No positive blood culture;
3. No apparent source of infection from another site;
4. The clinical features have led to the institution of treatment for sepsis.

Secondary outcomes

1. Proportion of infants or catheters with catheter colonisation, defined as a significant growth of a micro-organism (more than 15 CFU) from the catheter tip, subcutaneous segment or catheter hub in the absence of clinical signs of infection (CDC 2011; Pagani 2008); assessed at catheter removal;
2. Proportion of infants or catheters with exit-site infection, either microbiologically documented (i.e. exudates at the catheter exit site yield a micro-organism with or without concomitant BSI) or clinically documented (i.e. erythema or induration within 2 cm of the catheter exit site in the absence of associated BSI and without concomitant purulence (Pagani 2008)); assessed throughout the in-dwelling period of the catheter;
3. Proportion of infants with drug-resistant organisms from cultures, including exit site cultures, catheter cultures and blood cultures; assessed throughout the in-dwelling period of the catheter;
4. Number of infants with adverse events, including skin irritation, contact dermatitis, systemic allergic reaction and anaphylaxis; assessed throughout the in-dwelling period of the catheter;
5. Antibiotic usage during hospitalisation, either the proportion of infants in whom antibiotics are required due to suspected or proven infection (as detailed under primary outcomes 1 and 2) or the mean duration of antibiotics use; assessed throughout the infants' hospital stay;
6. Length of hospitalisation in days;
7. Long-term neurodevelopmental outcomes, measured using validated scales such as the Bayley Scale of Infant Development (Washington 1998), at 12, 18 or 24 months of age. Data on clinically diagnosed non-ambulatory cerebral palsy or significant auditory and visual impairment would be accepted if available.

Search methods for identification of studies

We followed the search strategy as used by the Cochrane Neonatal Review Group (CNRG).

Electronic searches

We searched following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, issue 9, 2015);
2. MEDLINE (via PubMed (National Library of Medicine)) (1950 to September 2015);
3. EMBASE databases (1980 to September 2015);
4. CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to September 2015).

We outline detailed search strategies for each of the above databases in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#) and [Appendix 4](#), respectively.

We searched ongoing clinical trials and unpublished studies via the following sites:

1. <http://www.clinicaltrials.gov>;
2. <http://www.controlled-trials.com>;
3. <http://clinicalstudyresults.org>.

We did not apply any language restrictions.

Searching other resources

We searched the references cited in relevant studies, Cochrane reviews, guidelines, review articles and conference proceedings, including abstracts from Annual Meetings of the Pediatric Academic Societies (American Pediatric Society/Society for Pediatric Research and European Society for Paediatric Research) and the Perinatal Society of Australia and New Zealand. We planned to contact expert informants if necessary to identify further relevant studies.

Data collection and analysis

We employed Cochrane's standard methods, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Two review authors (YMC, NAM) independently performed the first round of searching for relevant studies. They then screened these studies for inclusion in the analysis with the help of an arbiter (NML), using the predefined inclusion and exclusion criteria.

Selection of studies

We accepted published and unpublished studies, both in full article and abstract forms, as long as a complete assessment of risk of bias was possible. We planned to contact the authors of unpublished studies and studies available only as abstracts to request further information about the studies, including specific details, such as the methods of sequence generation, allocation and blinding, participant withdrawal and prespecified outcomes, as well as full outcome data, to enable them to be included in our meta-analysis. We included only final data from each study and not data from interim analyses.

Data extraction and management

Two review authors (NML and JT) independently extracted and coded all data from each included study using a pro forma designed specifically for this review. We screened for duplicate entry of participants by matching the initial number of participants recruited against the total numbers at each step in the study. If we discovered a discrepancy, we looked for an explanation in the

article (e.g. multiple enrolment of the same participants in different hospital admissions). Any disagreement among the review authors was resolved by discussion leading to a consensus.

Assessment of risk of bias in included studies

Two authors (NML and AAK) independently assessed each included study for risk of bias according to seven major criteria as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

1. Random sequence generation (selection bias);
2. Allocation concealment (selection bias);
3. Blinding of participants and personnel (performance bias);
4. Blinding of outcome assessment (detection bias);
5. Incomplete outcome data (attrition bias);
6. Selective reporting (reporting bias);
7. Other bias.

We accorded a judgement of low risk, high risk or unclear risk of bias, with justifications based on the information obtained from the papers.

Below is a detailed description on how we judged the study according to each domain.

1. Was the allocation sequence randomly generated?

- Yes, low risk of bias
 - A random (unpredictable) assignment sequence
 - Examples of adequate methods of sequence generation are computer-generated random sequence, coin toss (for studies with two groups), rolling a die (for studies with two or more groups), drawing of balls of different colours, dealing previously shuffled cards
- No, high risk of bias
 - Quasi-randomised approach: examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number
 - Non-random approaches: allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests
- Unclear
 - Insufficient information about the sequence generation process to permit judgement

2. Was the treatment allocation adequately concealed?

- Yes, low risk of bias
 - Assignment must be generated independently by a person not responsible for determining the eligibility of the participants. This person has no information about the people included in the trial and has no influence on the assignment sequence or on the decision about whether the person is eligible to enter the trial. Examples of adequate methods of allocation concealment are: central allocation, including telephone, web-based and pharmacy-controlled randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque sealed envelopes
- No, high risk of bias

- Examples of inadequate methods of allocation concealment are: alternate medical record numbers, unsealed envelopes; date of birth; case record number; alternation or rotation; an open list of random numbers; any information in the study that indicated that investigators or participants could influence the intervention group
- Unclear
 - Randomisation stated but no information on method of allocation used is available

3 and 4. Blinding was knowledge of the allocated interventions adequately prevented during the study?

Was the participant blinded to the intervention?

- Yes, low risk of bias
 - The treatment and control groups are indistinguishable for the participants or the participant was described as blinded and the method of blinding was described
- No, high risk of bias
 - Blinding of study participants attempted, but likely that the blinding could have been broken; participants were not blinded, and the non-blinding of others likely to introduce bias
- Unclear

Was the care provider blinded to the intervention?

- Yes, low risk of bias
 - The treatment and control groups are indistinguishable for the care/treatment providers or the care provider was described as blinded and the method of blinding was described
- No, high risk of bias
 - Blinding of care/treatment providers attempted, but likely that the blinding could have been broken; care/treatment providers were not blinded, and the non-blinding of others likely to introduce bias
- Unclear

Was the outcome assessor blinded to the intervention?

- Yes, low risk of bias
 - Adequacy of blinding should be assessed for the primary outcomes. The outcome assessor was described as blinded and the method of blinding was described
- No, high risk of bias
 - No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding
- Unclear

We assessed the blinding of data for each outcome separately where necessary: namely, if there were two distinct categories of outcomes, one subjective and one objective, although in this review we decided to assess blinding for all outcomes as they were sufficiently similar.

5. Were incomplete outcome data adequately addressed?

Was the drop-out rate described and acceptable?

The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given

- Yes, low risk of bias
 - If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias (NB these percentages are arbitrary, not supported by literature)
 - No missing outcome data
 - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias)
 - Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
 - Missing data have been imputed using appropriate methods
- No, high risk of bias
 - Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
- Unclear

Were all randomised participants analysed in the group to which they were allocated? (ITT analysis)

- Yes, low risk of bias
 - Specifically reported by authors that ITT was undertaken and this was confirmed on study assessment, or not stated but evident from study assessment that all randomised participants are reported/analysed in the group they were allocated to for the most important time point of outcome measurement (minus missing values) irrespective of non-compliance and co-interventions
- No, high risk of bias
 - Lack of ITT confirmed on study assessment (participants who were randomised were not included in the analysis because they did not receive the study intervention; they withdrew from the study; or were not included because of protocol violation) regardless of whether ITT reported or not
 - 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
- Unclear
 - Described as ITT analysis, but unable to confirm on study assessment, or not reported and unable to confirm by study assessment

6. Are reports of the study free of suggestion of selective outcome reporting?

- Yes, low risk of bias
 - If all the results from all prespecified outcomes have been adequately reported in the published report of the

trial. This information is either obtained by comparing the protocol and the final trial report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgement. Alternatively, a judgement could be made if the trial report lists the outcomes of interest in the methods of the trial and then reports all these outcomes in the results section of the trial report

- No, high risk of bias
 - Not all of the study's prespecified primary outcomes have been reported
 - One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified
 - One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect)
 - One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis
 - The study report fails to include results for a key outcome that would be expected to have been reported for such a study
- Unclear

7. Other sources of potential bias

Were the groups similar at baseline regarding the most important prognostic indicators?

- Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints (e.g. indication and intended duration of CVC). Alternatively if there were imbalances at baseline these have been accounted for in the analysis of the study.

Were co-interventions avoided or similar?

- There were no co-interventions or there were co-interventions but they were similar between the treatment and control groups.

Was compliance acceptable in all groups?

- The review author determines whether compliance with interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the treatment intervention and control intervention(s). For example, ultrasound treatment is usually administered over several sessions; therefore, it is necessary to assess how many sessions each participant attended or if participants completed the course of an oral drug therapy. For single-session interventions (e.g. surgery), this item is irrelevant.

Were the trials or trialists in receipt of financial support from agencies or organisations with a financial interest in the outcome of the trial?

We completed a 'Risk of bias' table for each eligible study and present our overall assessment of risk of bias using a 'Risk of bias' graph (Figure 1) and 'Risk of bias' summary (Figure 2). Any disagreement among the review authors was resolved by discussion to achieve a consensus.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Garland 2001	+	+	-	?	+	+	+
Hill 2010	+	+	-	?	+	+	-
Khattak 2010	?	+	-	?	+	+	+

Quality of evidence

We assessed the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This methodological approach considers randomised controlled trials as high-quality evidence that may be rated down by limitations in any of five areas: design (risk of bias); consistency across studies; directness of the evidence; precision of estimates; and presence of publication bias (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: 1) High: We are very confident that the true effect lies close to that of the estimate of the effect; 2) 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; 3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; 4) 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 (Schünemann 2013).

The review authors independently assessed the quality of the evidence found for the following outcomes, which were identified as critical or important for clinical decision making: sepsis (without a source); catheter-related blood stream infection; catheter colonization; mortality; adverse effects – contact dermatitis/adverse skin reaction.

In cases where study authors did not take measures to ensure concealment of allocation, randomised assignment, completed follow-up or blinded outcome assessment, the quality of evidence was downgraded because of design limitations (Guyatt 2011b). Consistency was evaluated by similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including test for heterogeneity (I^2), as elaborated under the subsequent heading of [Assessment of heterogeneity](#). The quality of evidence was downgraded when inconsistency across results of studies

was present and large and unexplained (i.e. some studies suggest important benefit and others no effect or harm without a clinical explanation) (Guyatt 2011d). Precision was assessed according with the 95% confidence interval around the pooled estimation (Guyatt 2011c). When trials were conducted in populations other than the target population, when they used interventions that were different from the intervention of interest, or when the outcomes assessed were not directly patient-important — for instance, using a surrogate rather than a clinical outcome — we downgraded the quality of evidence because of indirectness (Guyatt 2011e).

Data (i.e. pooled estimates of the effects and corresponding 95% confidence intervals) and explicit judgements done for each of the above aspects assessed were entered into the GRADEprofiler, a web-based software used to create 'Summary of findings' (SoF) tables (<http://gdt.guidelinedevelopment.org/>). All judgements involved in the assessment of the study characteristics described above are explained in the comments or footnotes in the SoF tables.

Measures of treatment effect

We reported the outcome estimates for categorical data using relative risks (RRs), risk differences (RDs) and the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH); for continuous data we planned to use mean differences (MDs) with their respective 95% confidence intervals (CIs). There was no major discrepancy in the characteristics of the included studies to render a pooled analysis impossible. However if this had been the case, we would have adopted an approach as detailed under [Assessment of heterogeneity](#) and reported the results of the studies individually.

Unit of analysis issues

We anticipated two major categories of unit of analysis issues: first, those related to studies that report outcomes using catheters rather than infants as the unit of analysis; and second, those related to cluster-RCTs such as randomisation by NICU. In the current review, we only encountered the first issue relating to the use of catheter as the unit of analysis. In two studies (Garland 2001; Khattak 2010), the number of catheters matched the number of participants, and so we considered the studies to be free of unit of analysis issues in terms of the use of catheters. However, in the third paper (Hill 2010), the number of catheters exceeded the number of participants, as 16 participants received two and two participants received three catheters. Unfortunately, there was no information in the paper to enable us to re-analyse the data by including only the first catheter of each infant. Consequently, we were unable to re-assign the unit of analysis in this review to infants. We have acknowledged this as a limitation in our discussion.

We did not include any cluster-RCT in the current version of the review.

Dealing with missing data

We determined the drop-out rates from each study and assessed whether intention-to-treat analysis was performed by comparing the number of infants that were initially randomised and the total number analysed. We considered an absolute drop-out rate of 20% or higher as significant. Additionally, we adopted a 'worst-case approach' in judging the drop-out rate: if we found the drop-out rate higher than the difference between the event rates of the

intervention and control groups, we would consider the drop-out rate as significant; if we found a significant drop-out rate with no reasonable explanation, we would assign the study as having a high risk of bias with regard to the criterion 'completeness of outcome data'; if we had considered the missing data to be critical to the final estimates in our meta-analysis (which did not happen in the current version of the review), we would have contacted the authors of the individual studies to request further data.

If there were multiple studies in any comparison, we would have performed sensitivity analyses to assess how the overall results were affected by the inclusion of studies with a high risk of attrition bias from incomplete outcome data. However, we did not perform any sensitivity analysis due to an insufficient number of included studies.

Assessment of heterogeneity

We visually inspected forest plots for any gross evidence of heterogeneity of treatment effects. We used the I^2 statistic (Higgins 2011) to quantify the degree of inconsistency in the results. In accordance with the recommendations of the CNRG, we used the following cut-offs for the reporting of heterogeneity: less than 25%, no heterogeneity; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and 75% or higher, high heterogeneity. If a moderate or high degree of heterogeneity was found, we would evaluate the studies in terms of their clinical and methodological characteristics using the criteria listed as follows to determine whether the degree of heterogeneity might be explained by differences in those characteristics, and whether a meta-analysis was appropriate.

The criteria that we would assess include the following:

1. Baseline characteristics of the participants (postmenstrual age, birth weight, indications for CVCs);
2. Clinical settings of the studies (e.g. tertiary or secondary neonatal ICU);
3. Co-interventions;
4. Risk of bias (as detailed in the assessment of 'Risk of bias' section).

Assessment of reporting biases

We would have used a funnel plot to screen for publication bias if sufficient numbers of studies (> 10) had been included in the analysis of the relevant outcomes. If publication bias had been suggested by a significant asymmetry of the funnel plot, we would have included a statement in our results with a corresponding note of caution in our discussion. We did not generate a funnel plot due to an insufficient number of included studies.

Data synthesis

We performed meta-analyses using Review Manager 5 (RevMan 2014) with a fixed-effect model, following the recommendations of the CNRG. Where possible, our primary data analyses followed the intention-to-treat principle: namely, the original number of participants or catheters allocated to each study arm would be used as the denominator in subsequent analyses. We expressed our results as RRs, RDs, NNTB, NNTH and MDs with their respective 95% CIs, as detailed under [Measures of treatment effect](#).

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analyses if relevant data were available:

1. Different types of CVCs: UVCs, percutaneous long line and other types of CVCs;
2. Short-term CVCs (in place for less than 10 days) versus longer-term CVCs (in place for 10 days or longer);
3. Central venous catheters (CVCs) with antimicrobial modifications (antimicrobial impregnation, cuffs, hubs) versus CVCs with no antimicrobial modifications;
4. Studies involving clearly documented co-interventions (e.g. a sepsis-prevention bundle) versus those involving no clearly documented co-interventions.

However, we were unable to perform any subgroup analysis due to an insufficient number of studies.

We created two subgroups post-hoc to separate the two included studies with different units of analysis for the outcome of CRBSI under the comparison of silver-alginate dressing versus control: one with 'infant' as the unit of analysis ([Khattak 2010](#)); and another with 'catheter' as the unit of analysis ([Hill 2010](#)).

Sensitivity analysis

If there had been a sufficient number of studies available, we would have performed sensitivity analyses for the primary outcomes and any secondary outcomes to assess the impact of excluding studies with a high risk of:

1. selection bias (for either criterion or both criteria of random sequence generation and allocation concealment);
2. attrition bias (incomplete outcome data).

However, we were unable to perform any sensitivity analysis due to an insufficient number of studies.

RESULTS

Description of studies

Results of the search

We identified 173 records from the initial search of PubMed, CENTRAL, MEDLINE, EMBASE and CINAHL. We performed additional searches of clinicaltrials.gov and identified two further records that appeared to be relevant. After removing duplicates, there were 143 records. Among these, 48 articles appeared to be relevant after inspecting the titles. Additional searches in trial registries, conference proceedings and other Internet resources did not yield further relevant articles. We evaluated the abstracts and/or full-text of the articles and excluded 44 records (reasons below). We included four reports, but two reports described the same study ([Garland 2001](#)). This left three studies to be included in our meta-analysis. The flow diagram of the studies from the initial search to the meta-analysis is shown in [Figure 3](#). A description of all the included studies is displayed in the [Characteristics of included studies](#) table, and the excluded studies with the reasons for exclusion are given in the [Characteristics of excluded studies](#) table.

Figure 3. Study flow diagram.

Figure 3. (Continued)

in quantitative
synthesis
(meta-analysis)

Included studies

We included three RCTs, two of which were single-centre and one a multi-centre RCT. All three RCTs were conducted in the USA. The number of participants recruited in the three trials was 50 (Khattak 2010), 100 (Hill 2010) and 705 (Garland 2001). The number of catheters matched with number of participants in two studies (Garland 2001; Khattak 2010), and in Hill 2010 there were 118 central venous catheters studied, as 16 participants received two and two participants received three catheters. All three studies enrolled infants of both sexes. The duration of catheterization, where reported, varied from an average of 10 to 19 days, with a range from 5 to 29 days.

There were two major comparisons:

1. Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine dressing (Garland 2001).
2. Silver-alginate dressing versus no dressing (Hill 2010; Khattak 2010).

In Garland 2001, the concentration of chlorhexidine was 250 µg/mg, 70% isopropyl alcohol was used for cleansing in the intervention group and 10% povidone-iodine was used for cleansing in the control group.

In Hill 2010, all catheter insertion sites of the enrolled infants were cleansed with 10% povidone-iodine followed by 2% alcoholic chlorhexidine gluconate before catheter insertion, and 2% alcoholic chlorhexidine gluconate was used as cleansing agent before each dressing change. In Khattak 2010, 70% isopropyl alcohol was used for site cleansing prior to catheter insertion, and insertion site was cleansed during each dressing change although the agent used was not clearly stated.

In terms of concomitant CVC-related infection control measures, all three studies clearly described the use of maximal sterile barrier precaution or sterile techniques in the placement of the catheters.

The major outcomes assessed in all three studies were CRBSI and adverse effects, while Garland 2001 (chlorhexidine dressing/ alcohol cleansing compared to polyurethane dressing/povidone-iodine cleansing) evaluated sepsis and catheter colonisation in addition; and Hill 2010 and Khattak 2010 evaluated mortality. The secondary reference of Garland 2001, published in 1996, reported the rate of local reaction to the antimicrobial dressing, the description of which matched the definition of contact dermatitis, which was reported in the primary reference as well. We have therefore only taken data from the primary reference to avoid duplication. The baseline risks for CRBSI varied considerably in the included studies from 3% (Garland 2001) to 24% (Khattak 2010).

In terms of the definitions of primary outcomes, only one study (Garland 2001) provided detailed definitions. Garland 2001 defined CRBSI using criteria that were broadly in line with our review

definition, with the chief requirement being to show identical organisms from the blood culture as from the catheter tip culture. However, the same study defined the outcome of sepsis without a source as positive blood culture with or without clinical signs and symptoms of sepsis in the absence of catheter culture positivity. This outcome was not included in our pre-defined primary outcome of CRBSI or clinical sepsis, although we have included it as "sepsis without a source" in our analysis. Khattak 2010 defined 'infection' as "recovery of a bacterial pathogen or fungus from any single blood culture", while Hill 2010 did not provide any definition of the primary outcomes.

All three studies reported catheter-related outcomes such as CRBSI using the catheter as the units of analysis. In Garland 2001, not all catheters were available for culture while in Hill 2010 and Khattak 2010, all catheters appeared to be available for the analysis.

Excluded studies

We excluded studies based mainly on one or more of the following:

1. Article type (8 articles): not original studies but narrative reviews.
2. Study design (20 studies): the studies were either retrospective or prospective cohort studies, before-and-after intervention studies, prospective non-randomised intervention studies or meta-analyses.
2. Population (7 studies): the participants in the studies were not neonates.
3. Intervention (16 studies): the studies assessed intervention or comparison other than antimicrobial dressing.

A description of each study is available in the [Characteristics of excluded studies](#) table.

Studies awaiting classification

There was no study awaiting classification.

On-going studies

We did not identify any on-going study.

Risk of bias in included studies

The three included studies had low risks of bias in most domains, except for blinding, as all three studies were at high risk of bias for blinding of care personnel, and none provided any information on the blinding of outcome assessors. Figure 1 shows the proportions of studies with different risks of bias according to each domain, and Figure 2 shows the risk of bias profile according to the study. Additionally, we have provided a detailed description of the risk of bias of each study in the [Characteristics of included studies](#). Our risk of bias assessments under each domain are summarized below.

Allocation

For random sequence generation, two out of three included studies were judged to have low risk of bias as the authors provided clear description of random sequence generation methods using computers. One trial had unclear risk of bias as the authors stated that they used "block randomisation" without describing how the random sequence was generated (Khattak 2010). For allocation concealment, all three studies had low risk of bias, as evidenced by the statements that random sequence was generated independently from the actual allocation, or that the allocation involved the use of envelopes containing allocation details that were unknown to the study personnel.

Blinding

All three studies had high risk of bias in blinding of the care personnel, as the interventions in all three studies were different from the comparisons and no measures were in place to mask the personnel such as the use of dressing with identical appearance. Blinding of outcome assessors, which would have been possible for at least certain outcomes, was however not reported in all three studies.

Incomplete outcome data

There were either no missing data (Hill 2010; Khattak 2010); or low rate of missing data that were balanced between the two groups (Garland 2001).

Selective reporting

All three studies reported the major outcomes as stated in the methods in sufficient detail and so were accorded low risks of bias in this domain.

Other potential sources of bias

We screened for other potential sources of bias including unit of analysis issues, extreme baseline imbalance, block randomisation of unblinded trials and any evidence of fraud. Apart from a possible unit of analysis issue in Hill 2010 in which some infants received multiple catheters that were included in the analysis, no other sources of bias were identified.

Effects of interventions

See: [Summary of findings for the main comparison Chlorhexidine dressing following alcohol cleansing compared to polyurethane dressing following aqueous povidone-iodine cleansing for the prevention of catheter-related infections in newborn infants with central venous catheters](#); [Summary of findings 2 Silver-alginate dressing versus control for the prevention of catheter-related infections in newborn infants with central venous catheters](#)

In this review, a total of 855 infants and 873 catheters were assessed in 3 studies.

Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing (comparison 1)

Primary outcomes

Catheter-related blood stream infection (CRBSI) (Outcome 1.1; Analysis 1.1)

Based on a single study (Garland 2001), there was no difference in the risk of CRBSI between the group that received chlorhexidine dressing/alcohol cleansing compared to polyurethane dressing/povidone-iodine cleansing (risk ratio (RR) 1.18, 95% confidence interval (CI) 0.53 to 2.65; risk difference (RD) 0.01, 95% CI -0.02 to 0.03; 655 participants and catheters) (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, outcome: 1.1 CRBSI.

Sepsis without a source (Outcome 1.2; Analysis 1.2)

Based on a single study (Garland 2001), there was no statistically significant difference in the risk of sepsis without a source between the group that received chlorhexidine dressing/alcohol cleansing compared to polyurethane dressing/povidone-iodine cleansing (RR 1.06, 95% CI 0.75 to 1.52; RD 0.01, 95% CI -0.04 to 0.06; 705 infants) (Analysis 1.2).

Secondary outcomes

Catheter colonisation (Outcome 1.3; Analysis 1.3)

Based on one study (Garland 2001), chlorhexidine dressing/alcohol cleansing was significantly more effective in reducing catheter colonisation compared to polyurethane dressing/povidone-iodine

cleansing (RR 0.62, 95% CI 0.45 to 0.86; RD -0.09, 95% CI -0.15 to -0.03; number needed to treat for an additional beneficial outcome (NNTB) 11, 95% CI 7 to 33; 705 catheters) (Analysis 1.3).

Adverse effects: contact dermatitis (Outcome 1.4; Analysis 1.4)

A single study reported this outcome. Garland 2001 showed that infants who received chlorhexidine dressing/alcohol cleansing were significantly more likely to develop contact dermatitis compared to infants who received polyurethane dressing/povidone-iodine cleansing (RR 43.06, 95% CI 2.61 to 710.44; RD 0.06, 95% CI 0.03 to 0.08; number needed to treat for an additional harmful outcome (NNTH) 17, 95% CI 13 to 33; 705 infants) (Analysis 1.4)

Adverse effects: pressure necrosis (Outcome 1.5; Analysis 1.5)

Based on the findings of [Garland 2001](#), there were no differences between infants who received chlorhexidine dressing/alcohol cleansing and infants who received polyurethane dressing/povidone-iodine cleansing in the risk of developing pressure necrosis (RR 5.52, 95% CI 0.27 to 114.58; RD 0.01, 95% CI 0.00 to 0.02; 705 infants) ([Analysis 1.5](#)).

Silver-alginate dressing versus control (no dressing) (comparison 2)

Primary outcomes

Catheter-related blood stream infection (CRBSI) (Outcome 2.1; Analysis 2.1.1 and 2.1.2)

Two studies reported this outcome. In one study ([Khattak 2010](#)), the number of patients matched the number of catheters and

the authors used the number of infants as the unit of analysis, while in another study ([Hill 2010](#)), there were more catheters than infants, and the authors used the number of catheters as the unit of analysis. It was impossible to separate the data of the participants with single catheter studied from those with multiple catheters from the information provided in [Hill 2010](#), and we are awaiting further information from the author. Consequently, we separated the data of the two studies into two different subgroups based on the unit of analysis.

Subgroup 1: CRBSI; unit of analysis: infants

Based on a single study ([Khattak 2010](#)), there was no significant difference between the two groups in the number of infants with CRBSI (RR 0.50, 95% CI 0.14 to 1.78; RD -0.12, 95% CI -0.33 to 0.09; 1 study, 50 participants) ([Analysis 2.1.1](#), [Figure 5](#)).

Figure 5. Forest plot of comparison: 2 Silver-alginate dressing versus control, outcome: 2.1 CRBSI.

Subgroup 2: CRBSI; unit of analysis: catheters

Based on a single study ([Hill 2010](#)), there was no significant difference between the two groups in the risk of CRBSI when the unit of analysis was catheters (RR 0.72, 95% CI 0.27 to 1.89; RD -0.05, 95% CI -0.20 to 0.10; 1 study, 118 participants) ([Analysis 2.1.2](#), [Figure 5](#)).

Mortality (Outcome 2.2; Analysis 2.2)

Based on the findings of two studies, there was no significant difference between the two groups in mortality (RR 0.55, 95% CI 0.15 to 2.05; RD -0.04, 95% CI -0.13 to 0.05; 150 infants, I² = 0%) ([Analysis 2.2](#), [Figure 6](#)).

Figure 6. Forest plot of comparison: 2 Silver-alginate dressing versus control, outcome: 2.2 Mortality.

Secondary outcomes

Adverse effects: contact dermatitis (Outcome 2.3; Analysis 2.3)

There were no events recorded among all the participants in both included studies under this comparison, so the effect was not estimable.

Exit site infection

No data from included studies.

Proportion of infants with drug-resistant organisms

No data from included studies.

Antibiotic usage

No data from included studies.

Length of hospital stay

No data from included studies.

Long-term neurodevelopment

No data from included studies.

Subgroup analyses

Due to insufficient studies, we did not perform any additional subgroup analysis as specified in our [Methods](#).

Sensitivity analysis

We did not perform any sensitivity analysis because there was no study to be excluded based on our pre-specified criteria in terms of selection and attrition biases.

DISCUSSION

Summary of main results

We identified two major types of antimicrobial dressings that were evaluated in newborn infants: chlorhexidine dressing and silver-alginate dressing. However, each type of dressing was only represented by one or two studies, and one of the included studies examined chlorhexidine dressing versus polyurethane dressing alongside a skin preparation regimen that differed between the two groups (chlorhexidine dressing/alcohol cleansing compared to polyurethane dressing/povidone-iodine cleansing). Overall, the use of chlorhexidine dressing following alcohol skin cleansing has not been shown to achieve statistically significant reductions in CRBSI, sepsis or mortality. The only significant benefit observed in chlorhexidine dressing following alcohol skin cleansing was a reduction in catheter colonisation compared to polyurethane dressing following povidone-iodine skin cleansing. On the other hand, infants who received chlorhexidine dressing following alcohol skin cleansing were at a significantly higher risk of contact dermatitis, although it was unclear whether this was contributed mainly by chlorhexidine dressing or alcohol skin cleansing. Limited evidence to date showed similar rates of CRBSI and mortality between infants who received silver-alginate dressing and those who had no dressing, although the data for CRBSI from the two included studies could not be combined as each used a different denominator as the unit of analysis.

Overall completeness and applicability of evidence

Through a comprehensive search strategy, we identified three studies (four reports) that matched our selection criteria in terms of population, intervention, comparison and outcomes. A total of 855 newborn infants (868 catheters) were assessed. We believe the studies gathered in this review, although small in number, represented the best available evidence to answer the question that we posed in conducting this review. However, the studies were all conducted in the US, which could limit the applicability of the findings to other parts of the world. We were unable to undertake any subgroup analyses to further determine applicability of the findings to infants with different prognostic factors due to insufficient data.

Quality of the evidence

There was overall moderate-quality evidence provided by a small number of studies. The three included studies had low risk of bias in most domains except blinding, but the quality of evidence was downgraded by wide 95% CI in the estimates or by the use of indirect outcome such as catheter colonisation (see [Summary of findings for the main comparison](#) and [Summary of findings 2](#) for the outcome data under the major comparisons in this review).

Potential biases in the review process

We performed a comprehensive search from multiple databases with independent screening, selection and assessment of eligible studies. However, there were some unit of analysis issues in one study which we could not resolve: in one study ([Hill 2010](#)), some infants received multiple catheters which were included in the analysis, and there was no adjustment for the effect of clustering either by statistically adjusting the final estimate, or by limiting the analysis to a single catheter from each infant or by excluding infants with multiple catheters. There were insufficient data provided in the article for us to perform any form of adjustment. Our failure to adjust for this unit of analysis issue has prevented us from combining the data of this study with that of another study which used infants as the unit of analysis, which might have improved the certainty of our estimates of the outcome.

Agreements and disagreements with other studies or reviews

Our findings are consistent with several published reviews that covered antimicrobial dressings or patches in newborn infants.

[Helder 2013](#) conducted a broad review that assessed the effectiveness of all non-pharmacological measures in reducing blood stream infections in newborn infants admitted to NICU in general, and antimicrobial patch was one of the interventions examined. In the analysis on antimicrobial patch, four randomised and non-randomised studies were included, and none has shown effectiveness in reducing blood stream infections.

[Lee 2005](#) conducted a broad systematic review of RCTs and quasi-RCTs that assessed the effectiveness of CVC management in paediatric patients, which included an assessment of antimicrobial patch in neonates. The review concluded that there was a lack of RCTs in informing practice in general, including on the use of antimicrobial patch.

[Li 2011](#) conducted a systematic review on strategies to prevent central line-associated bloodstream infections in critical care units including the NICU, and identified no evidence for the effectiveness of silver-alginate dressing in reducing CRBSI.

The closest review to the current review was provided by [Wielenga 2013](#). In this paper, the authors conducted a systematic literature review on all RCTs that assessed dressing techniques for CVCs in newborn infants, similar to our review. The same three articles were identified ([Garland 2001](#); [Hill 2010](#); [Khattak 2010](#)), and the authors reported the results narratively from each study without having performed a meta-analysis. The authors concluded that the use of antimicrobial dressings in newborn infants was not recommended in practice until further high-quality studies show that these dressings have a favourable benefit-harm profile for infants in NICU.

AUTHORS' CONCLUSIONS

Implications for practice

Based on moderate-quality evidence, chlorhexidine dressing/ alcohol skin cleansing as part of CVC care for newborn infants posed substantial risk of contact dermatitis against a modest effect on the surrogate outcomes of catheter colonisation, with a lack of significant benefits in major clinical outcomes such as sepsis and CRBSI. Silver-alginate patch appeared safe but there was insufficient evidence on its benefits.

Implications for research

Other than insufficient research on this topic, this review has identified several issues in the included studies that should be considered by researchers undertaking future studies. First, blinding of care personnel was not achieved in all included studies, and this could have affected the reporting of subjective but clinically important outcomes such as clinically diagnosed sepsis and length of hospital stay. Future research should ensure blinding

of care personnel by using dressing materials that are similar in appearance if possible. Blinding of outcome assessors, which is possible in such studies, should be clearly stated. Next, future research assessing the role of antimicrobial dressing needs to avoid bias that arises from different co-interventions in different assigned groups by ensuring that the concurrent infection control and other patient care measures, including the use of skin cleansing agent, are standardised in all participants regardless of their assigned group. Future research should include key outcomes such as the overall rate of sepsis and mortality alongside catheter-specific outcomes such as CRBSI and catheter colonisation, and report participant-level data as well as catheter-level data.

ACKNOWLEDGEMENTS

We gratefully acknowledge Drs Roger Soll, Arne Ohlsson, Jeffrey Horbar, Michael Bracken and Gautham Suresh for their comments on the draft protocol. We thank Ms Colleen Ovelman, Managing Editor and assistant TSC, and Ms Yolanda Brosseau, TSC and previous Managing Editor of the CNRG for their assistance leading to the publication of this review.

REFERENCES

References to studies included in this review

Garland 2001 {published data only}

Garland JS, Alex CP, Mueller CD, Cisler-Kahill LA. Local reactions to a chlorhexidine gluconate-impregnated antimicrobial dressing in very low birth weight infants. *Pediatric Infectious Disease Journal* 1996;**15**(10):912-4.

* Garland JS, Alex CP, Mueller CD, Otten D, Shivpuri C, Harris MC, et al. A randomized trial comparing povidone-iodine to a chlorhexidine gluconate-impregnated dressing for prevention of central venous catheter infections in neonates. *Pediatrics* 2001;**107**(6):1431-6.

Hill 2010 {published data only}

Hill ML, Baldwin L, Slaughter JC, Walsh WF, Weitkamp JH. A silver-alginate-coated dressing to reduce peripherally inserted central catheter (PICC) infections in NICU patients: a pilot randomized controlled trial. *Journal of Perinatology* 2010;**30**(7):469-73.

Khattak 2010 {published data only}

Khattak AZ, Ross R, Ngo T, Shoemaker CT. A randomized controlled evaluation of absorption of silver with the use of silver alginate (Algidex) patches in very low birth weight (VLBW) infants with central lines. *Journal of Perinatology* 2010;**30**(5):337-42.

References to studies excluded from this review

Bertini 2013 {published data only}

Bertini G, Elia S, Ceciari 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.

Brito 2014 {published data only}

Brito CS, Marques Ribas R, Resende DS, Von Dolinger de Brito D, Abdallah VO, dos Santos KR, et al. Genotypic study documents divergence in the pathogenesis of bloodstream infection related central venous catheters in neonates. *Brazilian Journal of Infectious Diseases* 2014;**18**(4):387-93.

Brooker 2007 {published data only}

Brooker RW, Keenan WJ. Catheter related bloodstream infection following PICC removal in preterm infants. *Journal of Perinatology* 2007;**27**(3):171-4.

Casner 2014 {published data only}

Casner M, Hoesli SJ, Slaughter JC, Hill M, Weitkamp JH. Incidence of catheter-related bloodstream infections in neonates following removal of peripherally inserted central venous catheters. *Pediatric Critical Care Medicine* 2014;**15**(1):42-8.

Cox 2013 {published data only}

Cox EG, Knoderer CA, Jennings A, Brown JW, Rodefeld MD, Walker SG, et al. A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated

catheters versus conventional catheters in pediatric cardiovascular surgery patients. *Journal of the Pediatric Infectious Diseases Society* 2013;**2**(1):67-70.

Dawson 2000 {published data only}

Dawson S, Fitzgerald P, Langer JC, Walton M, Winthrop A, Lau G, et al. A preoperative protocol for the prevention of infection in children with tunnelled right atrial catheters. *Oncology Reports* 2000;**7**(6):1239-42.

Fallat 1998 {published data only}

Fallat ME, Gallinaro RN, Stover BH, Wilkerson S, Goldsmith LJ. Central venous catheter bloodstream infections in the neonatal intensive care unit. *Journal of Pediatric Surgery* 1998;**33**(9):1383-7.

Fanos 1999 {published data only}

Fanos V, Dall'Agnola A. Antibiotics in neonatal infections: a review. *Drugs* 1999;**58**(3):405-27.

Filippi 2007 {published data only}

Filippi L, Pezzati M, Di Amario S, Poggi C, Pecile P. Fusidic acid and heparin lock solution for the prevention of catheter-related bloodstream infections in critically ill neonates: a retrospective study and a prospective, randomized trial. *Pediatric Critical Care Medicine* 2007;**8**(6):556-62.

Garcia-Teresa 2007 {published data only}

Garcia-Teresa MA, Casado-Flores J, Delgado Dominguez M A, Roqueta-Mas J, Cambra-Lasaosa F, Concha-Torre A, et al. Infectious complications of percutaneous central venous catheterization in pediatric patients: a Spanish multicenter study. *Intensive Care Medicine* 2007;**33**(3):466-76.

Garland 2005 {published data only}

Garland JS, Alex CP, Henrickson KJ, McAuliffe TL, Maki DG. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics* 2005;**116**(2):e198-205.

Garland 2008 {published data only}

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.

Garland 2009 {published data only}

Garland JS, Alex CP, Uhing MR, Peterside IE, Rentz A, Harris MC. Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antiseptic for central venous catheter placement in neonates. *Journal of Perinatology* 2009;**29**(12):808-13.

Gilad 2006 {published data only}

Gilad J, Borer A. Prevention of catheter-related bloodstream infections in the neonatal intensive care setting. *Expert Review of Anti-Infective Therapy* 2006;**4**(5):861-73.

Gilbert 2008 {published data only}

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.

Golombek 2002 {published data only}

Golombek SG, Rohan AJ, Parvez B, Salice AL, LaGamma EF. "Proactive" management of percutaneously inserted central catheters results in decreased incidence of infection in the ELBW population. *Journal of Perinatology* 2002;**22**(3):209-13.

Gravel 2007 {published data only}

Gravel D, Matlow A, Ofner-Agostini M, Loeb M, Johnston L, Bryce E, et al. A point prevalence survey of health care-associated infections in pediatric populations in major Canadian acute care hospitals. *American Journal of Infection Control* 2007;**35**(3):157-62.

Grigor'ev 1993 {published data only}

Grigor'ev VE, Pankova VP. Prevention of suppurative-inflammatory complications in catheterization of central veins. *Anesteziologiya i Reanimatologiya* 1993;**2**(2):63-4.

Handrup 2012 {published data only}

Handrup MM, Fuursted K, Funch P, Moller JK, Schroder H. Biofilm formation in long-term central venous catheters in children with cancer: A randomized controlled open-labelled trial of taurolidine versus heparin. *Acta Pathologica, Microbiologica, et Immunologica Scandinavica* 2012;**120**(10):794-801.

Harms 1995 {published data only}

Harms K, Herting E, Kron M, Schiffmann H, Schulz-Ehlbeck H. Randomized, controlled trial of amoxicillin prophylaxis for prevention of catheter-related infections in newborn infants with central venous silicone elastomer catheters. *Journal of Pediatrics* 1995;**127**(4):615-9.

Hei 2012 {published data only}

Hei MY, Zhang XC, Gao XY, Zhao LL, Wu ZX, Tian L, et al. Catheter-related infection and pathogens of umbilical venous catheterization in a neonatal intensive care unit in China. *American Journal of Perinatology* 2012;**29**(2):107-14.

Helder 2013 {published data only}

Helder O, Van Den Hoogen A, De Boer C, Van Goudoever J, Verboon-Macielek M, Kornelisse R. Non pharmacological interventions to reduce bloodstream infections in infants admitted to a neonatal intensive care unit. *Intensive Care Medicine* 2013;**39**:S6.

Hemels 2011 {published data only}

Hemels MA, van den Hoogen A, Verboon-Macielek MA, Fleer A, Krediet TG. Prevention of neonatal late-onset sepsis associated with the removal of percutaneously inserted central venous

catheters in preterm infants. *Pediatric Critical Care Medicine* 2011;**12**(4):445-8.

Huang 2011 {published data only}

Huang YC, Lien RI, Su LH, Chou YH, Lin TY. Successful control of methicillin-resistant *Staphylococcus aureus* in endemic neonatal intensive care units-A 7-year campaign. *PLoS ONE* 2011;**6**(8):e23001.

Hussain 2007 {published data only}

Hussain S, Gomez MM, Wludyka P, Chiu T, Rathore MH. Survival times and complications of catheters used for outpatient parenteral antibiotic therapy in children. *Clinical Pediatrics* 2007;**46**(3):247-51.

Inglis 2005 {published data only}

Inglis GD, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: [10.1002/14651858.CD005251.pub2](https://doi.org/10.1002/14651858.CD005251.pub2)]

Kellam 1988 {published data only}

Kellam B, Frazee DE, Kanarek KS. Central line dressing material and neonatal skin integrity. *Nutrition in Clinical Practice* 1988;**3**(2):65-8.

Larsen 2011 {published data only}

Larsen LN, Malchau E, Kristensen B, Schroeder H. Hydrochloric acid treatment of tunneled central venous catheter infections in children with cancer. *Journal of Pediatric Hematology/oncology* 2011;**33**(2):e64-8.

Lee 2005 {published data only}

Lee OK, Johnston L. A systematic review for effective management of central venous catheters and catheter sites in acute care paediatric patients. *Worldviews on Evidence-based Nursing / Sigma Theta Tau International, Honor Society of Nursing* 2005;**2**(1):4-13; discussion 14-5.

Leibovitz 1992 {published data only}

Leibovitz E, Luster-Reicher A, Amitai M, Mogilner B. Systemic candidal infections associated with use of peripheral venous catheters in neonates: A 9-year experience. *Clinical Infectious Diseases* 1992;**14**(2):485-91.

Li 2011 {published data only}

Li S, Bizzarro MJ. Prevention of central line associated bloodstream infections in critical care units. *Current Opinion in Pediatrics* 2011;**23**(1):85-90.

Machado 2005 {published data only}

Machado AF, Pedreira ML, Chaud MN. Prospective, randomized and controlled trial on the dwell time of peripheral intravenous catheters in children, according to three dressing regimens. *Revista Latino-Americana Enfermagem* 2005;**13**(3):291-8.

Mahieu 2001 {published data only}

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. *Journal of Hospital Infection* 2001;**48**(1):20-6.

Millar 2011 {published data only}

Millar M, Zhou W, Skinner R, Pizer B, Hennessy E, Wilks M, et al. Accuracy of bacterial DNA testing for central venous catheter-associated bloodstream infection in children with cancer. *Health Technology Assessment* 2011;**15**(7):1-114.

Quach 2014 {published data only}

Quach C, Milstone AM, Perpete C, Bonenfant M, Moore DL, Perreault T. Chlorhexidine bathing in a tertiary care neonatal intensive care unit: Impact on central line-associated bloodstream infections. *Infection Control and Hospital Epidemiology* 2014;**35**(2):158-63.

Ragavan 2010 {published data only}

Ragavan M, Gazula S, Yadav DK, Agarwala S, Srinivas M, Bajpai M, et al. Peripherally inserted central venous lines versus central lines in surgical newborns - A comparison. *Indian Journal of Pediatrics* 2010;**77**(2):171-4.

Sannoh 2010 {published data only}

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.

Seliem 2010 {published data only}

Seliem W, Abdel-Hady H, El-Nady G. Amikacin-heparin lock for prevention of catheter-related bloodstream infection in neonates with extended umbilical venous catheters use: A randomized controlled trial. *Journal of Neonatal-Perinatal Medicine* 2010;**3**(1):33-41.

Shapey 2009 {published data only}

Shapey IM, Foster MA, Whitehouse T, Jumaa P, Bion JF. Central venous catheter-related bloodstream infections: improving post-insertion catheter care. *Journal of Hospital Infection* 2009;**71**(2):117-22.

Spafford 1994 {published data only}

Spafford PS, Sinkin RA, Cox C, Reubens L, Powell KR. Prevention of central venous catheter-related coagulase-negative staphylococcal sepsis in neonates. *Journal of Pediatrics* 1994;**125**(2):259-63.

Westergaard 2013 {published data only}

Westergaard B, Classen V, Walther-Larsen S. Peripherally inserted central catheters in infants and children - Indications, techniques, complications and clinical recommendations. *Acta Anaesthesiologica Scandinavica* 2013;**57**(3):278-87.

Wielenga 2013 {published data only}

Wielenga J, Hilberdink A, Van Den Hoogen A. A systematic literature review of dressing techniques for peripherally inserted central venous catheters (CVC) in neonatal intensive care units. *Intensive Care Med* 2013;**39**:S133.

Wilson 2007 {published data only}

Wilson D, Verklan MT, Kennedy KA. Randomized trial of percutaneous central venous lines versus peripheral intravenous lines. *Journal of Perinatology* 2007;**27**(2):92-6.

Wirtschafter 2011 {published data only}

Wirtschafter DD, Padilla G, Suh O, Wan K, Trupp D, Fayard EE. Antibiotic use for presumed neonatally acquired infections far exceeds that for central line-associated blood stream infections: an exploratory critique. *Journal of Perinatology* 2011;**31**(8):514-8.

Additional references
Afsar 2009

Afsar FS. Skin care for preterm and term neonates. *Clinical and Experimental Dermatology* 2009;**34**(8):855-8. [PUBMED: 19575734]

Arora 2010

Arora RS, Roberts R, Eden TO, Pizer B. Interventions other than anticoagulants and systemic antibiotics for prevention of central venous catheter-related infections in children with cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: [10.1002/14651858.CD007785.pub2](https://doi.org/10.1002/14651858.CD007785.pub2)]

Bashir 2012

Bashir MH, Olson LK, Walters SA. Suppression of regrowth of normal skin flora under chlorhexidine gluconate dressings applied to chlorhexidine gluconate-prepped skin. *American Journal of Infection Control* 2012;**40**(4):344-8.

Bizzarro 2010

Bizzarro MJ, Sabo B, Noonan M, Bonfiglio MP, Northrup V, Diefenbach K. A quality improvement initiative to reduce central line-associated bloodstream infections in a neonatal intensive care unit. *Infection Control and Hospital Epidemiology* 2010;**31**(3):241-8.

Brown 1989

Brown E, Wenzel RP, Hendley JO. Exploration of the microbial anatomy of normal human skin by using plasmid profiles of coagulase-negative staphylococci: search for the reservoir of resident skin flora. *Journal of Infectious Diseases* 1989;**160**(4):644-50.

CDC 2011

O'Grady N, Alexander M, Burns LA, Dellinger P, Garland J, Heard SO, et al. Guidelines for the Prevention of Intravascular Catheter-Related Infections, 2011. Centers for Disease Control and Prevention (CDC), Healthcare Infection Control Practices Advisory Committee (HICPAC) publications. <http://www.cdc.gov/hicpac/pdf/guidelines/bsi-guidelines-2011.pdf> (accessed 3 April 2014).

CDC 2014

Central Line-Associated Bloodstream Infection (CLABSI) Event. Centers for Disease Control and Prevention (CDC), Device-associated module publication. http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABSCurrent.pdf (accessed 12 April 2014).

Chien 2002

Chien LY, Macnab Y, Aziz K, Andrews W, McMillan DD, Lee SK. Variations in central venous catheter-related infection risks

among Canadian neonatal intensive care units. *Pediatric Infectious Disease Journal* 2002;**21**(6):505-11.

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.

Costello 2008

Costello JM, Morrow DF, Graham DA, Potter-Bynoe G, Sandora T, Laussen PC. Systematic intervention to reduce central line-associated bloodstream infection rates in a pediatric cardiac intensive care unit. *Pediatrics* 2008;**121**(5):915-23.

Couto 2006

Couto RC, Pedrosa TM, Tofani Cde P, Pedroso ER. Risk factors for nosocomial infection in a neonatal intensive care unit. *Infection Control and Hospital Epidemiology* 2006;**27**(6):571-5.

Fisher 2013

Fisher D, Cochran KM, Provost LP, Patterson J, Bristol T, Metzger K, et al. Reducing central line-associated bloodstream infections in North Carolina NICUs. *Pediatrics* 2013;**132**(6):e1664-71. [PUBMED: 24249819]

Foster 2006

Foster J, Richards R, Showell M. Intravenous in-line filters for preventing morbidity and mortality in neonates. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: [10.1002/14651858.CD005248.pub2](https://doi.org/10.1002/14651858.CD005248.pub2)]

Gavin 2011

Gavin NC, Webster J, Chan RJ, Rickard CM. Frequency of dressing changes for central venous access devices on catheter-related infections. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: [10.1002/14651858.CD009213](https://doi.org/10.1002/14651858.CD009213)]

Ge 2012

Ge X, Cavallazzi R, Li C, Pan SM, Wang YW, Wang F-L. Central venous access sites for the prevention of venous thrombosis, stenosis and infection. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, 2012, issue 3. [DOI: [10.1002/14651858.CD004084.pub3](https://doi.org/10.1002/14651858.CD004084.pub3); CD004084]

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, 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 2011d

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 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.

Jaggi 2013

Jaggi N, Rodrigues C, Rosenthal VD, Todi SK, Shah S, Saini N, et al. Impact of an international nosocomial infection control consortium multidimensional approach on central line-associated bloodstream infection rates in adult intensive care units in eight cities in India. *International Journal of Infectious Diseases* 2013;**17**(12):e1218-24.

Jardine 2008

Jardine LA, Inglis GD, Davies MW. Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: [10.1002/14651858.CD006179.pub2](https://doi.org/10.1002/14651858.CD006179.pub2)]

Kabra 2005

Kabra NS, Kumar M, Shah SS. Multiple versus single lumen umbilical venous catheters for newborn infants. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: [10.1002/14651858.CD004498.pub2](https://doi.org/10.1002/14651858.CD004498.pub2)]

Karpanen 2009

Karpanen TJ, Worthington T, Conway BR, Hilton AC, Elliott TS, Lambert PA. Permeation of chlorhexidine from alcoholic and aqueous solutions within excised human skin. *Antimicrobial Agents and Chemotherapy* 2009;**53**(4):1717-9.

Karpanen 2011

Karpanen TJ, Casey AL, Conway BR, Lambert PA, Elliott TS. Antimicrobial activity of a chlorhexidine intravascular catheter site gel dressing. *Journal of Antimicrobial Chemotherapy* 2011;**66**(8):1777-84.

Lai 2012

Lai NA, Lai NM, O'Riordan E, Chaiyakunapruk N, Taylor JE, Tan K. Skin antisepsis during catheter insertion for reducing central venous catheter related infections. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: [10.1002/14651858.CD010140](https://doi.org/10.1002/14651858.CD010140)]

Lai 2013

Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WS, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults.

Cochrane Database of Systematic Reviews 2013, Issue 6. [DOI: [10.1002/14651858.CD007878.pub2](https://doi.org/10.1002/14651858.CD007878.pub2)]

Leeming 1984

Leeming JP, Holland KT, Cunliffe WJ. The microbial ecology of pilosebaceous units isolated from human skin. *Journal of General Microbiology* 1984;**130**(4):803-7.

Linares 2007

Linares J. Diagnosis of catheter-related bloodstream infection: conservative techniques. *Clinical Infectious Diseases* 2007; Vol. 44, issue 6:827-9. [PUBMED: 17304455]

Maki 1977

Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *The New England Journal of Medicine* 1977;**296**(23):1305-9.

McDonnell 1999

McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clinical Microbiology Reviews* 1999;**12**(1):147-79. [PUBMED: 9880479]

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.

Pagani 2008

Pagani JL, Eggimann P. Management of catheter-related infection. *Expert Review of Anti-infective Therapy* 2008;**6**(1):31-7.

Payne 2004

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

Pratt 2007

Pratt RJ, Pellowe CM, Wilson JA, Loveday HP, Harper PJ, Jones SR, et al. epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *Journal of Hospital Infection* 2007;**65**(Suppl 1):S1-64.

Raad 2002

Raad II, Hanna HA. Intravascular catheter-related infections: new horizons and recent advances. *Archives of Internal Medicine* 2002;**162**(8):871-8. [PUBMED: 11966337]

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rijnders 2002

Rijnders BJ, Van Wijngaarden E, Peetermans WE. Catheter-tip colonization as a surrogate end point in clinical studies on catheter-related bloodstream infection: how strong is the evidence?. *Clinical Infectious Diseases* 2002;**35**(9):1053-8.

Rosenthal 2013

Rosenthal VD, Duenas L, Sobreyra-Oropeza M, Ammar K, Navoa-Ng JA, de Casares AC, et al. Findings of the International Nosocomial Infection Control Consortium (INICC), part III: effectiveness of a multidimensional infection control approach to reduce central line-associated bloodstream infections in the neonatal intensive care units of 4 developing countries. *Infection Control and Hospital Epidemiology* 2013;**34**(3):229-37.

Schoot 2011

Schoot RA, van Dalen EC, van Ommen CH, van de Wetering MD. Antibiotic and other lock treatments for tunnelled central venous catheter related infections in children with cancer. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd, 2011, issue 2. [DOI: [10.1002/14651858.CD008975](https://doi.org/10.1002/14651858.CD008975); CD008975]

Schünemann 2013

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

Sengupta 2010

Sengupta A, Lehmann C, Diener-West M, Perl TM, Milstone AM. Catheter duration and risk of CLA-BSI in neonates with PICCs. *Pediatrics* 2010;**125**(4):648-53. [PUBMED: 20231192]

Shah 2007

Shah PS, Shah N. Heparin-bonded catheters for prolonging the patency of central venous catheters in children. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: [10.1002/14651858.CD005983.pub2](https://doi.org/10.1002/14651858.CD005983.pub2)]

Taylor 2013

Taylor JE, Tan K, Lai NM, McDonald SJ. Antibiotic lock for the prevention of catheter-related sepsis in neonates. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: [10.1002/14651858.CD010336](https://doi.org/10.1002/14651858.CD010336)]

Ullman 2013

Ullman AJ, Cooke ML, Mitchell M, Lin F, New K, Long DA, et al. Dressings and securement devices for central venous catheters (CVC). *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: [10.1002/14651858.CD010367](https://doi.org/10.1002/14651858.CD010367)]

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](https://doi.org/10.1002/14651858.CD008436.pub2)]

Washington 1998

Washington K. The Bayley Scales of Infant Development-II and children with developmental delays: a clinical perspective. *Journal of Developmental and Behavioral Pediatrics* 1998;**19**(5):346-9.

Webster 2011

Webster J, Gillies D, O'Riordan E, Sherriff KL, Rickard CM. Gauze and tape and transparent polyurethane dressings for central venous catheters. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: [10.1002/14651858.CD003827.pub2](https://doi.org/10.1002/14651858.CD003827.pub2)]

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.

Worthington 2005

Worthington T, Elliott TS. Diagnosis of central venous catheter related infection in adult patients. *Journal of Infection* 2005;**51**(4):267-80.

Ygberg 2012

Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. *Acta Paediatrica* 2012;**101**(2):120-7.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Garland 2001

Methods	Multi-centre RCT (US). Study period: June 1994 to August 1997.
Participants	Setting: 6 level III neonatal intensive care units. Participants: "Neonates admitted to units who would likely require a CVC for at least 48 hours were eligible for the study."
Interventions	Intervention: chlorhexidine dressing applied after CVC insertion through an insertion site cleansed with 70% isopropyl alcohol. Control: standard polyurethane dressing applied after CVC insertion through an insertion site cleansed with aqueous 10% povidone-iodine solution.
Outcomes	Catheter colonisation, CRBSI, BSI without a source, adverse effects
Notes	Funded in part by Johnson and Johnson Medical; Children's Foundation; Children's Hospital, Milwaukee and National Institute of Health 1. The number of catheters reported matched the number of infants, suggesting that each infant only had one catheter evaluated. This was confirmed by the author's statement under Data Collection and Analysis: "To preserve statistical independence, only 1 catheter per patient was enrolled in the trial." 2. There was an issue regarding compatibility of the two groups if chlorhexidine dressing was to be considered the intervention being assessed, as different skin cleansing agents were used in the two assigned groups (70% isopropyl alcohol in the chlorhexidine group versus povidone-iodine in the control group). In view of the different co-interventions used, we have decided to consider chlorhexidine dressing following alcohol skin cleansing, rather than chlorhexidine dressing alone, as the intervention of interest in all analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Methods, treatment: "Computer-generated randomisation codes developed by the study statistician were maintained by center pharmacists."
Allocation concealment (selection bias)	Low risk	Methods, treatment: "Computer-generated randomisation codes developed by the study statistician were maintained by center pharmacists." Although not clearly stated, it was likely that centre pharmacists were not involved in patient recruitment.

Garland 2001 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Although not clearly stated, blinding to care personnel was highly unlikely, as the intervention and control groups differed in their catheter care regimes from insertion to maintenance of the catheters.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether the clinical and microbiological outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	655 out of 705 (92.9%) catheters/infants were cultured and analysed. The number of catheters not cultured (21 in chlorhexidine dressing group and 29 in the control group) did not differ substantially between the two groups. A worst-case scenario approach on the outcome of catheter colonisation and CRBSI did not substantively affect the results.
Selective reporting (reporting bias)	Low risk	There was no mention by the authors whether the trial was registered in a trial registry. We could not identify the trial protocol in clinicaltrials.gov. As a result, there was no protocol to evaluate the pre-specified outcomes against the outcomes reported. However, all outcomes that were specified in the methods were reported in sufficient detail in the results, and the outcomes reported — namely catheter colonisation, CRBSI, BSI without a source and adverse effects — were major and relevant outcomes. Therefore we have accorded the study a low risk of reporting bias.
Other bias	Low risk	

Hill 2010

Methods	A single-centre RCT (US). Study period: June 2008 to February 2009.
Participants	Newborn infants from a level III NICU who were admitted for a minimum of 72 hours who required a peripherally inserted central catheter (PICC). Infants were declared ineligible if they already had a central line in place (including umbilical lines); if there was a pre-existing skin condition or discolouration; or if written informed consent could not be obtained.
Interventions	After cleansing with povidone-iodine swab and 2% alcoholic chlorhexidine solution, a silver-alginate patch on top of the catheter dressing was applied at the catheter insertion site in the intervention group, and a sterile transparent polyurethane insertion site dressing was applied in the control group. The dressing was changed every 14 days for all infants.
Outcomes	CRBSI and adverse skin reactions.
Notes	Funded by the Vanderbilt NICU Research Fund. The participants was assigned in a ratio of 3:1 to a study or control group. However, some infants received multiple PICCS and patches or dressings during their hospital stay, which could have introduced a unit of analysis issue, as detailed under 'Other bias' below. As a result of this, the data of this study for the outcome of CRBSI could not be combined with Khattak 2010 as this study used catheters as the denominator/unit of analysis while Khattak 2010 used the number of infants as denominator.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerized randomisation" was used (Results, Patients and catheters).

Hill 2010 (Continued)

Allocation concealment (selection bias)	Low risk	"A statistician assigned a status to each study number and envelopes containing the status were assembled unknown to the principal investigator and study nurse. After each patient was enrolled, the envelope with the number corresponding to order of enrolment was opened and the patient was placed in their assigned group." (Methods, Study patients).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although not stated in the study, blinding to the care personnel appeared very unlikely as the intervention group received a patch in addition to the dressing, and the catheter insertion site was covered with a transparent dressing.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether the microbiological outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 100 infants who were randomised were included in the analysis.
Selective reporting (reporting bias)	Low risk	There was no mention by the authors whether the trial was registered in a trial registry. We could not identify the trial protocol in clinicaltrials.gov. As a result, there was no protocol to evaluate the pre-specified outcomes against the outcomes reported. However, both outcomes specified in the methods, namely CRBSI and adverse skin reactions, were reported in sufficient detail in the results. Additionally, mortality was reported. We therefore considered the study to have low risk of reporting bias.
Other bias	High risk	There was a possible unit of analysis issue pertaining to infants who received multiple PICCs and patches during the study, as there were 118 patches included in the analysis in 100 infants randomised. The author stated that "Some infants received multiple patches during the study, but for purposes of all presented analyses, these repeated measures were treated as independent observations." (Statistical analysis).

Khattak 2010

Methods	Single-centre RCT (US). Study period: not reported.
Participants	Infants within 72 hours of birth with birth weights between 500 and 1500 grams admitted to a level III NICU with any of the following lines were eligible for inclusion into this study: umbilical arterial line, umbilical venous line, peripheral arterial line, peripheral long line, and central venous line.
Interventions	Silver-alginate patch in addition to standard line dressing (Tegaderm or Opsite) versus standard line dressing alone. Dressing was changed every 7 days.
Outcomes	Mortality, serum silver concentration, CRBSI (labelled as "blood stream infection" but displayed along line days) and adverse skin reaction. However, it was unclear how CRBSI was determined as there was no description in the paper.
Notes	Source of funding was not stated in the paper. The authors reported the results using the infants rather than the catheter or patch/dressing as the unit of analysis. As such, the data for the outcome of CRBSI could not be combined with Hill 2010 which used catheters as the denominator/unit of analysis.

Risk of bias

Khattak 2010 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors stated that "blocked randomisation method was used", but it was unclear how the random sequence was generated.
Allocation concealment (selection bias)	Low risk	"Blocked randomisation method was used. Randomisation cards, marked either treatment or control, were placed in opaque envelopes with the study number noted on envelopes. The participants were then assigned to either the treatment or control group based on the randomisation card." (Materials and procedure, paragraph 2). These statements provide sufficient detail to convince us that random sequence generation was performed independently away from allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although not stated in the paper, blinding to care personnel appeared highly unlikely, as the intervention group received a patch in addition to the line dressing.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether the laboratory outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There appeared to be no missing data for the clinical outcomes of mortality, sepsis and adverse skin reaction (which did not occur in any of the infants enrolled).
Selective reporting (reporting bias)	Low risk	There was no mention by the authors whether the trial was registered in a trial registry. We could not identify the trial protocol in clinicaltrials.gov. As a result, there was no protocol to evaluate the pre-specified outcomes against the outcomes reported. However, the major outcomes specified in the methods, namely, serum silver concentration, CRBSI and adverse skin reaction were reported in sufficient detail in the results. Additionally, mortality was reported. We therefore consider the study as having low risk of reporting bias.
Other bias	Low risk	None identified.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bertini 2013	An RCT comparing silver zeolite-impregnated umbilical catheter (AgION technology) against non-impregnated catheters in reducing catheter-related infections. Basis of exclusion: intervention.
Brito 2014	A prospective cohort study to investigate the pathogenesis of blood stream infection by <i>Staphylococcus epidermidis</i> in high-risk neonates, using the molecular epidemiology. Basis of exclusion: study design.
Brooker 2007	A retrospective cohort study that investigates the incidence of catheter-related blood stream infection (CRBSI), following removal of peripherally inserted central venous catheters (PICC) in preterm infants. Basis of exclusion: study design.
Casner 2014	A retrospective cohort study that examines the incidence and risk factors of catheter-related infections associated with peripherally inserted central venous catheter. Basis of exclusion: study design.

Study	Reason for exclusion
Cox 2013	An RCT that compares minocyclin-rifampicin-impregnated CVCs with non-impregnated CVCs for reducing catheter-related blood stream infections in paediatric patients undergoing cardiac surgery. Basis of exclusion: intervention.
Dawson 2000	A prospective cohort study on paediatric cancer patients with central venous line, which evaluates the effect of a protocol on skin colonisation prevention with antiseptic skin scrubs using 4% chlorhexidine gluconate prior to any invasive procedure. Basis of exclusion: study design, population and intervention.
Fallat 1998	This is a retrospective cohort study that evaluates the symptoms and signs related to central venous catheter (CVC) blood stream infections (BSI) in neonatal intensive care unit (NICU). Basis of exclusion: study design.
Fanos 1999	A narrative review on the use of antibiotics in neonatal infections. Basis of exclusion: article type.
Filippi 2007	A two-part study — first a retrospective cohort study, and second an RCT — to assess the use of fusidic acid heparin lock to prevent catheter-related blood stream infections. Basis of exclusion: intervention.
Garcia-Teresa 2007	A prospective multi-centre cohort study on the risk factors and infectious complications of percutaneous central venous catheters in paediatric intensive care units. Basis of exclusion: study design.
Garland 2005	An RCT comparing vancomycin-heparin lock solution versus normal saline flush for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters. Basis of exclusion: intervention.
Garland 2008	An additional publication from Garland 2005 in which the findings of molecular subtyping of the blood culture samples were reported. Basis of exclusion: intervention.
Garland 2009	An RCT comparing cutaneous antisepsis using chlorhexidine gluconate versus povidone-iodine for neonates with central venous catheter inserted. Basis of exclusion: intervention.
Gilad 2006	A narrative review on various strategies to prevent catheter-related bloodstream infection in NICU. Basis of exclusion: article type.
Gilbert 2008	A systematic review on the effectiveness of antimicrobial impregnation for CVCs in reducing catheter-related infections. Basis of exclusion: article type.
Golombek 2002	A prospective cohort study comparing the effect of a dedicated proactive "PICC management team" in reducing catheter-related infections. Basis of exclusion: study design.
Gravel 2007	A cross-sectional survey to estimate the prevalence of paediatric health care-associated infections (HAI) in Canadian acute care hospitals. Basis of exclusion: study design.
Grigor'ev 1993	This is an article published in Russian about a study on a "new technique of catheter fixation using a film-forming preparation 'Lifusol'". Based on the information from a translator, this study was very unlikely to be an RCT and the population was not newborn infants. Basis of exclusion: study design and population.
Handrup 2012	An RCT comparing catheter locking with taurolidine versus heparin in biofilm formation in central venous catheters in children with cancers. Basis of exclusion: population and intervention.
Harms 1995	An RCT that evaluates amoxicillin prophylaxis versus no prophylaxis for newborn infants with a CVC. Basis of exclusion: intervention.

Study	Reason for exclusion
Hei 2012	A cohort study that evaluates the incidence of umbilical venous catheterization (UVC)-related infection and pathogens in a neonatal intensive care unit (NICU) in China. Basis of exclusion: study design.
Helder 2013	A systematic review that examines various non-pharmacological measures to prevent blood stream infections in NICU. Basis of exclusion: article type and intervention.
Hemels 2011	An RCT that assesses the effect of prophylactic administration of cefazolin during PICC removal on catheter-related infections. Basis of exclusion: intervention.
Huang 2011	A cohort study that reports the effects of a series of infection control measures instituted over 7 years at the NICU on the incidence of MRSA in the unit. Basis of exclusion: study design.
Hussain 2007	A cohort study that compares the catheter-associated complications and catheter survival times in peripherally inserted central catheters and central venous catheters used for outpatient parenteral antibiotic therapy in children. Basis of exclusion: study design and population.
Inglis 2005	A Cochrane review in 2005 that examines the role of prophylactic antibiotics in reducing morbidity and mortality in neonates with umbilical venous catheters. Basis of exclusion: article type.
Kellam 1988	An RCT in which 32 infants requiring central venous parenteral nutrition in a regional neonatal intensive care centre were randomly assigned to one of two groups (Tegaderm dressing, n = 17 and silk tape, n = 15). No antimicrobial dressing was evaluated in this study. Basis of exclusion: intervention.
Larsen 2011	This is a prospective cohort study with historical control that evaluates the effectiveness of 2 M hydrochloric acid (HCl) as an adjuvant to the intravenous antibiotic treatment of children in cancer wards with bacteraemia compared with antibiotic alone in the preceding period. Basis of exclusion: study design and population.
Lee 2005	A systematic review that evaluates all measures to reduce CVC-related infections in children. Basis of exclusion: article type.
Leibovitz 1992	A case series that describes the clinical courses of 25 infants with systemic candidiasis who were treated in the neonatal intensive care unit at Kaplan Hospital, Rehovot, Israel, during the period 1980 to 1989. Basis of exclusion: study design.
Li 2011	A narrative review that examines various strategies to reduce CVC-related blood stream infections in paediatric and neonatal intensive care units. Basis of exclusion: article type.
Machado 2005	A three-arm RCT that evaluates the effects of three catheter dressings: sterile gauze (EG 1), sterile transparent film (EG 2) and hypoallergenic adhesive tape (CG) in children with CVC in place. Basis of exclusion: population and intervention.
Mahieu 2001	A prospective cohort study that assesses the effect of catheter manipulations on catheter-associated bloodstream infection (CABSI) in neonates. Basis of exclusion: study design.
Millar 2011	A multi-faceted study, the major component of which evaluates the diagnostic accuracy of bacterial DNA detection in catheter-related blood stream infections in children with cancer. Basis of exclusion: study design.
Quach 2014	A non-randomised clinical controlled study that examines the impact of chlorhexidine gluconate (CHG) bathing on central line-associated blood stream infection (CLABSI) rates in neonates. Basis of exclusion: study design.

Study	Reason for exclusion
Ragavan 2010	A cohort study that compares the clinical characteristics of newborn infants who received peripherally inserted central venous line versus central lines. Basis of exclusion: study design.
Sannoh 2010	A prospective before-and-after study that investigates the effects of a multimodal central venous catheter hub care strategy, involving the use of 2% chlorhexidine in 70% isopropyl alcohol and education of medical staff by audiovisual presentations on catheter-related blood stream infection. Basis of exclusion: study design.
Seliem 2010	An RCT that evaluates the effectiveness of amikacin-heparin lock for prevention of catheter-related bloodstream infection in neonates with extended umbilical venous catheter use. Basis of exclusion: intervention.
Shapey 2009	A clinical audit to assess current practice and staff knowledge of CVC post-insertion care and identify aspects of CVC care with potential for improvement. Basis of exclusion: study design.
Spafford 1994	An RCT that assesses the effects of prophylactic vancomycin added to parenteral alimentation solution on the incidence of catheter-related coagulase-negative staphylococcal sepsis. Basis of exclusion: intervention.
Westergaard 2013	A narrative review that evaluates the indications, methods of insertion and complications of PICC lines for children beyond the neonatal age. Basis of exclusion: article type and population.
Wielenga 2013	A systematic review of various dressing techniques for peripherally inserted central venous catheters (CVC) in NICU on the rates of catheter-related infections. Basis of exclusion: article type.
Wilson 2007	An RCT that compares elective percutaneous central venous line (PCVL) placement versus peripheral intravenous catheter (PIV) placement in preterm infants on the rates of systemic infection or death. Basis of exclusion: intervention.
Wirtschafter 2011	A prospective cohort study that analyses the use of antibiotics in neonatal intensive care unit (NICU) against the rates of central line-associated blood stream infection. Basis of exclusion: study design and intervention.

DATA AND ANALYSES

Comparison 1. Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRBSI	1	655	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.53, 2.65]
2 Sepsis without a source	1	705	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.52]
3 Catheter colonisation	1	655	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.86]
4 Adverse effects: contact dermatitis	1	705	Risk Ratio (M-H, Fixed, 95% CI)	43.06 [2.61, 710.44]
5 Adverse effects: pressure necrosis	1	705	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.00, 0.02]

Analysis 1.1. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 1 CRBSI.

Analysis 1.2. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 2 Sepsis without a source.

Analysis 1.3. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 3 Catheter colonisation.

Analysis 1.4. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 4 Adverse effects: contact dermatitis.

Analysis 1.5. Comparison 1 Chlorhexidine dressing following alcohol cleansing versus polyurethane dressing following aqueous povidone-iodine cleansing, Outcome 5 Adverse effects: pressure necrosis.

Comparison 2. Silver-Alginate dressing versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRBSI	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Unit of analysis: infants	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.14, 1.78]
1.2 Unit of analysis: catheters	1	118	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.27, 1.89]
2 Mortality	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.15, 2.05]
3 Adverse effects: contact dermatitis	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Silver-Alginate dressing versus control, Outcome 1 CRBSI.

Analysis 2.2. Comparison 2 Silver-Alginate dressing versus control, Outcome 2 Mortality.

Analysis 2.3. Comparison 2 Silver-Alginate dressing versus control, Outcome 3 Adverse effects: contact dermatitis.

APPENDICES

Appendix 1. Search Strategy (CENTRAL)

#1	MeSH descriptor: [Catheterization, Central Venous] explode all trees
#2	(catheter near (central and ven*)):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Infant, Newborn] explode all trees
#5	newborn*:ti,ab,kw
#6	neonat*:ti,ab,kw
#7	#4 or #5 or #6
#8	MeSH descriptor: [Antisepsis] explode all trees
#9	MeSH descriptor: [Anti-Infective Agents, Local] explode all trees
#10	antisept*:ti,ab,kw
#11	patch:ti,ab,kw
#12	dressing:ti,ab,kw
#13	#8 or #9 or #10 or #11 or #12
#14	#3 and #7 and #13

Appendix 2. Search Strategy (MEDLINE via PubMed)

#1	Search "Infant, newborn"[Mesh]
#2	Search newborn* [TIAB]
#3	Search neonat* [TIAB]
#4	Search #1 OR #2 OR #3
#5	Search "Catheterization, Central Venous"[Mesh]
#6	Search (venous OR vein) AND catheter* [TIAB]
#7	Search #5 OR #6
#8	Search "Anti-Infective Agents, Local"[Mesh]
#9	Search antisept* [TIAB]

(Continued)

#10	Search "Antisepsis"[Mesh]
#11	Search Antimicrobial [Mesh]
#12	Search patch [TIAB]
#13	Search dressing [TIAB]
#14	Search #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	Search clinical trial [PT]
#16	Search clinical trials [Mesh]
#17	Search randomised [TIAB]
#18	Search randomly [TIAB]
#19	Search trial [TI]
#20	Search #15 OR #16 OR #17 OR #18 OR #19
#21	Search #4 AND #7 AND #14 AND #20

Appendix 3. Search strategy (EMBASE)

#1	exp newborn
#2	newborn*.ab,ti
#3	neonat*.ab,ti
#4	#1 OR #2 OR #3
#5	exp Catheterization, Central Venous
#6	((venous OR vein) AND catheter).ab,ti
#7	#5 OR #6
#8	exp antisepsis
#9	exp anti-infective agents
#10	antisept*.ab,ti
#11	patch*.ab,ti
#12	dressing.ab,ti
#13	#8 OR #9 OR #10 OR #11 OR #12

(Continued)

#14	exp RANDOMIZED-CONTROLLED-TRIAL/
#15	exp RANDOMIZATION
#16	exp CONTROLLED-STUDY
#17	exp MULTICENTER-STUDY
#18	exp DOUBLE-BLIND-PROCEDURE
#19	exp SINGLE-BLIND-PROCEDURE
#20	(RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*).ab,ti
#21	(SINGL* or DOUBL* or TREBL* or TRIPL*) AND (BLIND* or MASK*).ab,ti
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	#4 AND #7 AND #13 AND #22

Appendix 4. Search strategy (CINAHL)

#1	MH "Infant, newborn"
#2	TI newborn* or AB newborn*
#3	TI neonat* or AB neonat*
#4	#1 or #2 or #3
#5	MH "Catheterization, Central Venous"
#6	TI catheter or AB catheter
#7	#5 or #6
#8	MH "Antisepsis"
#9	MH "Anti-infective agent"
#10	TI antisept* or AB antisept*
#11	TI patch* or AB patch*
#12	TI dressing or AB dressing
#13	#8 or #9 or #10 or #11 or #12
#14	PT Clinical trial
#15	AB randomised or AB randomised or AB random*

(Continued)

#16	TI trial
#17	MH "Clinical Trials"/explode
#18	#14 or #15 or #16 or #17
#19	#4 AND #7 AND #13 AND #18

WHAT'S NEW

Date	Event	Description
25 January 2017	Amended	Add external source of support.

CONTRIBUTIONS OF AUTHORS

KT conceived the review title.

NML, JET, KT, YMC, AAK, NAM and RK wrote the protocol.

NML developed the search strategy.

NML and JT performed the search and identified relevant articles.

NML and JT acquired full texts for articles identified to be potentially suitable.

NML and JT independently assessed the eligibility of the articles identified.

NML, JT, KT, AAK, NAM and YMC wrote the description of studies, the results, discussion and conclusions.

NML and KT wrote the abstract.

NML wrote the plain language summary.

All authors approved the final review draft.

DECLARATIONS OF INTEREST

None declared by the authors

SOURCES OF SUPPORT

Internal sources

- Department of Paediatrics, University of Malaya, Malaysia.
- School of Medicine, Taylor's University, Malaysia.
- High Impact Research Grant, the University of Malaya, Malaysia.

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.

Editorial support for Cochrane Neonatal has been funded with funds from 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

1. EMBASE search strategy: we have updated the format of EMBASE search to be in line with the update of database, without changing the search terms.
2. CINAHL search strategy: amended as the previous search strategy yielded no article.
3. We have added a subheading of 'Quality of evidence' under the heading of [Assessment of risk of bias in included studies](#) to be in line with the updated format of Cochrane reviews.
4. Under 'Subgroup analysis and investigation of heterogeneity', we have added the following statement to explain our decision to introduce subgroups based on different units of analysis for the outcome of CRBSI under the comparison of silver-alginate dressing versus control:

"We created two subgroups post-hoc to separate the two included studies with different units of analysis for the outcome of CRBSI under the comparison of silver-alginate dressing versus control: one with infant as the unit of analysis ([Khattak 2010](#)) and another with catheter as the unit of analysis ([Hill 2010](#))."

INDEX TERMS

Medical Subject Headings (MeSH)

*Bandages [adverse effects]; Alginates [therapeutic use]; Anti-Bacterial Agents [therapeutic use]; Anti-Infective Agents [*therapeutic use]; Catheter-Related Infections [*prevention & control]; Catheterization, Central Venous [*adverse effects]; Central Venous Catheters [*adverse effects]; Chlorhexidine [therapeutic use]; Dermatitis, Contact [etiology]; Ethanol [therapeutic use]; Glucuronic Acid [therapeutic use]; Hexuronic Acids [therapeutic use]; Polyurethanes; Povidone-Iodine [therapeutic use]; Randomized Controlled Trials as Topic; Silver Compounds [therapeutic use]

MeSH check words

Humans; Infant, Newborn