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Prophylactic antibiotics for preventing Gram positive infections associated with long-term central venous catheters in oncology patients (Review)

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TABLE OF CONTENTS

[Intervention Review]

Prophylactic antibiotics for preventing Gram positive infections associated with long-term central venous catheters in oncology patients

Marianne D van de Wetering[1], Job BM van Woensel[2], Theresa A Lawrie[3]

[1]Department of Paediatric Oncology, Emma Children's Hospital/Academic Medical Center, Amsterdam, Netherlands. [2]Pediatrics, Emma Children's Hospital / Academic Medical Centre, Amsterdam, Netherlands. [3]Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group, Royal United Hospital, Bath, UK

Contact address: Marianne D van de Wetering, Department of Paediatric Oncology, Emma Children's Hospital/Academic Medical Center, PO Box 22660, Amsterdam, 1100 DD, Netherlands. m.d.vandewetering@amc.uva.nl.

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ABSTRACT

Background

This is an updated version of the review which was first published in *the Cochrane Database of Systematic Reviews* in 2006. Long-term central venous catheters (CVCs), including tunnelled CVCs (TCVCs) and totally implanted devices or ports (TIDs), are increasingly used when treating oncology patients. Despite international guidelines on sterile insertion and appropriate CVC maintenance and use, infection remains a common complication. These infections are mainly caused by Gram positive bacteria. Antimicrobial prevention strategies aimed at these micro-organisms could potentially decrease the majority of CVC infections. The aim of this review was to evaluate the efficacy of antibiotics in the prevention of Gram positive infections in long-term CVCs.

Objectives

To determine the efficacy of administering antibiotics prior to the insertion of long-term CVCs, or flushing or locking long-term CVCs with a combined antibiotic and heparin solution, or both, to prevent Gram positive catheter-related infections in adults and children receiving treatment for cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (to June 2013) and the MEDLINE and EMBASE databases (1966 to 2013).

Selection criteria

Randomised controlled trials (RCTs) comparing prophylactic antibiotics given prior to long-term CVC insertion with no antibiotics, RCTs comparing a combined antibiotic and heparin solution with a heparin-only solution to flush or lock newly inserted long-term CVCs, and RCTs comparing a combination of these interventions in adults and children receiving treatment for cancer.

Data collection and analysis

Two authors independently selected studies, classified them and extracted data on to a pre-designed data collection form. We pooled data using the RevMan software version 5.2 and used random-effects (RE) model methods for meta-analyses.

Main results

We included 11 trials with a total of 828 oncology patients (adults and children). We assessed most included studies to be at a low or unclear risk of bias. Five trials compared the use of antibiotics (vancomycin, teicoplanin or ceftazidime) given before the insertion of the long-term CVC with no antibiotics, and six trials compared antibiotics (vancomycin, amikacin or taurolidine) and heparin with a heparin-only solution for flushing or locking the long-term CVC after use. Administering an antibiotic prior to insertion of the CVC did not significantly reduce Gram positive catheter-related sepsis (CRS) (five trials, 360 adults; risk ratio (RR) 0.72, 95% confidence interval (CI) 0.33 to 1.58; I^2 = 5 2%; P = 0.41).

Flushing and locking long-term CVCs with a combined antibiotic and heparin solution significantly reduced the risk of Gram positive catheter-related sepsis compared with a heparin-only solution (468 participants, mostly children; RR 0.47, 95% CI 0.28 to 0.80; I^2 = 0%; P = 0.005). For a baseline infection rate of 15%, this reduction translated into a number needed to treat (NNT) of 12 (95% CI 9 to 33) to prevent one catheter-related infection. We considered this evidence to be of a moderate quality.

Authors' conclusions

There was no benefit to administering antibiotics before the insertion of long-term CVCs to prevent Gram positive catheter-related infections. Flushing or locking long-term CVCs with a combined antibiotic and heparin solution appeared to reduce Gram positive catheter-related sepsis experienced in people at risk of neutropenia through chemotherapy or disease. Due to insufficient data it was not clear whether this applied equally to TCVCs and totally implanted devices (TIDs), or equally to adults and children. The use of a combined antibiotic and heparin solution may increase microbial antibiotic resistance, therefore it should be reserved for high risk people or where baseline CVC infection rates are high (> 15%). Further research is needed to identify high risk groups most likely to benefit.

PLAIN LANGUAGE SUMMARY

Antibiotics for preventing early central venous catheter Gram positive infections in people with cancer

What is the problem?

People with cancer who undergo anti-cancer treatment (chemotherapy) often have a tube inserted into a large vein (central venous catheter or CVC) through which their chemotherapy is given. As chemotherapy is usually administered at regular intervals over several months to years, long-term, semi-permanent, tunnelled CVCs (TCVCs) or totally implanted devices (TIDs) are frequently used. Despite sterile insertion and post-insertion care, these long-term CVCs may become infected. These infections are usually caused by Gram positive bacteria.

Flushing or locking means to instil a solution to dwell in the tube when it is not in use. Usually, after use, the tube is flushed or locked with a saline or heparin-saline solution to prevent clot formation within the tube.

What was the aim of this review?

The aim of this review was to determine whether giving antibiotics before inserting the tube, or giving antibiotics with the solution used to flush and lock the tube, can prevent Gram positive bacterial infections.

What are the findings?

We searched the literature from 1966 to 2013 for relevant studies (randomised controlled trials only).

We included five studies (involving 360 children and adults) that compared antibiotics given before the insertion of the CVC with no antibiotics before insertion. We found that giving an antibiotic before inserting a tunnelled CVC did not prevent Gram positive catheter-related infections.

We included six studies (involving 468 people, mainly children) that tested flushing or locking the newly inserted CVC with a combination of an antibiotic and heparin compared with heparin only. We found that flushing the catheter with a solution containing

an antibiotic and heparin reduced the number of catheter-related infections. This practice is most likely to be of value where the risk of such infections is high. We considered this evidence to be of a moderate quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics compared with no antibiotics prior to long-term CVC insertion to prevent catheter-related infections

Patient or population: adults with a newly inserted long-term CVC who were at risk of neutropenia due to chemotherapy or disease
Settings: inpatient and outpatient
Intervention: intravenous antibiotics (vancomycin, teicoplanin or ceftazidime)
Comparison: placebo or no antibiotics

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	Antibiotics				
Catheter-related sepsis	200 per 1000	144 per 1000 (66 to 316)	RR 0.72 (0.33 to 1.58)	360 (5)	⊕⊕⊕◯ **moderate**	The difference between the comparison groups was not significant (P = 0.41). We downgraded this evidence to moderate due to the substantial heterogeneity (I^2 = 52%) between studies

*The basis for the **assumed risk** is the mean control group risk across studies. 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.

BACKGROUND

Description of the condition

This is an updated version of the review which was first published in *the Cochrane Database of Systematic Reviews* in 2006.

People undergoing treatment for cancer need adequate venous access because of the frequent administration of chemotherapy and requirements for intravenous fluids, blood products and other medications. To limit the discomfort of short-term venous access, long-term central venous catheters (CVCs), including tunnelled central venous catheters (TCVCs) and totally implanted devices or ports (TIDs), are used in more than two thirds of children and adults undergoing chemotherapy (Groeger 1993; Ingram 1991; Simon 2006). However, the use of long-term CVCs is limited by the risk of blood clot formation and infection. The risk of infection ranges from 1.4 (Bagnall-Reeb 2004; Press 1984; Schinabeck 2003) to 2.2 (Groeger 1993; Sarper 2006) infections per 1000 catheter days. The duration of antimicrobial therapy to treat these infections ranges from seven to 21 days. Success rates of 60% to 91% are reported, although often the device has to be removed (Bagnall-Reeb 2004). Approximately one third of people experience an episode of infection while having a long-term CVC in place. Seventy per cent of the organisms that are cultured are Gram positive organisms, mainly coagulase negative staphylococci (*Staphylococcus aureus* and *enterococci*). Other organisms include Gram negative organisms (15%) (mainly *E coli*), fungal organisms (8%) (mainly *Candida* species) and anaerobic organisms (7%) (O'Grady 2002).

The adherence to and colonization of CVCs with micro-organisms is facilitated by the formation of a very thin biofilm inside the catheter lumen. This process is influenced by several factors such as the production of fibroglycocalyx (extracellular slime) by coagulase negative staphylococci. In addition, the host reaction to the CVC results in the formation of a thrombin sleeve rich in clotting factors such as fibronectin, fibrinogen and fibrin, which contributes to the formation of the biofilm (Bagnall-Reeb 2004; Darouiche 1999). This means that adequate antibiotic treatment may lead to resolution of the CVC infection only in certain cases (that is when caused by coagulase negative staphylococci) whereas in other cases (that is when caused by *Pseudomonas*, *Staphylococcus aureus* or fungi) this will be much more difficult to clear and therefore removal of the catheter is necessary (Simon 2006).

The organisms responsible for catheter colonization and infection come from four sources. These are the skin, the catheter hub (the part through which the catheter is tunnelled under the skin), haematogenous seeding (infections originating outside the catheter can reach the CVC via the bloodstream) and contamination of the intravenous fluids given to the patient (for example intravenous total parenteral nutrition) (Hachem 2002).

Early catheter-related infections (infections that develop within 45 days after placement of the catheter) are mostly due to organisms from the skin insertion site. This is the time period during which many manipulations of the CVC are necessary due to the intensity of the chemotherapy. After 45 days the catheter hub becomes a far more important source of infection (Abbas 2004; Shaul 1998). International guidelines have been developed to prevent catheter-related infections (CPAC 1990; O'Grady 2002). These include guidelines for catheter insertion and care and handling, as well as restrictions on the number of catheter interruptions (the number of times per day one is allowed to open the catheter, to give medication or to draw blood). Most recently, a clinical care management bundle (including hand hygiene, barrier precautions for insertion, chlorhexidine skin antisepsis, optimal catheter site selection and assessment of CVC necessity) sets the standard for CVC care (Schiffer 2013).

Description of the intervention

Standard maintenance of long-term CVCs includes flushing the lumen with a saline solution following access or closing the CVC with a locking solution which is instilled into the lumen of the CVC after chemotherapy and left to dwell in the CVC until the next use. There are conflicting data about the relative value of adding prophylactic heparin to saline flushes (Schiffer 2013); however, heparinised saline is commonly used. Adding an antibiotic to the flush solution may prevent biofilm formation and eliminate bacteria introduced into the CVC via the skin or during CVC access, from any source. Antibiotics which have activity against Gram positive organisms and which have been evaluated for this purpose include vancomycin, taurolidine, teicoplanin and minocycline. Systemic antibiotics may be given intravenously before the insertion of the CVC in an attempt to reduce early infections; however, in the original version of this review we found no evidence to support the use of antibiotics in this way.

How the intervention might work

Oncology patients are at increased risk of infection due to the immunosuppressive effects of chemotherapy or their disease, for example with haematological malignancy. Administering antibiotics prophylactically may reduce the likelihood that Gram positive bacteria, introduced at the time of CVC insertion or following access, will thrive and lead to a catheter-related infection.

Why it is important to do this review

This is an updated version of the original review in which we found weak evidence to support adding an antibiotic with activity against Gram positive organisms to the standard flush or lock solution, and no evidence to support the use of systemic antibiotics prior to long-term CVC insertion. There remains uncertainty as to whether antibiotic prophylaxis is of benefit to adults and children

at high risk of catheter-related infections. By updating this review and incorporating new evidence we hoped to clarify the role of prophylactic antibiotics to prevent Gram positive infections in long-term CVCs.

OBJECTIVES

To determine the efficacy of administering antibiotics prior to the insertion of long-term CVCs, or flushing or locking long-term CVCs with a combined antibiotic and heparin solution, or both, to prevent Gram positive catheter-related infections in adults and children receiving treatment for cancer.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled trial (RCTs) comparing antibiotics with placebo prior to insertion of the long-term CVC to reduce Gram positive infections related to the CVC.
2. RCTs comparing an antibiotic flush or lock solution with a standard solution to reduce Gram positive infections related to the CVC.
3. RCTs combining the first two comparisons.

Types of participants

Adults and children with newly inserted long-term CVCs (TCVCs or TIDs) to facilitate chemotherapy.

Types of interventions

1. Intravenous antibiotics for Gram positive organisms, e.g. vancomycin, taurolidine, teicoplanin and minocycline, administered before long-term CVC insertion.
2. An antibiotic solution administered as a catheter flush or lock solution after catheter insertion and use.

Types of outcome measures

Catheter-related sepsis (CRS) or proxy outcomes, to include the following.

- Catheter-related blood stream infections (CRBSI), defined as an isolation of the same organism from a percutaneous blood culture and from one of the following: an exudate at the catheter site, a semi-quantitative catheter segment culture following catheter removal, or quantitative blood culture with recovery of at least a five-fold higher colony count from blood obtained through the catheter than from a percutaneous blood culture (Mermel 2001; O'Grady 2002).
- Exit-site infections, defined as evidence of cellulitis around the exit site.
- Tunnel infections, defined as spreading cellulitis overlying the tunnel tract of subcutaneously tunnelled catheters.
- A catheter-related infection diagnosed following a temporal succession of catheter flushing by the onset of chills and fever and a positive blood culture (bloodstream infection (BSI)).

If studies reported CRBSI and proxy outcomes, we preferentially used the CRBSI data in our meta-analyses.

Search methods for identification of studies

Electronic searches

For the original review, the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (to July 2006), MEDLINE and EMBASE (from 1966 to September 2006) were searched. For this updated review, these databases were searched from September 2006 to June 2013. The search strategies are outline in Appendix 1; Appendix 2; Appendix 3.

Searching other resources

We handsearched the following conference proceedings: International Society for Paediatric Oncology (SIOP) (1995 to 2005), Multinational Association of Supportive Care in Cancer (MASCC) (1995 to 2005), American Society of Clinical Oncology (ASCO) (1995 to 2005), Interscience Conference of Antimicrobial agents and Chemotherapy (ICAAC) (1995 to 2005). No extra information was obtained from the conference proceedings. For this updated review, we did not handsearch conference proceedings however we handsearched reference lists of included studies and other related publications.

Data collection and analysis

Selection of studies

Two authors independently identified and classified the eligible studies. For the original review this was performed by Marianne van der Wetering (MvdW) and Job van Woensel (JvW) and for the updated review by Theresa Lawrie (TAL) and MvdW.

Data extraction and management

We extracted data on to a pre-designed data extraction and collection form. In addition, we recorded the following information for each study, where possible:

- study location, accrual dates;
- participant inclusion and exclusion criteria;
- type of long-term CVCs used, site, technique and timing of insertion;
- type of intervention(s), dose and timing of administration;
- methods of randomisation and allocation concealment;
- baseline characteristics of participants including age, type of cancer and previous chemotherapy;
- types of outcomes.

Assessment of risk of bias in included studies

For the updated review, we retained the original methods for assessing risk of bias. We assessed the methodological quality (quality of randomisation, blinding and analysis) according to the van Tulder 1997 criteria and assessed allocation concealment according to the *Cochrane Handbook for Systematic Reviews of Interventions* (2006 version) as follows.

(A) Adequate: some form of centralised or pharmacy controlled randomisation scheme, or the use of pre-coded identical containers administered sequentially to participants or the use of sequentially numbered sealed opaque envelopes, alternatively using an on-site computer with a locked file which could only be accessed after entering participant details, or a mixture of these approaches and including innovative schemes provided that the method appears impervious to allocation bias.

(B) Uncertain: when only terms such as lists, tables, sealed envelopes or randomly assigned were mentioned in the text, or any trial where intervention or placebo assignments were mentioned without specifying the method of allocation.

(C) Inadequate: when quasi-randomisation methods were used, e.g. alternation, date of birth, case record, day of the week, enrolment order or when an open system of random numbers or unblinded assignment was used.

We contacted the authors for additional information, where necessary, and resolved disagreements between review authors by discussion.

Measures of treatment effect

All review outcomes required dichotomous data, for which we presented the results as summary risk ratios (RR) with 95% confidence intervals (CIs) (RevMan 2012).

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We considered heterogeneity to be substantial if the I^2 was equal to or greater than 50%.

Data synthesis

We grouped studies according to the interventions evaluated and analysed these groups separately, as follows:

1. studies of intravenous antibiotic prophylaxis prior to insertion of the long-term CVC versus placebo or no antibiotics; and
2. studies of antibiotic flush or lock solutions versus standard (heparin only) flush or lock solutions following long-term CVC insertion.

We pooled data in the meta-analyses using RevMan 5.2 (RevMan 2012). Where the results for catheter-related sepsis were separated into Gram positive and Gram negative infections, we included the Gram positive data only. We used the random-effects model for all meta-analyses due to substantial heterogeneity between studies with regard to design, interventions and populations.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity we investigated it using subgroup analyses and sensitivity analyses, where possible. Potential reasons for heterogeneity included types of participants (adults versus children), types of antibiotics (vancomycin versus others) and types of CVCs.

Sensitivity analysis

We performed sensitivity analyses where there was a high risk of bias associated with the quality of one of the included studies (Ljungman 1997). Where six or more trials contributed to a meta-analysis, we visually assessed the risk of publication bias using funnel plots.

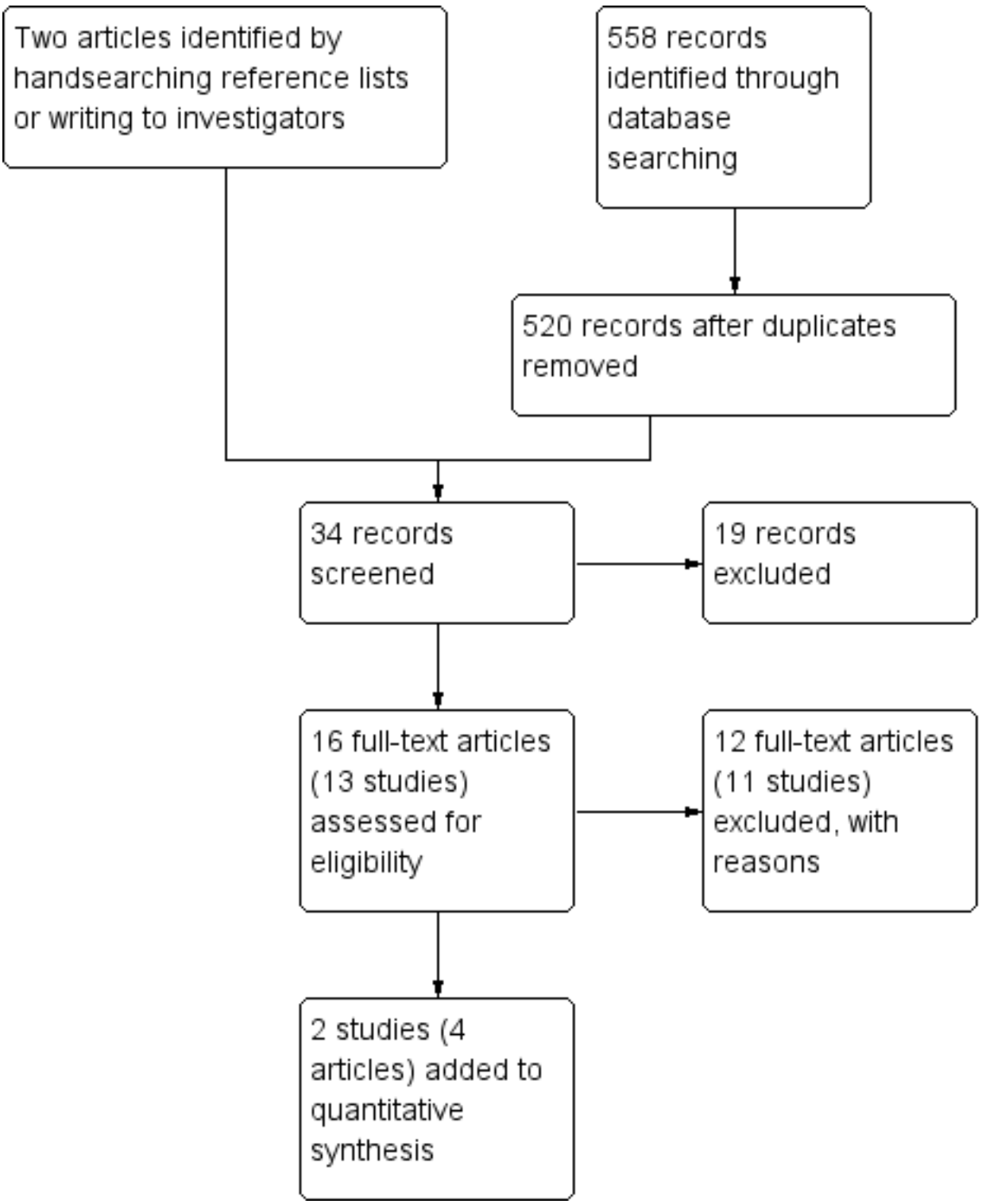
RESULTS

Description of studies

Results of the search

For the original review, we identified the abstracts of 40 potentially relevant studies and on screening excluded 20 of these. Of the remaining 20 studies, we classified 11 as excluded and nine as included. Following the 2013 search, we identified an additional 16 records for classification (see Figure 1). Of these, we included two studies (four citations) and excluded 11 studies (12 citations). Thus, for this updated review there were 11 included studies and 22 excluded studies in total.

Figure 1. Study flow diagram of updated (June 2013) search.



Included studies

The 11 studies enrolled 828 participants. Five studies were conducted in adults (N = 360) (Di Carlo 2011; Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995), four studies in children (N = 321) (Handrup 2013; Henrickson 2000; Rackoff 1995; Schwartz 1990) and two studies enrolled both (N = 147) (Barriga 1997; Daghistani 1996). Eight trials included participants with solid tumours or haematological malignancies, two trials included participants with haematological malignancies only (Lim 1993; Ljungman 1997) and one trial included participants with solid tumours only (Di Carlo 2011). We only included studies of newly inserted catheters except for one study (Henrickson 2000) which also enrolled an unspecified number of children with TCVCs already in situ. Most studies evaluated infections in TCVCs, however two studies (Di Carlo 2011; Handrup 2013) used totally implantable devices (TIDs). The latter study used both TCVCs and TIDs.

Five studies evaluated the administration of antibiotics prior to CVC insertion. The antibiotics used in these studies were as follows:

- vancomycin (Ranson 1990; Vassilomaniakis 1995);
- teicoplanin (Lim 1993; Ljungman 1997);
- ceftazidime (Di Carlo 2011).

Six studies evaluated flushing or locking the TCVC with a combination of an antibiotic and heparin. Antibiotics used in these studies were as follows:

- vancomycin (Barriga 1997; Henrickson 2000; Rackoff 1995; Schwartz 1990);
- vancomycin and amikacin (Daghistani 1996);
- taurolidine (antimicrobial) (Handrup 2013).

Most studies evaluated and reported catheter-related infections over the lifespan of the CVC. Three studies (Di Carlo 2011; Ljungman 1997; Ranson 1990) reported early catheter-related infections, occurring within 21 to 30 days of insertion. Most studies reported CRBSIs (Handrup 2013; Henrickson 2000; Lim 1993; Ljungman 1997; Schwartz 1990) or BSIs (Barriga 1997; Daghistani 1996; Rackoff 1995); one study reported surgical site infections (Di Carlo 2011) and two studies did not have clearly defined outcome measures (Ranson 1990; Vassilomaniakis 1995).

Excluded studies

We excluded 22 studies (11 for the original review and 11 for the updated review) for the following reasons:

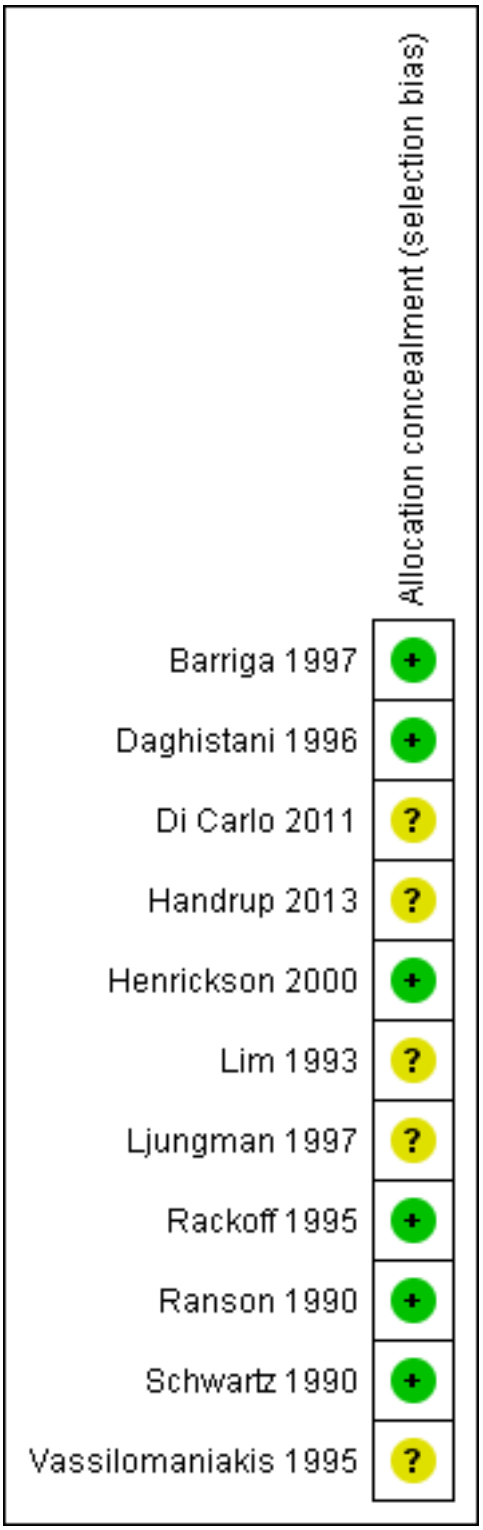
- participants were ill neonates and not people with cancer (two studies: Garland 2005; Ocete 1998);
- non-tunnelled CVCs were used (six studies: Carratala 1999; Chatzinikolaou 2003b; Hanna 2004; Jaeger 2005; Raad 1998; Schierholz 2010);
- studies were not RCTs (six studies: Al Sibai 1987; Chatzinikolaou 2003a; Dawson 2000; Fourcade 2001; Rubie 1995; Scaife 2010; Simon 2008);
- RCT did not evaluate newly inserted catheters (three studies: Akyuz 2012; Dumichen 2012; Ferreira Chacon 2011);
- RCT did not evaluate prophylactic antibiotics (four studies: Chambers 2005; Hitz 2012; Abdelkefi 2005; Raad 2005).

Risk of bias in included studies

The methodology of the included studies was mostly of a reasonable quality, however sample sizes were relatively small and ranged from 27 (Vassilomaniakis 1995) to 108 participants (Di Carlo 2011). All studies described the eligibility criteria sufficiently and included adults or children, or both, who were at risk of neutropenia due to their disease or chemotherapy. Most studies excluded participants already receiving antibiotics except those used orally for selective gut decontamination (that is the use of oral antibiotics before a neutropenic episode is expected in which the potentially pathogenic aerobic organisms are eliminated without affecting the non-pathogenic anaerobic organisms). All studies evaluated participants with newly inserted CVCs, however Henrickson 2000 also included an unspecified number of participants with CVCs already in situ.

Randomisation was adequately described in six studies with adequate concealment of treatment allocation (A) (Figure 2). Two studies used a quasi-randomisation method (B) (Lim 1993; Vassilomaniakis 1995), two did not specify the method of randomisation (B) (Di Carlo 2011; Ljungman 1997) and one study did not specify how allocation concealment was achieved (B) (Handrup 2013). In all studies the experimental and control interventions were explicitly described. In five trials the participants were not blinded to the treatment (Di Carlo 2011; Handrup 2013; Lim 1993; Ljungman 1997; Vassilomaniakis 1995) and in five trials the outcome assessor was not blinded to the intervention (Di Carlo 2011; Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995).

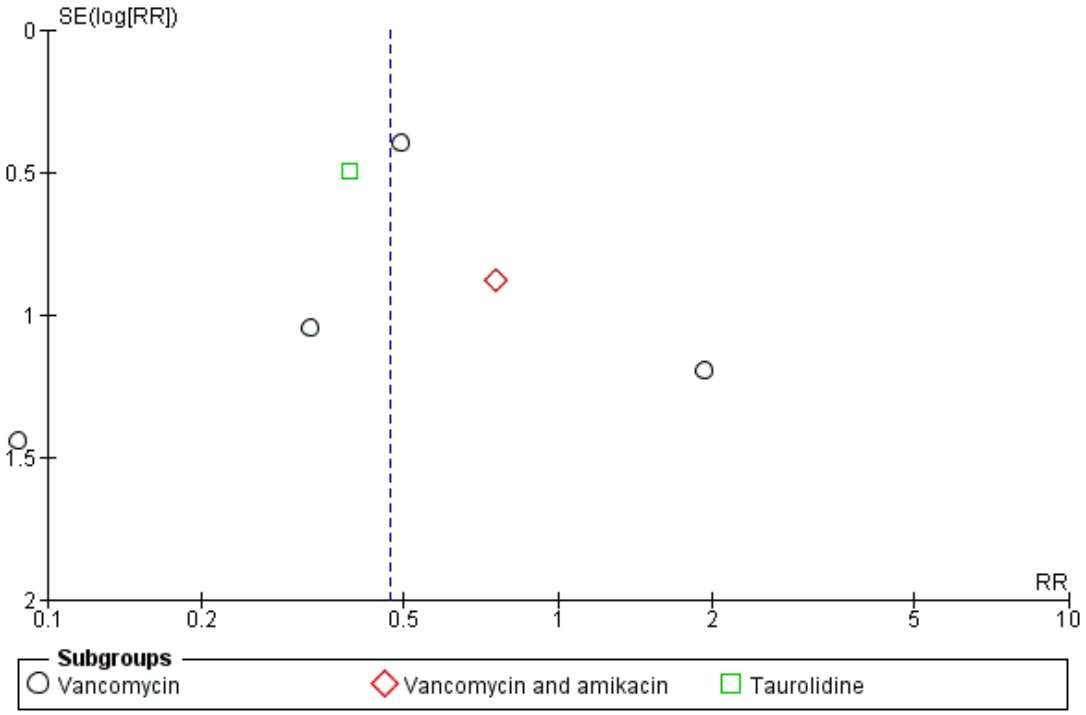
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



In Vassilomaniakis 1995, randomisation was initially performed but later all participants were included in the experimental group; therefore we only used the first part of the study in our analyses. In Ljungman 1997, open randomisation was performed and the study was stopped after an interim analysis. We considered the latter study to be at high risk of bias and performed sensitivity analyses with and without these data.

There was no evidence of publication bias (see Figure 3). Further details regarding the risk of bias and assessment of methodological quality can be found in Table 1, Table 2 and Table 3.

Figure 3. Funnel plot of comparison: 2 Antibiotic and heparin flush or lock solution versus heparin only, outcome: 2.1 Catheter-related sepsis.



Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings: prophylactic antibiotics before long-term CVC insertion; **Summary of findings 2** Summary of findings: antibiotic and heparin versus heparin only flush or lock solution

Antibiotics before long-term central venous catheter (CVC) insertion

We included five studies in this meta-analysis: two used vancomycin, two used teicoplanin, and one used ceftazadime prophylaxis versus control (placebo or no antibiotic). All five studies were conducted in adults. There was no significant difference in the risk of CRS between the prophylactic antibiotic and control groups (360 adults; RR 0.72, 95% CI 0.33 to 1.58; I^2 = 52%;

P = 0.41) (Analysis 1.1). Differences were not significant for any of the antibiotic subgroups either. In the sensitivity analysis, we removed a study that was at high risk of bias (Ljungman 1997), which made little difference to the overall effect (295 adults; RR 0.54, 95% CI 0.23 to 1.27; I^2 = 61%).

Antibiotic and heparin flush or lock solutions versus heparin only solutions

We included six studies that were conducted mainly in children in this meta-analysis. Most used a vancomycin and heparin solution; one used a vancomycin, amikacin and heparin solution (Daghistani 1996) and one used a taurolidine and heparin solution (Handrup 2013). The combined antibiotic and heparin solution was associated with significantly less CRS than the heparin only solution (468 participants; RR 0.47, 95% CI 0.28 to 0.80; I^2 = 0%; P = 0.005) (Analysis 2.1). Using these data, the number needed to treat (NNT) to prevent CRS in one patient, for an assumed baseline rate of 15%, would be 12 participants (95% CI 9 to 33).

When we excluded the studies which enrolled both adults and children (Barriga 1997; Daghistani 1996) and restricted our analyses to children only (N = 321), the RR was similar to the overall result (RR 0.41, 95% CI 0.18 to 0.89), in favour of antibiotics.

Henrickson 2000 included some participants with existing CVCs; we performed a sensitivity analysis by excluding this study from the analysis and the results remained true to the overall finding.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Antibiotic and heparin solution compared with a heparin only solution for flushing or locking long-term CVCs to prevent Gram positive catheter-related sepsis

Patient or population: adults and children with a newly inserted long-term CVC who were at risk of neutropenia due to chemotherapy or disease
Settings: inpatient and outpatient
Intervention: antibiotic (vancomycin, vancomycin and amikacon, or taurolidine) plus heparin solution
Comparison: heparin only solution

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Heparin-only	Antibiotic/heparin				
Catheter-related sepsis	200 per 1000	94 per 1000 (56 to 160)	RR 0.47 (0.28 to 0.80)	468 (6)	⊕⊕⊕◯ moderate	Data consistent across included studies; I^2 = 0%; P = 0.005. For an assumed risk of 15%, the NNT = 12 (9 to 33). We downgraded this evidence to moderate as the sample was clinically heterogeneous

*The basis for the **assumed risk** is the mean control group risk across included studies. 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; **NNT:** number needed to treat

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.

DISCUSSION

Summary of main results

Administering antibiotics before the insertion of long-term CVCs did not reduce the risk of subsequent catheter-related infections (Summary of findings for the main comparison). Combining antibiotics with heparin in a solution to flush or lock long-term CVCs approximately halved the risk of subsequent catheter-related infections in oncology patients (Summary of findings 2).

Overall completeness and applicability of evidence

In this review, we included studies that enrolled adults, children, or both. However, as the first meta-analysis included studies comprising adults only (Analysis 1.1) it is possible that the results of this meta-analysis are not generalisable to children. Similarly, the second meta-analysis (Analysis 2.1) included studies that were mainly conducted in children. Therefore, it is possible that the associated evidence, which indicates a beneficial effect of adding antibiotics to the standard flush or lock solution, may not be generalisable to adults. We consider the prevention, detection and treatment of infections in CVCs to be comparable in adults and children and therefore consider this evidence to be applicable to both.

We included studies evaluating the risk of CRS in TIDs and TCVCs. We were unable to distinguish between infection rates for TCVCs and TIDs due to insufficient data. Ports may be associated with a lower risk of CRS, however we pooled the data on ports and TCVCs as both are tunnelled central venous catheters and both are used to administer chemotherapy. One included study evaluated participants with TCVCs or TIDs (Handrup 2013) and one study evaluated participants with TIDs only (Di Carlo 2011). In the latter study no early infections occurred in the 108 participants that were included. In Handrup 2013, which comprised mainly TIDs, long-term infection rates in the control group were comparable to those reported in the TCVC studies.

Although the risk of infection is considered to be greatest during the first 45 to 100 days after placement (Abbas 2004; Salzman 1995), few of the included studies defined or evaluated early CRS. Baseline infection rates differ between institutions and should always be assessed before the introduction of antibiotic prophylaxis.

Quality of the evidence

Overall, we consider the evidence synthesized in this review to be of a moderate quality. Analysis 1.1 suffered from substantial heterogeneity due to the small sample sizes and inconsistent findings of the included studies. We considered Analysis 2.1 to be high quality evidence with respect to children, however we downgraded the evidence to moderate quality due to the clinical heterogeneity of the studies (types of antibiotics, CVCs and participants).

Potential biases in the review process

We attempted to reduce bias in this review by excluding studies in which long-term CVCs were already in situ, that is were not newly inserted. Catheters that are in situ and in use prior to enrolment were likely to be pre-colonized with bacteria. Including such studies may have led to spurious findings or higher rates of infections observed and would have introduced another variable by which to adjust the results.

Some included studies reported Gram negative and Gram positive CRS (for example Barriga 1997; Handrup 2013; Henrickson 2000). In these instances we only used the Gram positive data. However, the antibiotic group in Handrup 2013 and Henrickson 2000 also experienced lower rates of Gram negative CRS. Had we included these data, the RR would have more strongly favoured the antibiotic group in Analysis 2.1.

Like Snaterse 2010, we did not differentiate between flush and lock solutions in our meta-analyses as we considered them to have the same effect on the catheter lumen. Similarly, we combined the results of studies using various antibiotics with activity against Gram positive organisms into one meta-analysis.

Agreements and disagreements with other studies or reviews

The original review found weak evidence in favour of antibiotic flush solutions and no evidence to support systemic antibiotics. There remains no demonstrable benefit from prophylactic intravenous antibiotics before long-term CVC insertion. However, evidence from our updated meta-analysis supports a beneficial effect of an antibiotic and heparin solution for flushing or locking long-term CVCs. In a 2010 review, Snaterse 2010 points out that the lack of specificity in the outcomes measured in many of the included studies may lead to overestimation of the effect. We agree that more evidence is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Flushing or locking long-term CVCs with an antibiotic and heparin solution appears to reduce Gram positive catheter-related sepsis experienced in people at risk of neutropenia through chemotherapy or disease. Due to insufficient data it is not clear whether this applies equally to TCVCs and TIDs, or equally to adults and children. The use of an antibiotic and heparin solution may be of

value in high risk people and where baseline CVC infection rates are high (> 15%). However, routine antibiotic administration, irrespective of risk, is likely to increase microbial resistance.

Implications for research

Although some of the included studies stratified risk groups (for example neutropenic and non-neutropenic) none analysed these separately due to insufficient numbers. A large multicentre study to investigate the role of antibiotics for different risk groups is needed. Such a trial would also be valuable in identifying high risk groups that are most likely to benefit from antibiotic prophylaxis. It was not possible to draw any conclusions about the types of CVCs and antibiotics; further research would be valuable.

Antibiotic coatings for long-term tunnelled CVCs are currently under investigation and studies comparing these new types of catheters with antibiotic and heparin lock solutions are required. Due to the risk of developing microbial resistance, research into non-antibiotic solutions to reduce catheter-related infections is warranted. Ethanol (70%) lock solutions to prevent catheter-related infections are currently being investigated in both adults and children.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barriga 1997

Methods	Double blind randomisation	
Participants	N = 83 adults and paediatric patients with various malignancies, mainly leukaemia; 143 febrile episodes recorded	
Interventions	Vancomycin/heparin versus heparin-only flush (25 ug/ml vanco and 25 units/ml heparin)	
Outcomes	*Bacteraemia (BSI) *Vanco-sensitive organism bacteraemia	
Notes	A difference was stated in neutropenia and non-neutropenia	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Daghistani 1996

Methods	Double blind randomisation	
Participants	N = 61 adult and paediatric patients Various malignancies	
Interventions	Vancomycin/amikacin/heparin flush (25 ug/ml vanco, 25 ug/ml amikin and 100 units/ml hep) versus heparin only flush	
Outcomes	*Catheter-related sepsis (BSI) *Cellulitis	
Notes	The only study in which amikacin was added	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Di Carlo 2011

Methods	Consecutive people randomised; allocation by sealed envelopes	
Participants	N = 108 adult patients receiving a TID (Port-a-cath) to facilitate chemotherapy	
Interventions	Ceftazidime (1g IVI 10 min before skin incision) versus no antibiotic (control)	
Outcomes	*Surgical site infections (superficial and deep) *Infection considered if T°>37.5°C, WCC >10x10/L, and one or more of: pain, swelling, redness, or heat	
Notes	Outcomes assessed for 30 days after insertion	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear; method of randomisation not described; allocation by sealed envelopes; not blinded

Handrup 2013

Methods	Open-label RCT; computer generated randomisation code in blocks of 20	
Participants	n = 112 children aged 0-19 years receiving a newly placed TCVC to facilitate chemotherapy (49% haematological, 51% solid tumours) 129 TCVCs inserted, including 113 TIDs and 16 TCVCs with external lines (TEs)	
Interventions	Taurolidine/heparin/sodium citrate lock solution versus heparin lock solution	
Outcomes	*CRBSI *Exit-site and tunnel infections *Mechanical complications	
Notes	Followed up (catheters in situ) from 12 to 1176 days Type of CVC was a risk factor for CRBSI (TIDs were less likely to get infected than TEs)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Henrickson 2000

Methods	Double blind randomisation Stratified for risk groups
Participants	N = 126 paediatric patients (44% ALL, 40% solid, 7 % BMT). There were 153 assessable TCVCs
Interventions	Vancomycin/heparin versus heparin only flush (25 ug/ml vanco and 100 units/ml heparin)
Outcomes	*Exit-site infection *Bacteraemia (CRBSI) *Time to first infection
Notes	The third group included vanco/heparin ciprofloxacin Quantitative cultures were done

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Lim 1993

Methods	Method of randomisation not clear
Participants	N = 88 adult oncology patients with haematological malignancies Baseline characteristics reported - no significant difference
Interventions	Teicoplanin before insertion 400 mg before insertion catheter versus control
Outcomes	*Soft tissue infection *Catheter-related sepsis (CRS)
Notes	All episodes of CRS occurred in people who were neutropenic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Ljungman 1997

Methods	Method of randomisation not clear	
Participants	N = 66 adult oncology patients, BMT and leukaemia patients	
Interventions	Teicoplanin prior to insertion and 24 hrs after insertion	
Outcomes	*Bacteraemia (BSI) *Exit-site infection	
Notes	At interim analysis, the pre-set efficacy could not be met, therefore they stopped study	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Rackoff 1995

Methods	Double blind randomisation	
Participants	N = 55 paediatric patients, one centre (total group was 63 patients, 8 were receiving TPN) Analysis was done on the oncology patients only	
Interventions	Vancomycin/heparin versus heparin only flush (25 ug/ml vanco and 100 units/ml heparin)	
Outcomes	*Bacteraemia with a vanco sensitive organism (CRBSI) *Time to first infection	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Ranson 1990

Methods	Double blind randomisation
Participants	N = 98 adults A) N = 48 and 35 catheters, acute leukaemia and BMT B) N = 50 and 37 catheters (solid tumour)

Ranson 1990 (*Continued*)

Interventions	Vancomycin versus control (2 doses one prior to insertion, one after positioning of the catheter) 500 mg vanco	
Outcomes	*Catheter-related sepsis in first 30 days *Tunnel sepsis *Coagulase negative staphylococcal bacteraemia	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Schwartz 1990

Methods	Double blind randomisation	
Participants	N = 45 paediatric patients	
Interventions	Vancomycin/heparin versus heparin only flush (25 ug/ml vanco and 100 units/ml heparin)	
Outcomes	*Bacteraemia (quantitative culture) *Time to first infection	
Notes	Statistics on the number of children not catheters Quantitative blood cultures	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Vassilomaniakis 1995

Methods	Randomisation by cards in closed envelopes
Participants	N = 40 adult patients
Interventions	Vancomycin versus control (vanco in 3 doses of 500 mg 1 hr prior to insertion, 6 and 12 h afterwards)

Vassilomaniakis 1995 (*Continued*)

Outcomes	*Exit-site infection *CRBSI *Gram positive infections	
Notes	Only initially randomised	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

CRS = catheter-related sepsis; BMT = bone marrow transplant; TCVC = tunnelled central venous catheter; TPN = total parenteral nutrition; CVC = central venous catheter; TID = totally implantable device; CRBSI = catheter-related blood stream infection

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

Study	Reason for exclusion
Abdelkefi 2005	An RCT of low-dose heparin prophylaxis not antibiotic prophylaxis to reduce non-tunnelled CVC-related infections in haemato-oncological disease
Akyuz 2012	RCT of taurolidine lock solution versus heparin lock solution in children undergoing treatment for cancer. This study did not specifically include patients with newly inserted TCVCs
Al Sibai 1987	146 patients with malignant disease received 160 Hickman catheters. 70 of these patients received prophylactic antibiotics during and after insertion of the catheter. The catheter infection rate dropped from 0.5-0. 25 per 100 days. Excluded because the antibiotic use and duration were at the discretion of the attending physician, and the results were retrospectively analysed
Carratala 1999	Adult haematology patients with non-tunnelled CVC's received 10 U heparin per ml (N = 57) or 10 U heparin + 25 µg vancomycin per ml (N = 60) allowed to dwell in catheter 1 hour every 2 days. Catheter-related bacteraemia in 7% of people in control group and 0% in experimental group (P = 0.05). Mainly excluded because non-tunnelled catheters
Chambers 2005	RCT of sustained release chlorhexidine dressings (not antibiotics) versus standard dressings for TCVCs in neutropenic people
Chatzinikolaou 2003a	Prospective cohort study. M-EDTA was used as lock solution in indwelling ports in 14 children. No catheter-related infections were observed. In 48 control participants locked with heparin 10 port infections were observed. Not included because cohort study

(*Continued*)

Chatzinikolaou 2003b	Haemodialysis catheters in people with cancer. 66 people impregnated catheters with minocycline and rifampin and 64 non-impregnated catheters. 0 catheter-related infections in the impregnated group and 7 in the non-impregnated group, duration catheter 8 days. Excluded because this concerns non-tunnelled catheters and the duration of insertion was short
Dawson 2000	143 paediatric oncology patients, with 176 TCVC. Intervention cephalothin 100 mg/kg iv or vancomycin 20-25 mg/kg iv prior to insertion of the catheter. Rate of infections <30 days dropped 40%. No randomisation performed and intervention period was compared to pre-intervention period
Dumichen 2012	RCT of taurolidine citrate versus heparin as a catheter lock solution in 71 paediatric oncology patients. The lock solution was not used immediately after TCVC insertion in most participants (given up to 2 months after insertion in some cases)
Ferreira Chacon 2011	RCT of minocycline/EDTA versus heparin lock solution in children with TCVCs for chemotherapy, however TCVCs were not newly placed
Fourcade 2001	Prospective cohort study using antibiotic lock technique to prevent bacteraemia in chronic haemodialysis catheters. The incidence of bacteraemia dropped from 4.6 per 1000 catheter days to 0.88 per 1000 catheter days. Not RCT, comparison with historical control, non-tunnelled catheters
Garland 2005	Prospective RCT in critically ill neonates. Vanco lock solution was used in 42 infants and heparin lock in 43 infants. Two people in the vanco/heparin lock group developed a catheter-related infection, 13 people in the control group developed a catheter-related infection, RR 0.13 (95% CI 0.01 to 0.57) highly significant, duration catheter 20 days. Excluded because it concerns non-tunnelled catheters and done in neonates, which is not the appropriate group for our inclusion criteria
Hanna 2004	Prospective RCT at MD Anderson in cancer patients, 356 catheters placed, 182 impregnated with minocyclin and rifampin, 174 non-impregnated. Mean duration of the catheter 66 days. Three catheter-related infections in the MR group and 14 in the non-impregnated group, highly significant. Not included because these are non-tunnelled catheters and baseline risk for these catheters is higher than the tunnelled catheters. Also, we included studies of newly inserted tunnelled central venous catheters only
Hitz 2012	RCT of TCVCs coated with athrombogenic coating versus no coating in cancer patients, not an RCT of prophylactic antibiotics
Jaeger 2005	RCT of chlorhexidine/sulfadiazine impregnated CVCs versus standard CVCs in leukaemia patients. This study did not use tunnelled catheters
Ocete 1998	Single-centre trial; 2 groups control group - 61 newborns and experimental group 85 newborns, all receiving a central catheter (umbilical artery, umbilical vein and/or silastic). The study group received prophylactic vancomycin 25 ug/ml. All participants received parenteral nutrition. Results CNS 21/61 in the control group and 19/85 in the vancomycin group ($P < 0.05$). The patient group is not the group studied in this review. Methods of the study poor. Not specified how often the prophylactic vanco was given. Clinical criteria were used to determine if the neonate was infected, and then peripheral and central cultures were done. Not specified if quantitative or qualitative cultures were done. Trial not blinded, no tunnelled catheters used, inappropriate patient group

(*Continued*)

Raad 1998	Crossover study: 26 people with melanoma on IL2 treatment enrolled. All people received a double lumen non-tunnelled silicone catheter in subclavian vein. People randomised to receive prophylactic antibiotics novobiocin 500 mg + rifampin 300 mg orally. Significant results 41% in control group catheter-related bacteraemia and 6% in experimental group, excluded because of non-tunnelled catheters. Very specific group with high incidence of infection, not representative of the participant group for this Cochrane review
Raad 2005	RCT evaluating dalbavancin versus vancomycin for the treatment of adults with CRBSIs
Rubie 1995	163 paediatric patients with cancer had 180 subcutaneous ports inserted. Over time a change of policy was made from only flushing with heparin to a V/H solution. The infection rate dropped from 31% to 4%. This study was not randomised and the results were retrospectively analysed
Scaife 2010	A retrospective study of perioperative antibiotic prophylaxis for TCVCs implanted to facilitate chemotherapy in adults
Schierholz 2010	RCT evaluating an antibiotic-releasing CVC (rifampicin-miconazole) versus a standard CVC in adults (38% with cancer). Non-tunnelled CVCs were compared
Simon 2008	Not a RCT. A prospective cohort study of heparin versus taurolidine lock solution in 188 adults receiving chemotherapy for cancer. The taurolidine lock solution significantly reduced the rate of CRBSIs

CRS = catheter-related sepsis; BMT = bone marrow transplant; TCVC = tunnelled central venous catheter; TPN = total parenteral nutrition; CVC = central venous catheter; TID = totally implantable device; CRBSI = catheter-related blood stream infection

DATA AND ANALYSES

Comparison 1. Antibiotics prior to long-term CVC insertion versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related sepsis	5	360	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.58]
1.1 Vancomycin	2	99	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.07, 3.20]
1.2 Teicoplanin	2	153	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.25, 2.91]
1.3 Ceftazadime	1	108	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Antibiotic and heparin flush or lock solution versus heparin only

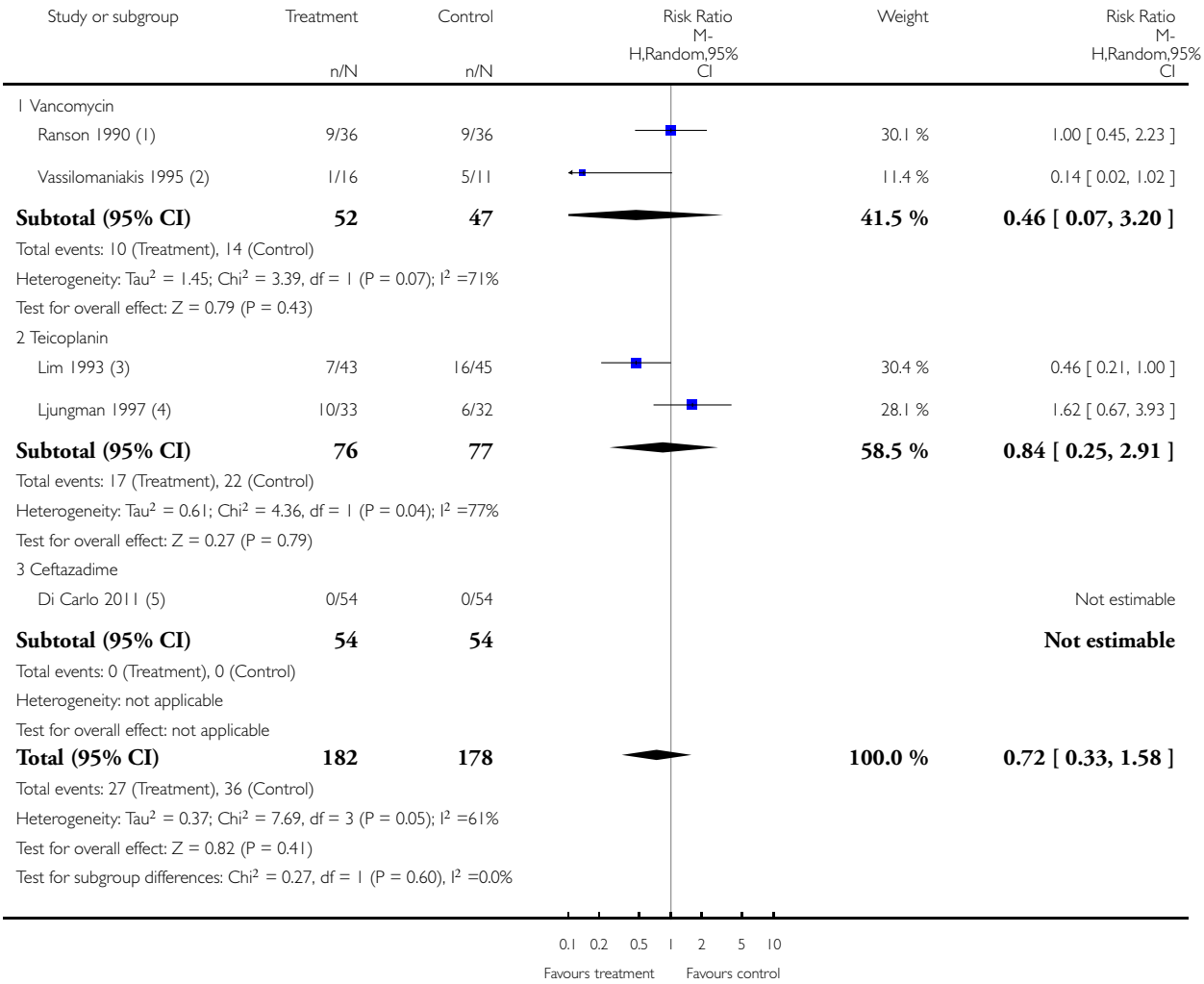
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related sepsis	6	468	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.28, 0.80]
1.1 Vancomycin	4	275	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.24, 0.94]
1.2 Vancomycin and amikacin	1	64	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.14, 4.22]
1.3 Taurolidine	1	129	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.15, 1.03]

Analysis 1.1. Comparison 1 Antibiotics prior to long-term CVC insertion versus control, Outcome 1 Catheter-related sepsis.

Review: Prophylactic antibiotics for preventing Gram positive infections associated with long-term central venous catheters in oncology patients

Comparison: 1 Antibiotics prior to long-term CVC insertion versus control

Outcome: 1 Catheter-related sepsis



(1) adults; vancomycin

(2) adults; vancomycin

(3) adults; teicoplanin

(4) adults; teicoplanin

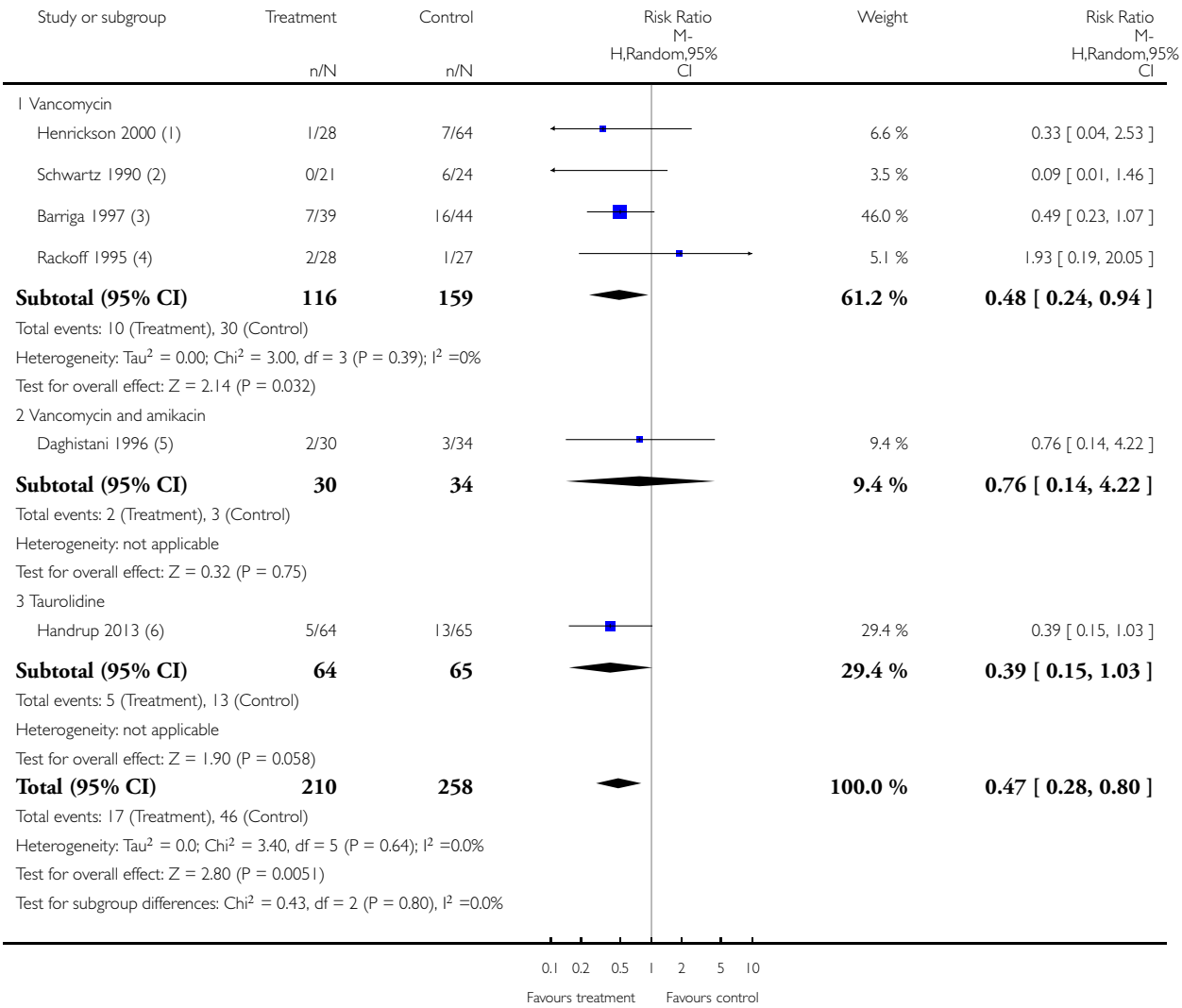
(5) adults; ceftazidime

Analysis 2.1. Comparison 2 Antibiotic and heparin flush or lock solution versus heparin only, Outcome 1 Catheter-related sepsis.

Review: Prophylactic antibiotics for preventing Gram positive infections associated with long-term central venous catheters in oncology patients

Comparison: 2 Antibiotic and heparin flush or lock solution versus heparin only

Outcome: 1 Catheter-related sepsis



(1) children

(2) children

(3) adults and children

(4) children

(5) adults and children

(6) children

ADDITIONAL TABLES

Table 1. Criteria for the assessment of methodological quality of included studies

Item ID	Description	Implementation
Patient selection		Note: all criteria were scored yes (+), no (-) or don't know
a	Were the eligibility criteria specified?	Patient inclusion/exclusion criteria must have been described appropriately according to the reviewer
b1	Was a method of randomisation applied?	A random (unpredictable) allocation must have been applied
b2	Was the treatment allocation concealed?	Allocation should have been performed by an independent person not responsible for determining eligibility for inclusion
c	Were the groups similar at baseline with regard to the most important prognostic indicators?	Groups must be similar at baseline with regard to at least three of the four prognostic indicators of age sex duration of symptoms and value of main outcome measures
Intervention		
d1	Was the experimental intervention explicitly described?	Adequate description of the experimental intervention so that treatment can be replicated
d2	Was the control intervention explicitly described?	Adequate description of the control intervention so that treatment can be replicated
e	Were co-interventions avoided or similar for all groups?	Co-interventions should either have been avoided in the trial design or be similar in the 2 groups
f	Was the patient blinded for the intervention?	Adequate information about blinding must have been provided
Outcome measurement		
g	Was the outcome assessor blinded to the intervention?	Adequate information about blinding must have been provided
h	Were the outcome measures relevant?	At least one of the following outcome measures must be included: catheter-related sepsis, exit infections, tunnel infections and time to first infection
i	Were complications described?	Any adverse events should be noted

Table 1. Criteria for the assessment of methodological quality of included studies (*Continued*)

j	Was the dropout loss to follow up described and acceptable?	Included people who did not complete the follow up period or were not included in the analysis should be described, if the percentage of dropouts is less than 20% then a '+' is scored
k	Was a follow-up measurement performed?	Outcome assessment after randomization
l	Was the timing of the outcome similar for all groups?	Timing of outcome assessment should have started from the moment of treatment allocation and be identical for all intervention groups and all important outcome measures
S tatistics		
m	Was the sample size described for each group?	Sample size should have been presented for each group at randomisation and for the most important outcome measures
n	Did the analysis include an intention-to-treat analysis?	For all randomised people the most important moments of effect measurement should have been reported
o	Were point estimates and measures of variability presented for the primary outcome measures?	For continuous data mean, median, standard deviation with 95 % confidence interval should be presented. For nominal and ordinal outcomes the number of people to whom the outcome measure applies and the total number of people must be presented

Table 2. Internal validity scores (b1, b2, c, e, f, g, j, l, n)

reference	b1	b2	c	e	f	g	j	l	n
Vassilomaniakis 1995	+	-	+	+	-	-	+	+	+
Ranson 1990	+	+	+	+	+	+?	+	+	+?
Lim 1993	+	-	+	+	-	+?	+	+	+
Barriga 1997	+	+	+	+	+	+	+	+	+
Rackoff 1995	+	+	+	+	+	+	+	+	+

Table 2. Internal validity scores (b1, b2, c, e, f, g, j, l, n) (*Continued*)

Schwartz 1990	+	+	+	+	+	+	+	+	+
Henrickson 2000	+	+	+	+	+	+	+	+	+
Daghistani 1996	+	+	+	+	+	+?	+	+	+
Ljungman 1997	+	-	-	-	-	-	+	+	+
Di Carlo 2011	+	+	+	+	-	-	+	+	?
Handrup 2013	+	-	+	+	-	-	+	+	+

Table 3. External validity (a, d1, d2, h, i, k, m, o)

Reference	a	d1	d2	h	i	k	m	o
Vassilomaniakis 1995	+	+	+	+?	-	+	+	+
Ranson 1990	+	+	+	+?	-	+	+	+
Lim 1993	+	+	+	+	-	+	+	-
Barriga 1997	+	+	+	+	-	+	+	+
Rackoff 1995	+	+	+	+	-	+	+	+
Schwartz 1990	+	+	+	+	-	+	+	+
Henrickson 2000	+	+	+	+	-	+	+	+
Daghistani 1996	+	+	+	+	-	+	+	+
Ljungman 1997	+	+	+	+	-	+	+	+

Table 3. External validity (a, d1, d2, h, i, k, m, o) (*Continued*)

Di Carlo 2011	+	+	+	+	-	+	+	+
Handrup 2013	+	+	+	+	-	+	+	+

APPENDICES

Appendix 1. Search strategy for CENTRAL

#1 MeSH descriptor: [Neoplasms] explode all trees
#2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma* or metasta* or bone marrow transplant*)
#3 #1 or #2
#4 MeSH descriptor: [Catheters] explode all trees
#5 MeSH descriptor: [Catheterization] explode all trees
#6 MeSH descriptor: [Catheter-Related Infections] this term only
#7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*)
#8 #4 or #5 or #6 or #7
#9 MeSH descriptor: [Antibiotic Prophylaxis] this term only
#10 MeSH descriptor: [Anti-Infective Agents] explode all trees
#11 MeSH descriptor: [Gram-Positive Bacterial Infections] explode all trees and with qualifiers: [Drug therapy - DT]
#12 antibiotic*
#13 #9 or #10 or #11 or #12
#14 #3 and #8 and #13

Appendix 2. Search strategy for MEDLINE

MEDLINE Ovid
1 exp Neoplasms/
2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma* or metasta* or bone marrow transplant*).mp.
3 1 or 2
4 exp Catheters/
5 Catheter-Related Infections/
6 exp Catheterization/
7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*).mp.
8 4 or 5 or 6 or 7
9 Antibiotic Prophylaxis/
10 exp Anti-Infective Agents/
11 exp Gram-Positive Bacterial Infections/dt [Drug Therapy]
12 antibiotic*.mp.
13 9 or 10 or 11 or 12
14 randomized controlled trial.pt.

15 controlled clinical trial.pt.
16 randomized.ab.
17 placebo.ab.
18 clinical trials as topic.sh.
19 randomly.ab.
20 trial.ti.
21 14 or 15 or 16 or 17 or 18 or 19 or 20
22 3 and 8 and 13 and 21
23 exp animals/ not humans.sh.
24 22 not 23
key:
mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
sh = subject heading
ti = title

Appendix 3. Search strategy for EMBASE

EMBASE Ovid
1 exp neoplasm/
2 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or oncolog* or leukemia* or leukaemia* or lymphoma* or metasta* or bone marrow transplant*).mp.
3 1 or 2
4 exp catheter/
5 catheter infection/
6 catheterization/
7 (catheter* or central venous line* or central venous device* or CVC* or TCVC*).mp.
8 4 or 5 or 6 or 7
9 antibiotic prophylaxis/
10 exp antiinfective agent/
11 Gram positive infection/dt [Drug Therapy]
12 antibiotic*.mp.
13 9 or 10 or 11 or 12
14 crossover procedure/
15 double-blind procedure/
16 randomized controlled trial/
17 single-blind procedure/
18 random*.mp.
19 factorial*.mp.
20 (crossover* or cross over* or cross-over*).mp.
21 placebo*.mp.
22 (double* adj blind*).mp.
23 (singl* adj blind*).mp.
24 assign*.mp.
25 allocat*.mp.
26 volunteer*.mp.
27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 3 and 8 and 13 and 27
29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
30 28 not 29

key:
mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

WHAT'S NEW

Last assessed as up-to-date: 28 June 2013.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 3, 2003

Date	Event	Description
1 April 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
6 November 2013	New citation required but conclusions have not changed	New evidence supports conclusions of previous review
17 September 2013	New search has been performed	Two additional studies added (Di Carlo 2011; Handrup 2013)
28 June 2013	New search has been performed	New search performed
6 September 2011	Amended	PLS amended
9 November 2006	New citation required and conclusions have changed	Substantive amendment
9 November 2006	Amended	Minor update: 09/11/06 New studies sought but none found: 01/09/06 New studies found and included or excluded: 08/09/06 Conclusions changed: 19/09/06 Updating the search from July 2001 to July 2006 revealed no new RCTs in tunnelled central venous

(*Continued*)

		catheters. However, the improved method of testing heterogeneity I, has resulted in a change to the conclusions. Vanco prophylaxis at insertion of the catheter is not beneficial. Flushing the catheter is beneficial in high risk patients. In the excluded studies some new RCTs have been included. These were all RCTs with non-tunnelled central venous catheters
8 September 2006	New citation required and conclusions have changed	Original search performed.

CONTRIBUTIONS OF AUTHORS

- MD van de Wetering: reference search, article retrieval, assessment of studies for inclusion or exclusion, data extraction, analysis, manuscript preparation.
- J van Woensel: reference search, assessment of studies for inclusion or exclusion, data extraction, reviewing of manuscript.
- TA Lawrie: assessment of studies for inclusion or exclusion for the updated review, data extraction, analysis, and manuscript preparation.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- SKK Stichting kindergeneeskundig kankeronderzoek (Childrens Oncology Research Fund) Amsterdam, Netherlands.
(original review)
- Department of Health, UKNIHR Cochrane Programme Grant support from 'Optimising care, diagnosis and treatment pathways to ensure cost effectiveness and best practice in gynaecological cancer. Improving the evidence for the NHS.' CPG-10/4001/12, UK.
(updated review)

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies expanded to include lock solutions as well as flush solutions.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Anti-Bacterial Agents [administration & dosage]; Anticoagulants [administration & dosage]; Catheter-Related Infections [*prevention & control]; Catheterization, Central Venous [*adverse effects]; Gram-Positive Bacterial Infections [*prevention & control]; Heparin [administration & dosage]; Neoplasms [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans