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Antibiotic and other lock treatments for tunnelled central venous catheter-related infections in children with cancer (Review)

Schoot RA, van Dalen EC, van Ommen CH, van de Wetering MD

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TABLE OF CONTENTS

[Intervention Review]

Antibiotic and other lock treatments for tunnelled central venous catheter-related infections in children with cancer

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ABSTRACT

Background

The risk of developing a tunnelled central venous catheter (CVC)-related infection ranges between 0.1 and 2.3 per 1000 catheter days for children with cancer. These infections are difficult to treat with systemic antibiotics (salvage rate 24% - 66%) due to biofilm formation in the CVC. Lock treatments can achieve 100 - 1000 times higher concentrations locally without exposure to high systemic concentrations.

Objectives

Our objective was to investigate the efficacy of antibiotic and other lock treatments in the treatment of CVC-related infections in children with cancer compared to a control intervention. We also assessed adverse events of lock treatments.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, issue 3, 2011), MEDLINE/PubMed (1945 to August 2011) and EMBASE/Ovid (1980 to August 2011). In addition we searched reference lists from relevant articles and the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2006 to 2010), American Society of Clinical Oncology (ASCO) (from 2006 to 2010), the Multinational Association of Supportive Care in Cancer (MASCC) (from 2006 to 2011), the American Society of Hematology (ASH) (from 2006 to 2010) and the International Society of Thrombosis and Haematology (ISTH) (from 2006 to 2011). We scanned the ISRCTN Register and the National Institute of Health Register for ongoing trials (www.controlled-trials.com) (August 2011).

Selection criteria

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing an antibiotic lock or other lock treatment (with or without concomitant systemic antibiotics) with a control intervention (other lock treatment with or without concomitant systemic antibiotics or systemic antibiotics alone) for the treatment of CVC-related infections in children with cancer. For the description of adverse events, cohort studies were also eligible for inclusion.

Data collection and analysis

Two authors independently selected studies, extracted data and performed 'Risk of bias' assessments of included studies. Analyses were performed according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

Two RCTs evaluated urokinase lock treatment with concomitant systemic antibiotics (n = 56) versus systemic antibiotics alone (n = 48), and one CCT evaluated ethanol lock treatment with concomitant systemic antibiotics (n = 15) versus systemic antibiotics alone (n = 13). No RCTs or CCTs evaluating antibiotic lock treatments were identified. All studies had methodological limitations and clinical heterogeneity between studies was present. We found no evidence of significant difference between ethanol or urokinase lock treatments with concomitant systemic antibiotics and systemic antibiotics alone regarding the number of participants cured, the number of recurrent CVC-related infections, the number of days until the first negative blood culture, the number of CVCs prematurely removed, ICU admission and sepsis. Not all studies were included in all analyses. No adverse events occurred in the five publications of cohort studies (one cohort was included in two publications) assessing this outcome; CVC malfunctioning occurred in three out of five publications of cohort studies assessing this outcome.

Authors' conclusions

No significant effect of urokinase or ethanol lock in addition to systemic antibiotics was found. However, this could be due to low power or a too-short follow-up. The cohort studies identified no adverse events; some cohort studies reported CVC malfunctioning. No RCTs or CCTs were published on antibiotic lock treatment alone. More well-designed RCTs are needed to further explore the effect of antibiotic or other lock treatments in the treatment of CVC-related infections in children with cancer.

PLAIN LANGUAGE SUMMARY

Catheter lock treatments for catheter-related infections in children with cancer

Oncology patients require frequent venous access for their cancer treatment. Therefore, more permanent catheters (central venous catheters (CVCs)) are often inserted. However, these can become infected and once the CVC becomes occupied by bacteria it is difficult to eradicate these micro-organisms. Lock solutions are medicines that are placed in the CVC and left to dwell for a certain time period. These locks only treat the CVC and high concentrations can be achieved. In this review we investigated the effect of lock treatments on CVC-related infections. We identified three studies: two investigating the effect of urokinase lock treatments in addition to antibiotics and one study investigating the effect of ethanol locks in addition to antibiotics. We could detect no effect of urokinase or ethanol locks. However, the groups were very small. A similar study with a larger participant population might have different results.

BACKGROUND

Description of the condition

Adequate venous access is necessary in the treatment of people with cancer, for frequent administration of chemotherapeutics, intravenous (IV) medication, fluids and blood products. Sixty per cent and 73% of adults and children with cancer respectively therefore receive a tunnelled central venous catheter (CVC) (Hann 1997). The disadvantages of such devices include the increased risk of CVC-related infections or the development of (a) symptomatic thrombosis. The risk of developing a CVC-related infection ranges between 0.1 and 2.3 per 1000 catheter days (Adler 2006; Bagnall-Reeb 2004; Cesaro 2004; Fratino 2005; Maki 2006; Rotstein 1995; Simon 2000). As reported by Maki 2006, incidence rates are influenced by the heterogeneity of different patient populations, the great diversity in catheters and the definition of CVC-related infections. In a systematic review of 200 prospective studies in adult patients, a stricter definition of CVC-related infections led to an approximately 30% lower estimated risk (Maki 2006). However, (CVC-related) infections lead to significant morbidity and mortality in 5% to 10% of children with cancer and to subsequent additional hospital admissions (Fleischhack 2001a; Fleischhack 2001b). Most CVC-related infections occur within 100 days after placement. In the first 45 days early CVC-related infections are often caused by skin pathogens colonising the catheter. Colonisation of the external surface of the CVC occurs through insertion. After 45 days luminal colonisation, originating from the hub, is more frequently the source of infection, or a disseminating infection elsewhere in the body (Hachem 2002; O'Grady 2002; Raad 1993).The most common causative organisms in children with cancer are Gram-positive organisms (70%), followed by Gram-negative organisms (15%) and fungi or anaerobic organisms (both 7%) (van de Wetering 2007).

Description of the intervention

Treatment of CVC-related infections is difficult: it often requires prolonged use of several antibiotics, and still 24% to 66% of the CVCs cannot be salvaged, and require replacement (Flynn 2000; Fratino 2005; Mermel 2009; Rubin 1999; Wiener 1992).Treatment of CVC-related infections is difficult because micro-organisms adhere to the CVC and become embedded in a self-produced polymeric matrix, called a biofilm. To achieve therapeutic concentrations of antibiotics needed to kill microbes growing in a biofilm, concentrations 100 to 1000 times higher are required than for the killing of freely floating (planktonic) bacteria (Carratala 2002; Mermel 2009).These high concentrations can be achieved with lock treatments: antibiotics or other medications are installed in the CVC, thereby assuring high concentrations of the compound locally but without exposure to high concentrations systemically. Currently, antibiotic lock treatments (ALTs) are recommended in (immuno-competent) children in conjunction with systemic antibiotic treatments for the salvage of CVCs. No specific recommendations are given for immunocompromised patients (Mermel 2009).

Why it is important to do this review

A definitive diagnosis of a CVC-related infection can be challenging, especially in children. In adults, simultaneous withdrawal of central and peripheral blood cultures is recommended to differentiate between CVC-related infections and bacteraemia unrelated to the CVC (Mermel 2001). A CVC-related infection is defined either by a five-fold higher colony count in the culture obtained through the CVC or by differential time-to-positivity (DTTP). DTTP is the time taken between collection of the sample and the cultures becoming positive. Since the concentration of the micro-organisms is higher in the CVC, in the case of a CVC-related infection DTTP will be shorter for the culture obtained through the CVC. In paediatric oncology routine collection of peripheral blood samples is not feasible. Franklin 2004 reported that in St. Jude Children's Hospital peripheral blood cultures were only obtained in 58% of children presenting with febrile neutropenia, even though it was required by hospital guidelines. The Infectious Diseases Society of America (IDSA) have even suggested that diagnosis of CVC-related infections in children is often not possible (Mermel 2009). For adults with any sort of catheter and underlying disease the IDSA recommends systemic antibiotic treatment and removal of the catheter in case of a complicated CVC-related infection. A CVC-related infection is considered complicated when associated with: severe sepsis, suppurative thrombophlebitis, endocarditis, bloodstream infections that continue despite more than 72 hours of antimicrobial therapy, or infections due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, fungi or mycobacteria. In all other cases catheter salvage can be considered. For children these same recommendations apply, with an additional caveat that the benefits of catheter removal must be weighed against the difficulty of obtaining alternate venous access. Since vascular access in children is difficult to achieve, it is often necessary to attempt catheter salvage. Provided the clinical situation of the child permits salvage, treatment consists of systemic and antibiotic lock treatment simultaneously (Mermel 2009).

Evidence concerning the implementation of ALT is fragmentary. The first study describing it was published by Messing 1988, treating adults with CVC-related infections receiving home total parenteral nutrition (TPN). Thereafter, similar small case studies have investigated the use of ALT with or without concomitant systemic antibiotics. Segarra-Newnham 2005 published an overview of case studies investigating ALT in different patient populations. The authors pooled data from all cases reported so far, regardless of the underlying disease, age, therapeutic agent, ALT concentrations or the addition of systemic antibiotics, and found a total of 383 patients who received ALT, of which 295 (77%) were reported as successful. However, even the definition of cure differed between these reports, as did the definition of a CVC-related infection. Rijnders 2005 undertook a randomised, placebo-controlled trial in adults with cancer to investigate the addition of vancomycin (in case of Gram-positive pathogens) or ceftazidime (Gram-negative) to systemic antibiotics. Failure to cure the CVC-related infection was reduced from 57% to 33%. Unfortunately, the study had to be stopped prematurely due to poor accrual rates, and the results were not statistically significant. Data on children are even more scarce. Two studies reported favourable results with ALT in children with CVC-related infections; most had a CVC for home TPN (Cuntz 2002; Johnson 1994). These results from children receiving TPN, or from adults with a range of underlying diseases can not be extrapolated to children with cancer. Pathogens are different; TPN stimulates the growth of pathogens such as *Candida parapsilosis* and *Malassezia furfur* (Hachem 2002). Children are often immunocompromised due to cancer treatment, and more susceptible to severe infections and complications. CVCs in children are therefore used intensively during admission, which leaves little time for the ALT to dwell. In haemodialysis patients, on the other hand, the ALT can dwell after dialysis for a few hours. Other lock treatments such as

taurolidine, ethanol or the addition of urokinase to ALT have not been implemented in current guidelines, since reports are sparse (De Sio 2004; Koldehoff 2004; Onland 2006). We have therefore conducted this systematic review, to evaluate the current state of evidence on the use of lock treatments for the treatment of CVC-related infections in children with cancer.

OBJECTIVES

The primary objective of this systematic review was to evaluate the efficacy of lock treatments (antibiotic or other) in the treatment of CVC-related infections in children with cancer compared to a control intervention: this could be another lock treatment with or without systemic antibiotics, or treatment with systemic antibiotics alone, without the addition of a lock treatment.

Secondary objectives of this systematic review were:

- To evaluate which micro-organisms could be successfully treated with lock treatments, and in which cases early CVC removal was needed.
- To evaluate whether antibiotic lock treatments could be given alone, or if combination with systemic antibiotics was necessary.
- To assess adverse events of lock treatments

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing one lock treatment with another, or with systemic antibiotics alone, to treat CVC-related infections in children with cancer. For the assessment of adverse events, cohort studies were also eligible for inclusion.

Types of participants

Children with cancer (0 to 18 years) with a CVC-related infection.

Types of interventions

- Lock treatment (antibiotic or other) versus another lock treatment without systemic antibiotics.
- Lock treatment (antibiotic or other) versus systemic antibiotics alone.
- Lock treatment (antibiotic or other) versus another lock treatment with concomitant systemic antibiotics.
- Lock treatment (antibiotic or other) with concomitant systemic antibiotics versus systemic antibiotics alone.

Types of outcome measures

Primary outcomes

Primary outcomes were:

- the number of children cured of their CVC-related infection;
- the number of children experiencing a recurrence of their CVC-related infection.

A 'CVC-related infection' is defined as:

- Bacteraemia or fungaemia in a person who has an intravascular device and more than one positive blood culture result obtained from the peripheral vein, with clinical manifestations of infection (e.g. fever, chills, and/or hypotension), and no apparent source of bloodstream infection other than the catheter. One of the following should be present: a positive result of semiquantitative (15 CFU per catheter segment) or quantitative (10^2 CFU per catheter segment) catheter culture, whereby the same species of organism is isolated from a catheter segment and a peripheral blood culture; simultaneous quantitative cultures of blood with a ratio of more than 3:1 CFU/ml of blood (catheter versus peripheral blood); differential time-to-positivity (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least two hours earlier than a culture of simultaneously-drawn peripheral blood of equal volume) (Mermel 2009).

A 'CVC-associated infection' is defined as:

- The person has a recognised pathogen cultured from one or more blood cultures, and the pathogen cultured from the blood is not related to an infection at another site.
- The person has at least one of the following signs or symptoms: fever (over 38°C), chills, or hypotension, and at least one of the following:

1. Common skin contaminant (e.g. diphtheroids, *Bacillus* spp, coagulase-negative staphylococci, or micrococci) cultured from two or more blood cultures drawn on separate occasions.
2. Common skin contaminant (e.g. diphtheroids, *Bacillus* spp, coagulase-negative staphylococci, or micrococci) cultured from at least one blood culture from a person with an intravenous line, and the physician institutes appropriate antimicrobial therapy.
3. Positive antigen test on blood (e.g. *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides,* or group B streptococcus).

and signs and symptoms with positive laboratory results were not related to an infection at another site. (O'Grady 2002; Simon 2006).

- In the absence of catheter culture, defervescence after removal of an implicated catheter from a person with a primary bloodstream infection was considered as indirect evidence of a catheter-associated bloodstream infection (Eggiman 2004).

As the nomenclature and definition of catheter-related and catheter-associated infections differ between studies we will, for reasons of simplicity, from know on only use the term 'catheter-related infection'. Exact definitions used in the included studies will be summarised in Table 1.

A 'cure' is defined as:

Disappearance of fever and signs of catheter inflammation with negative follow-up blood culture(s). Removal of the CVC due to an infection within 30 days after discontinuation of the CVC-related infection-installed treatment was considered a treatment failure (Rubin 1999).

A 'recurrence' is defined as a new CVC-related infection with the same causative organism.

Secondary outcomes

We considered the following to be secondary outcomes:

- number of days until the first negative blood culture;
- time to recurrence;
- premature removal of the CVC;
- mortality;
- ICU admission;
- sepsis;
- adverse events (in cohort studies).

Search methods for identification of studies

See: Cochrane Childhood Cancer Group methods used in reviews (Module CCG).

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, issue 3, 2011), MEDLINE/PubMed (from 1945 to August 2011) and EMBASE/Ovid (from 1980 to August 2011).

The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are presented in the appendices (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE or EMBASE, either published or unpublished, by searching the reference lists of relevant articles and review articles. We handsearched the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2006 to 2010), American Society of Clinical Oncology (ASCO) (from 2006 to 2010), the Multinational Association of Supportive Care in Cancer (MASCC) (from 2006 to 2011), the American Society of Hematology (ASH) (from 2006 to 2010) and the International Society of Thrombosis and Haematology (ISTH) (from 2006 to 2011).
We scanned the International Standard Randomised Controlled Trial Number (ISRCTN) register and the National Institute of Health (NIH) Register for ongoing trials (www.controlled-trials.com) (August 2011).
We did not impose language restrictions. We will update the searches every two years.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, two review authors (MvdW and RS) independently identified studies meeting the inclusion criteria for this review. They were not blinded to the journal title, study author or the Institution. We resolved discrepancies between authors by consensus. If no agreement could be reached we asked for the opinion of a third party arbitrator. We obtained any study seemingly meeting the inclusion criteria on grounds of title, abstract, or both, in full for closer inspection. We would have contacted study authors for additional information if necessary. We gave details of reasons for the exclusion of any study considered for review and documented all excluded studies in a flow chart (see Figure 1).

Data extraction and management

Two authors (MvdW and RS) independently performed data extraction using standardised forms. Data extraction included characteristics of the participant group involved, the intervention described, the outcome assessed, and the duration of follow-up. If necessary we would have contacted study authors for additional information. We resolved disagreements by consensus. If no agreement could be reached we asked for the opinion of a third party arbitrator.

Assessment of risk of bias in included studies

Two authors (MvdW and RS) independently undertook the assessment of risk of bias of the included studies (i.e. selection bias, performance bias, detection bias, attrition bias and reporting bias). We used the risk of bias items as described in the module of the Childhood Cancer Group (Module CCG), which are based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook); to assess reporting bias we compared the methods section of included studies with their results section. We would have contacted study authors for additional information if necessary. We resolved discrepancies between authors by consensus. If no agreement could be reached we asked for the opinion of a third party arbitrator.

The results of the 'Risk of bias' assessment, i.e. how each trial scored on each risk of bias item, is presented in the 'Risk of bias' table and in a methodological quality summary. The risk of bias in included studies was taken into account in the interpretation of the review's results. For cohort studies we did not perform a 'Risk of bias' assessment.

Measures of treatment effect

For dichotomous outcomes, we expressed the effect estimate as a risk ratio (RR). Each result was presented with its corresponding 95% confidence interval (CI).

Adverse events reported in the cohort studies were summarised descriptively using the effect measures as reported in the individual studies.

Unit of analysis issues

If trials other than those with a simple parallel design, such as cluster-randomised trials or cross-over trials, had been included, we would have taken appropriate steps to avoid unit of analysis errors. However, since we included only studies with a parallel design this was not applicable.

Dealing with missing data

If relevant data had been missing, we would have attempted to contact the study authors to retrieve it, but since no relevant data were missing this was not necessary. We extracted data by allocation group, irrespective of compliance with the allocated condition, in order to allow an intention-to-treat analysis.

Assessment of heterogeneity

We assessed heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the I^2 statistic (Higgins 2003). If we detected significant heterogeneity (I^2 > 50%), we explored possible reasons for this and took appropriate

measures. We used a random-effects model for the estimation of treatment effects throughout the review.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the 'Assessment of risk of bias' section, we planned to assess reporting bias by constructing a funnel plot provided there were enough included studies (i.e. at least 10 studies included in a meta-analysis). Fewer than this would mean that the power of the test is too low to distinguish chance from real asymmetry (Cochrane Handbook). Since none of our meta-analyses included at least 10 studies, this was not applicable.

We took the following measures to reduce reporting bias:

- we searched multiple electronic databases, proceedings of scientific meetings and trial registries to deal with location and time lag bias;
- we applied no language restriction in the search strategy;
- we excluded duplicate reports of the same study to avoid duplicate publication bias.

Data synthesis

We entered data into Review Manager 5 and undertook analyses according to the guidelines in the Cochrane Handbook. The primary aim was to perform pooled analyses. However, if the included studies did not meet the criteria for good methodological quality and if groups were not comparable, we summarised the results descriptively. RCTs and CCTs were analysed separately. If people with more than one infectious episode were included in a study, we only included the results of the first episode in the analyses.

Subgroup analysis and investigation of heterogeneity

We planned to look at participants with haematological and solid tumours separately, but the included studies did not provide the required data so this was not feasible.

Sensitivity analysis

We performed a sensitivity analysis based on the risk of bias criteria (i.e. excluding studies with a high risk of bias and studies for which the risk of bias was unclear) and compared the results of studies with a low risk of bias with those of all available studies, for all analyses that included more than one study.

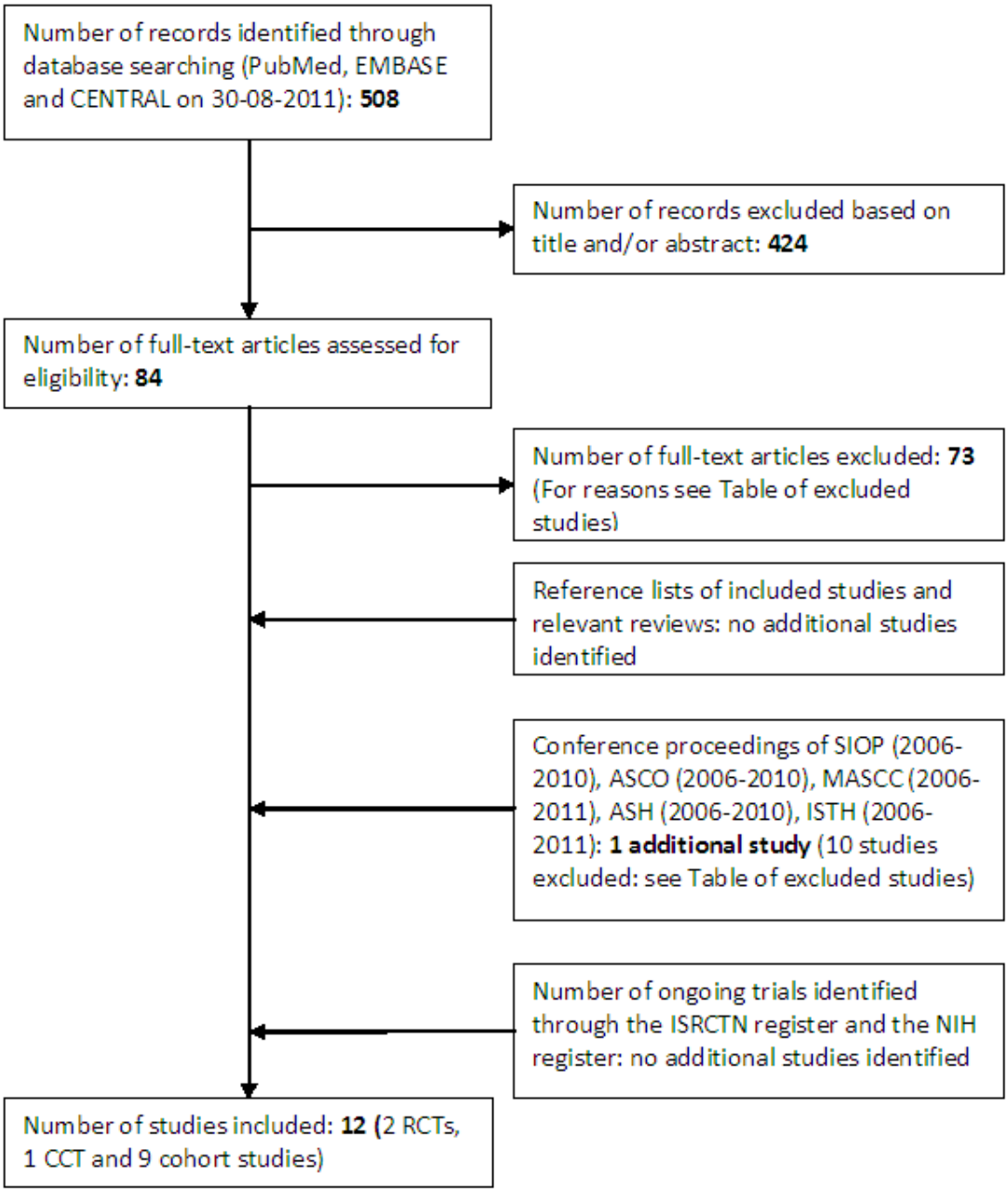
RESULTS

Description of studies

Results of the search

See: Characteristics of included studies table; Characteristics of excluded studies table; Figure 1. The searches of CENTRAL, MEDLINE and EMBASE identified 508 titles of reports of potentially relevant studies. We excluded 424 reports based on title and abstract alone, since they clearly did not meet all inclusion criteria. We screened the remaining 84 reports by full-text analysis, and excluded 73. After searching the conference proceedings, the ISRCTN trial register, the NIH register and reference lists of the relevant studies and reviews, we selected 11 additional abstracts. One of these 11 abstracts was included. No relevant ongoing trials were identified. We present a complete list with reasons for exclusion in the Characteristics of excluded studies table. We include 12 studies. Nine did not contain a control group and are presented in a separate overview Table. The remaining three studies are included in analyses.

Figure 1. Flow diagram of selection of studies



SIOP; International Society for Paediatric Oncology, ASCO; American Society of Clinical Oncology, MASCC; Multinational Association of Supportive Care in Cancer, ASH; the American Society of Hematology, ISTH; the International Society of Thrombosis and Haematology, NIH; National Institutes of Health, RCT; randomised controlled trial, CCT: controlled clinical trial

Included studies

Characteristics of the two included randomised controlled trials (RCTs) (Atkinson 1998; La Quaglia 1994) and one controlled clinical trial (CCT) (Dannenberg 2003), covering a total of 132 children, are presented in the Characteristics of included studies table. All studies evaluated lock treatments with concomitant systemic antibiotics versus systemic antibiotics alone. Different CVC devices were used. All studies applied different definitions for CVC-related/associated infections. These definitions are summarised in Table 1. Dannenberg 2003 investigated bloodstream infections and episodes of sepsis and did not fulfil the strict definition of CVC-related/associated infections as presented in the methods. Two studies compared urokinase locks and concomitant systemic antibiotics with systemic antibiotics alone (Atkinson 1998; La Quaglia 1994), whereas the other study compared ethanol locks and concomitant systemic antibiotics with systemic antibiotics alone (Dannenberg 2003). All studies used different treatment schedules. For a detailed description of the interventions see the Characteristics of included studies table. Two studies included children with non-malignant diseases (Atkinson 1998; La Quaglia 1994); in La Quaglia 1994 children without malignant disease received chemotherapy. The follow-up duration was specified in two studies (Atkinson 1998; Dannenberg 2003). In Dannenberg 2003 the follow-up period consisted of "the subsequent leukopenic periods or within four weeks of finishing treatment", while in Atkinson 1998 follow-up was completed when negative culture results were obtained and clinical signs resolved or when a failure was declared and the CVC removed. In La Quaglia 1994 no information on follow-up duration was provided.

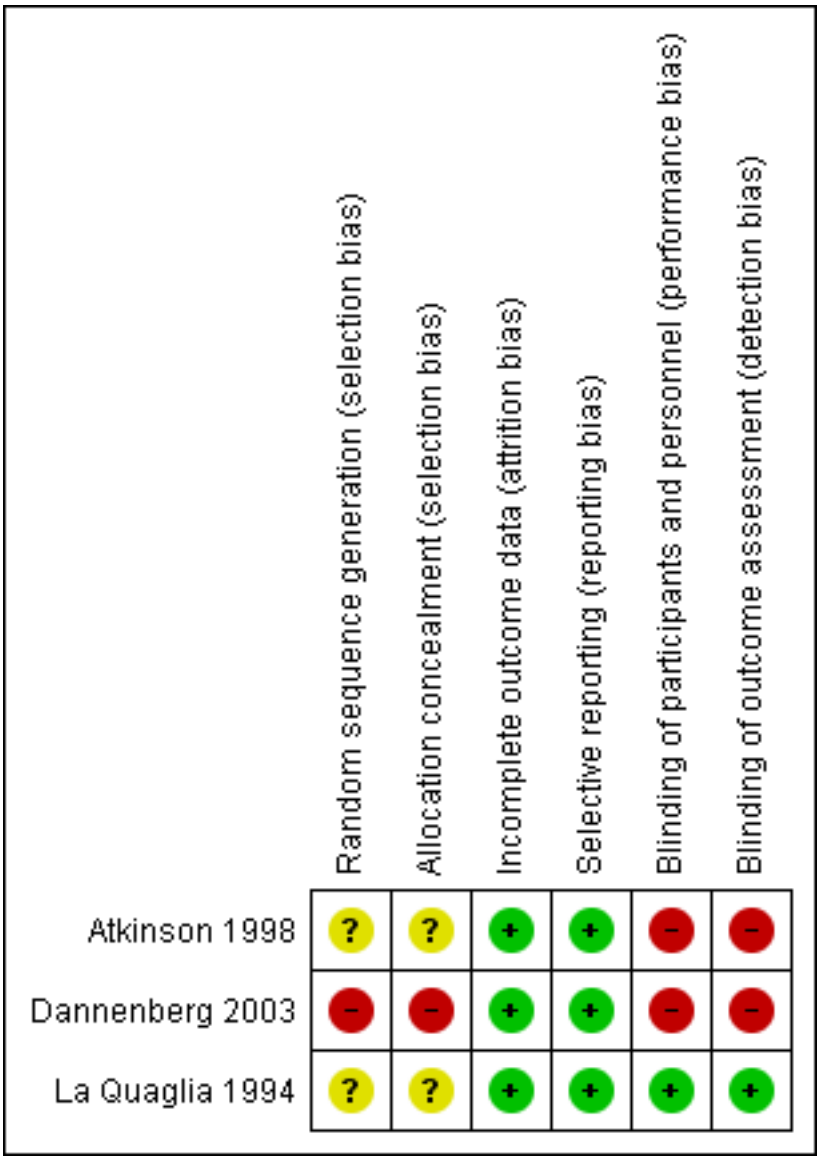
We found no eligible RCTs or CCTs for the following comparisons: one lock treatment versus another with systemic antibiotics; one lock treatment versus another without concomitant systemic antibiotics; lock treatment versus systemic antibiotics alone.

For the evaluation of adverse events we included nine publications of cohort studies (one cohort study described in two publications (Jones 1993; Jones 1996)). In five studies antibiotic locks with or without systemic antibiotics were evaluated; in four studies other lock treatments with or without systemic antibiotics were evaluated (i.e. 2M HCL, urokinase and ethanol locks). Different definitions of CVC-related/associated infections were used. All studies used different treatment schedules. For more detailed information on these studies see Table 2. Two studies used a CLC 2000 connector (Bernardi 2005; Cesaro 2004). This device creates a positive pressure forcing the flushing saline through the CVC distally and aims to prevent the distal CVC from clot occlusion (Cesaro 2007). Since it has been reported that heparin can precipitate when added to antibiotics (Droste 2003), the connector device was meant to replace heparin in the antibiotic locks.

Risk of bias in included studies

Data on the 'Risk of bias' assessment of the three included trials are described in the risk of bias section of the Characteristics of included studies table and presented in Figure 2. We did not assess the risk of bias in the included cohort studies. All studies were found to have methodological limitations. For the evaluation of internal validity we assessed the risk of selection bias, performance bias, detection bias, attrition bias and reporting bias.

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



Selection bias

To evaluate selection bias we have assessed the random sequence generation and the allocation concealment. Two of the three studies were RCTs (Atkinson 1998; La Quaglia 1994). However, neither study described the exact procedure for randomisation, and it therefore remains unclear whether sequence generation was random or whether the allocation sequence was concealed. The risk of selection bias in these studies is therefore rated as being unclear. The third study was a CCT (Dannenberg 2003). The risk for selection bias was high for this study, since randomisation was not performed.

Performance bias and detection bias

To evaluate performance bias we have assessed the blinding of participants and personnel. Two studies were open-label (one RCT and one CCT) and neither participants nor personnel were blinded (Atkinson 1998; Dannenberg 2003). The risk of performance bias in these studies was thus high. The third study was a double-blind RCT (La Quaglia 1994) and participants and personnel were both blinded, resulting in a low risk of performance bias.

To evaluate detection bias we have checked the blinding of outcome assessors for all separate outcomes. In Atkinson 1998 and Dannenberg 2003 outcome assessors were not blinded for any outcome, giving a high risk of detection bias in both studies. In La Quaglia 1994 outcome assessors were blinded for all outcomes, resulting in a low risk of detection bias.

Attrition bias

To evaluate attrition bias we have assessed incomplete outcome data for all separate outcomes. In all three studies follow-up was complete for all included participants for all outcomes, giving a low risk of attrition bias.

Reporting bias

To evaluate reporting bias we have assessed selective reporting of outcomes. In all three studies the risk of reporting bias was judged to be low .

Effects of interventions

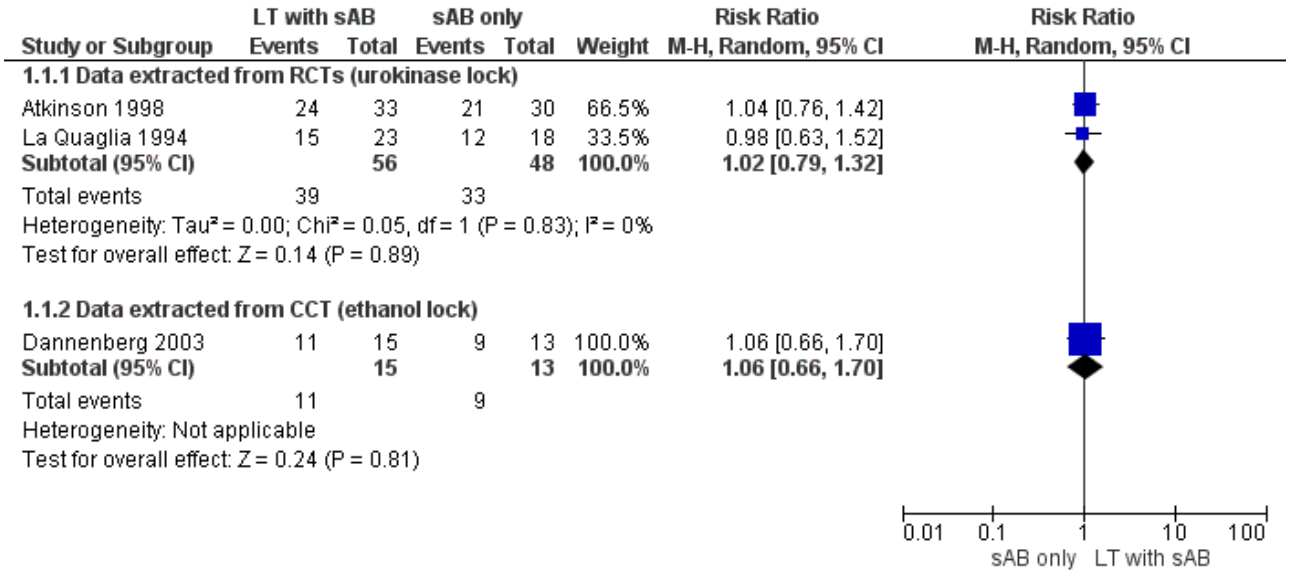
Not all studies allowed data extraction for all endpoints; see Characteristics of included studies table for a more detailed description of the extractable endpoints of each study.

Number of children cured from their CVC-related infection

We were able to extract data on the number of participants cured from all three included studies (Atkinson 1998; Dannenberg 2003; La Quaglia 1994).

We performed meta-analysis on results from the two randomised controlled trials (RCTs) with a total of 104 participant children (Atkinson 1998; La Quaglia 1994) (Figure 3). Thirty-nine of 56 children (70%) randomised to urokinase lock and systemic antibiotics were cured from their CVC-related infection, compared with 33 of the 48 children (69%) randomised to systemic antibiotics alone. We found no significant difference between urokinase lock treatment with concomitant systemic antibiotics and systemic antibiotics alone (risk ratio (RR) 1.02, 95% confidence Interval (CI) 0.79 to 1.32, P = 0.89). No heterogeneity was detected (I^2 = 0%).

Figure 3. Forest plot of comparison: 1 Lock treatment with systemic antibiotics versus systemic antibiotics only, outcome: 1.1 Number of patients cured from CVC related infection.



Data extracted from the CCT (Dannenberg 2003) covering 28 children also showed no significant difference between those treated with ethanol locks and concomitant systemic antibiotics and those treated with systemic antibiotics alone (RR 1.06, 95% CI 0.66 to 1.70, P = 0.81) (see Figure 3; Analysis 1.1). Eleven children out of 15 (73%) randomised to ethanol lock and systemic antibiotics were cured of their CVC-related infection, compared with nine of the 13 (69%) randomised to systemic antibiotics alone.

Please note that due to the nature of this outcome (i.e. the number of children cured from their CVC-related infection) a high event rate is favourable. Therefore, in the analysis graphs, "Favours systemic antibiotics alone" is on the left and "Favours lock treatment with systemic antibiotics" is on the right, in contrast with graphs for the other analyses.

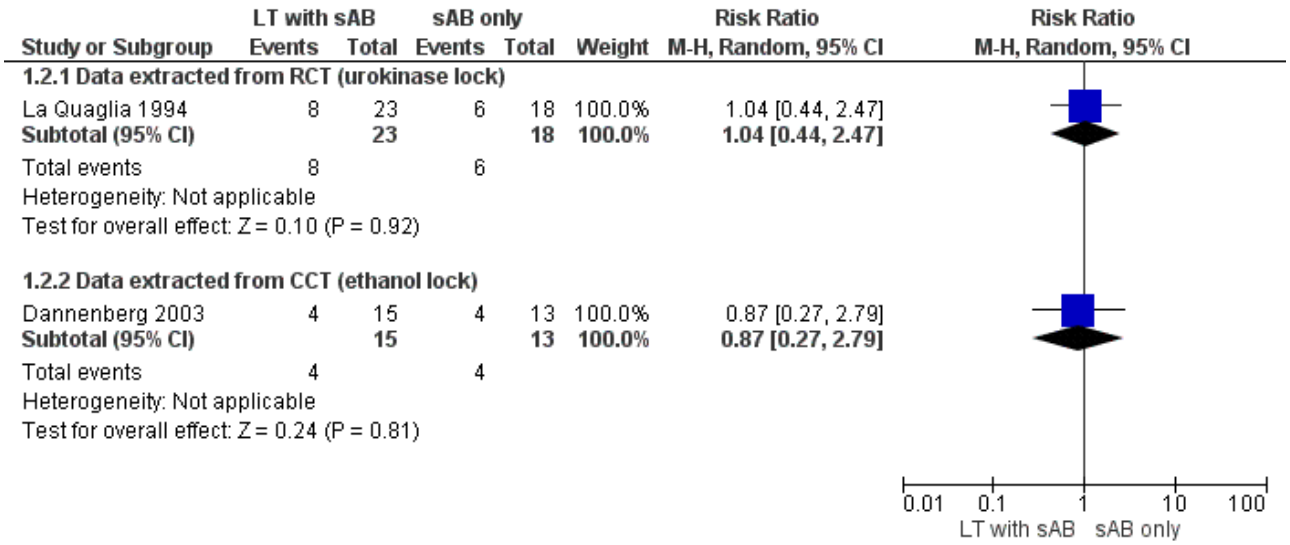
None of the included studies reported which pathogens could be treated with lock treatments, with or without systemic antibiotics, and which pathogens required immediate CVC removal.

Number of children experiencing a recurrence of their CVC-related infection

Two studies reported the number of children experiencing recurrences of their CVC-related infections (Dannenberg 2003; La Quaglia 1994).

No significant difference was found in the number of children with a recurrent CVC-related infection between lock treatment with concomitant systemic antibiotics and systemic antibiotics alone. In the RCT evaluating urokinase locks (La Quaglia 1994) the RR was 1.04 (95% CI 0.44 to 2.47, P = 0.92). There were eight children (35%) with a recurrence of their CVC-related infection from 23 randomised to urokinase lock and systemic antibiotics, compared with six from the 18 (33%) randomised to systemic antibiotics alone. In the CCT evaluating ethanol locks (Dannenberg 2003) the RR was 0.87 (95% CI 0.27 to 2.79, P = 0.81). There were four children (27%) from 15 randomised to ethanol lock and systemic antibiotics with a recurrence of their CVC-related infection, compared with four from 13 (31%) randomised to systemic antibiotics alone (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 Lock treatment with systemic antibiotics versus systemic antibiotics only, outcome: 1.2 Number of patients with a recurrence of the CVC-related infection.



Number of days until the first negative blood culture

Insufficient data were available to perform a meta-analysis, and we therefore provide descriptive results for this outcome measure. Two studies presented the number of days to achieve negative blood cultures (Atkinson 1998; La Quaglia 1994). Both studies evaluated urokinase locks. Atkinson 1998 presented the average number of days to achieve negative blood cultures (only salvaged catheters were included): 2.5 days for both the intervention and the control group (no P value reported). La Quaglia 1994 presented a graph representing the rate of fall of colony-forming units (CFU) of micro-organisms with time after the first positive blood culture. In the urokinase lock with systemic antibiotics group the number of CFUs reached zero after two days, compared with three days in the systemic antibiotics alone group. This difference was not statistically significant (no P value reported).

Time to recurrence

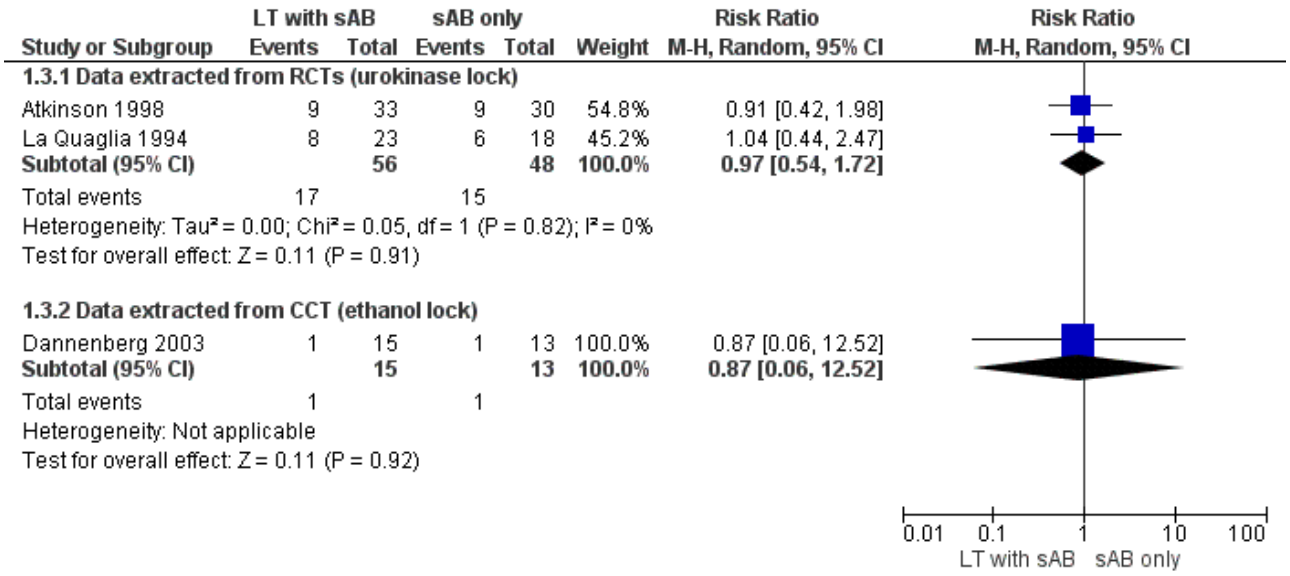
Time to recurrence was not reported in any of the included studies.

Premature removal of the CVC

Premature CVC removal was reported by all three included studies (Atkinson 1998; Dannenberg 2003; La Quaglia 1994). All CVCs were removed because of progressive or recurrent infections. In Atkinson 1998 CVCs were removed when cultures persisted positive for more than 72 hours beyond study entry, or when clinical signs suggested overt progression of the septic process. The policy regarding CVC removal was not specified in the remaining two studies (Dannenberg 2003; La Quaglia 1994), other than stating that catheter removal was due to infection.

Data extracted from the RCTs evaluating urokinase locks were pooled in a meta-analysis covering 104 children (Analysis 1.3; Figure 5). There were 17 CVC removals (30%) among 56 children randomised to urokinase lock and systemic antibiotics, compared with 15 (31%) among the 48 randomised to systemic antibiotics alone. No significant difference was found between urokinase lock treatments with concomitant systemic antibiotics and systemic antibiotics alone: RR 0.97, 95% CI 0.54 to 1.72, P = 0.91. No heterogeneity was detected (I^2 = 0%).

Figure 5. Forest plot of comparison: 1 Lock treatment with systemic antibiotics versus systemic antibiotics only, outcome: 1.3 Premature CVC removal.



Similarly, data extracted from the CCT evaluating ethanol locks and covering 41 children did not show a significant difference: RR 0.87, 95% CI 0.06 to 12.52, P = 0.92 (Dannenberg 2003). There was one CVC removal among 15 children (7%) randomised to ethanol lock and systemic antibiotics, compared with one among 13 (8%) randomised to systemic antibiotics alone (Figure 5).

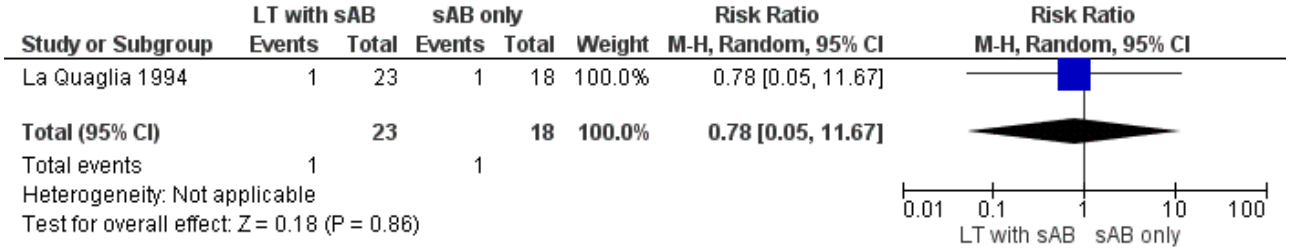
Mortality

Mortality was not reported in any of the included studies.

Intensive care unit (ICU) admission

Intensive care unit (ICU) admission was reported by one study evaluating urokinase locks (La Quaglia 1994). In both treatment groups one child was admitted to the ICU because of haemodynamic instability almost immediately after study drug infusion (Analysis 1.4; Figure 6) (RR 0.78, 95% CI 0.05 to 11.67, P = 0.86). Because of these episodes, a premature statistical analysis was performed. No significant improvement in CVC salvage with urokinase could be identified, and the protocol was ended.

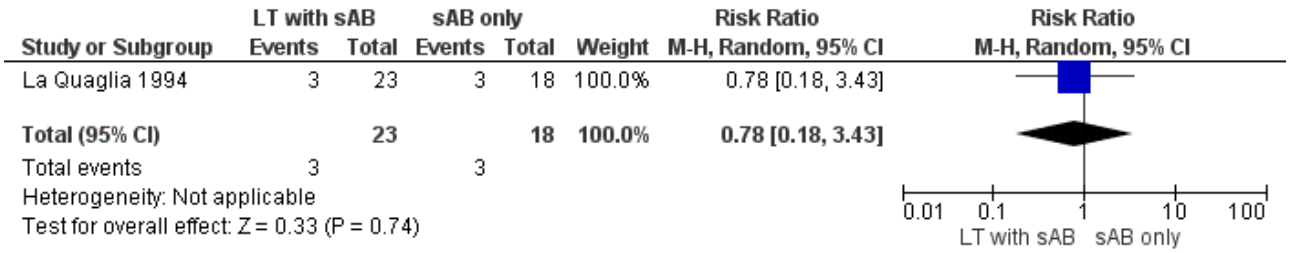
Figure 6. Forest plot of comparison: 1 Lock treatment with systemic antibiotics versus systemic antibiotics only, outcome: 1.5 ICU admittance (urokinase lock).



Sepsis

Sepsis was reported in one study (La Quaglia 1994) and no significant difference was found between urokinase lock treatment with systemic antibiotics and systemic antibiotics alone (RR 0.78, 95% CI 0.18 to 3.43, P = 0.74). Three children (13%) were diagnosed with sepsis among the 23 randomised to urokinase lock treatment and systemic antibiotics, compared with three (17%) of the 18 allocated to the systemic antibiotics alone (Analysis 1.5; Figure 7).

Figure 7. Forest plot of comparison: 1 Lock treatment with systemic antibiotics versus systemic antibiotics only, outcome: 1.4 Sepsis (urokinase lock).



Sensitivity analyses for the used risk of bias criteria

The results of the sensitivity analyses were consistent among the trials and did not differ from the overall analyses.

Cohort studies for the evaluation of adverse events (no control group included)

Cohort studies are described in detail in Table 2. Here we only present results for adverse events and CVC malfunction, as that was the purpose of including cohort studies. However, information on treatment results are included in Table 2. Five studies (including two studies describing the same cohort, i.e. Jones 1993 and Jones 1996) provided information on adverse events; none of the studies reported that any adverse events occurred. Five studies (four cohorts) provided information on CVC malfunctioning; in three studies CVC malfunctioning occurred in some of the children, while none occurred in the other two studies.

DISCUSSION

Central venous catheter (CVC)-related infections cause significant morbidity and mortality in children with cancer. As these infections are difficult to treat with systemic antibiotics, alternative treatments are needed. This is the first systematic review investigating the efficacy of antibiotic lock and other lock treatments for tunnelled CVC-related infections in children with cancer.

In this review we identified two randomised controlled trials (RCTs) and one controlled clinical trial (CCT). All three studies investigated the efficacy of a lock treatment (urokinase in two RCTs and ethanol in one CCT) with concomitant systemic antibiotics, and compared this with systemic antibiotics alone. We identified no eligible trials for the other comparisons in which we were interested: one lock treatment versus another without systemic antibiotics, lock treatment versus systemic antibiotics alone, and one lock treatment versus another with concomitant systemic antibiotics.

For urokinase locks with concomitant systemic antibiotics versus systemic antibiotics alone, we found two RCTs. Our meta-analysis of these trials showed no evidence of a significant difference between the treatment groups in the number of children cured from their CVC-related infection. The number of children experiencing a recurrence of their CVC-related infection was assessed in one study, which also showed no significant difference between the treatment groups. The studies provided insufficient data to pool the results for the number of days until first negative blood culture, but neither study found a statistically significant difference between the treatment groups. Nor did the meta-analysis of premature removal of the CVC show a significant difference between the treatment groups; in both studies CVCs were removed because of either progressive or recurrent infections. One study evaluated intensive care unit (ICU) admission and sepsis, and found no significant differences between the treatment groups. None of the studies provided information on time to recurrence or mortality, nor on which pathogens could be adequately treated and which pathogens required CVC removal. It was not possible to perform subgroup analyses for haematological and solid tumours.

For ethanol locks with concomitant systemic antibiotics versus systemic antibiotics alone, we found one CCT. As presented in Table 1, this study did not completely fit the definition of a CVC-related or CVC-associated infection as specified in the Methods section of this review, and it is possible that the bloodstream infections treated may not have been related to the CVC. Our analysis of this trial showed no evidence of a significant difference between the treatment groups in the number of children cured of their CVC-related infection, nor in the number experiencing a recurrence of their CVC-related infection. The analysis of premature removal of the CVC also showed no significant difference between the treatment groups; all CVCs were removed because of either progressive or recurrent infection. No information was provided on the number of days until first negative blood culture, time to recurrence, mortality, ICU admission and sepsis; the study did not report which pathogens could be adequately treated and which pathogens required CVC removal. It was not possible to perform subgroup analyses for haematological and solid tumours.

For the evaluation of adverse events we included nine publications of cohort studies (one cohort study described in two publications). These studies did not have a control arm. In five studies antibiotic locks with or without systemic antibiotics were evaluated; in four studies other lock treatments with or without systemic antibiotics (i.e. 2M HCL, urokinase and ethanol locks). Five studies (four cohorts) provided information on adverse events, reporting the occurrence of no adverse events. They also provided information on CVC malfunctioning, with three studies confirming this in some of the participants and two reporting that no CVC malfunctioning occurred.

Nevertheless, 'no evidence of effect', as identified in this review, is not the same as 'evidence of no effect'. Our results do not imply that there is no effect of the addition of lock treatments to systemic antibiotics. The reason that no significant difference between treatment groups was identified could be that the number of included studies and participants was small (total number of children 132), i.e. low power. Also, the length of follow-up could have been too short to detect a significant difference between the

treatment groups in the number experiencing a recurrence of their CVC-related infection. For one of the two studies evaluating this outcome (Dannenberg 2003) we felt that the length of follow-up was adequate, but for the other study no information was provided on the length of follow-up (La Quaglia 1994). Another limitation of this review is the significant clinical heterogeneity between studies: two studies included children with non-oncological diseases; one study excluded participants with (asymptomatic) thrombosis; the number of participants with haematological malignancies differed between the treatment groups in at least two studies; no information on pathogens was provided; the type of CVCs varied between studies; and studies employed different guidelines regarding systemic antibiotic treatment and follow-up duration. All these factors could influence the results of this review.

The risk of bias in the included studies varied. Sometimes bias could not be ruled out due to insufficient information in the trial report. However, at this time this is the best available evidence based on RCTs and CCTs comparing lock treatments and systemic antibiotics with systemic antibiotics alone for tunnelled CVC-related infections in children with cancer. Sensitivity analyses restricted to studies with a low risk of bias did not differ from the overall results. Although a RCT is the best study design to adequately ascertain efficacy, CCTs can also provide reliable information provided that the design and execution are correct. Due to the high risk of bias associated with other study designs, we did not include cohort studies without control groups in our efficacy analyses. These studies were included for the evaluation of adverse events, but without 'Risk of bias' assessment.

Currently, despite the paucity of evidence for the efficacy of (antibiotic) lock treatments, the Infections Diseases Society of America (IDSA) recommends the use of antibiotic lock treatment for CVC salvage in paediatric patients (Mermel 2001). The authors compared data from 11 cohort studies investigating antibiotic lock treatment with or without systemic antibiotics with 14 cohort studies treating CVC-related infections with systemic antibiotics alone (Mermel 2001). They found that in comparison to systemic antibiotics, treatment including antibiotic lock therapy was significantly more likely to result in CVC salvage, with a risk ratio (RR) of 1.24, 95% confidence interval (CI) 1.13 to 1.36. However, no 'Risk of bias' assessment was performed and the patient populations were heterogeneous, consisting of both adults and children with different underlying diseases: patients with malignancies, patients with renal diseases needing haemodialysis, and patients with gastrointestinal diseases requiring total parenteral nutrition (TPN). As a result, this meta-analysis cannot reliably be used to answer questions on the efficacy of lock treatments for tunnelled CVC-related infections in children with cancer. Our systematic review was unable to identify evidence which supports the use of lock treatments in children with cancer, but an effect cannot be ruled out. The best study design to adequately ascertain the efficacy of lock treatments, provided that it is correctly executed, is a randomised controlled trial in which the only difference between the intervention and control group is the use of a lock treatment. We therefore recommend the development of new RCTs to answer this important question.

When developing a new randomised controlled trial with antibiotic or other lock treatments for CVC-related infections it is important to consider the following aspects: 1. the occurrence of episodes of haemodynamic instability during/after lock treatments; 2. potential CVC malfunction; 3. the difficulty of defining a CVC-related infection; and 4. microbial resistance.

Episodes of haemodynamic instability were reported by La Quaglia 1994. As a similar number of events occurred in both study arms, the authors assumed that a slow intravenous push of study medication dislodged bacteria and/or endotoxins into the central circulation and caused the haemodynamic instability. However, none of the other cohort studies reported symptoms of haemodynamic instability after administration of lock treatments (Table 2). Jones 1993 and Jones 1996 also investigated the use of urokinase locks with concomitant systemic antibiotics, and argued that, in contrast with La Quaglia 1994, the risk of releasing bacteria and endotoxins into the bloodstream was minimised in their protocol by administration of systemic antibiotics for 24 hours preceding urokinase treatment, so that antibiotics could reach high concentrations before bacteria and endotoxins were released into the bloodstream. However, a similar approach was defined in the protocol by La Quaglia 1994. Systemic antibiotics were administered at presentation and study medication was started when the diagnosis of CVC-related sepsis was established. Mean duration of systemic antibiotic treatment preceding urokinase was two days. The method of administration of study medication was similar in both study groups (La Quaglia 1994; Jones 1993; Jones 1996). Medication was instilled and left to dwell for one hour and subsequently aspirated. We therefore cannot explain why these participants became haemodynamic instable.

Since few in vitro and in vivo studies have mentioned CVC malfunction due to lock treatments, future lock treatment studies should systematically screen for CVC malfunction until sufficient data are available regarding the safety of antibiotic lock and other lock treatments. Two in vitro studies have suggested that ethanol lock treatments might have an effect on polyurethane and silicone CVC integrity, but the authors also argue that these changes might not be clinically relevant (Bell 2006; Maiefski 2009). Despite changes in mechanical properties, the catheter segments tested could still be stretched to 22 times their length and withstand 11.5 kg (113 N) of force (Bell 2006). Several in vivo studies have been published on the effect of ethanol locks as preventive treatments for CVC-related infections. It has been suggested that withdrawal of ethanol through the CVC may induce precipitation and CVC malfunction (Wales 2011). Nine studies have been published describing preventive ethanol lock treatments in different patient groups; in four studies the ethanol was flushed (Dannenberg 2003; Mouw 2008; Slobbe 2010; Wales 2011) and in five the ethanol was withdrawn (Cober 2010; Jones 2010; Kayton 2010; Laird 2005; Onland 2006). None of the studies flushing the ethanol locks mentioned CVC malfunction, but of the five studies withdrawing ethanol two reported three participants with CVC malfunction after ethanol lock treatment (Kayton 2010; Laird 2005). Only one of the nine studies was a randomised controlled trial comparing preventive ethanol locks with placebo in adult haematology patients (Slobbe 2010). No significant difference was observed in the incidence of CVC malfunction in this study. It has been suggested that highly concentrated antibiotics may precipitate when combined with lower doses of heparin. Droste 2003, an in vitro study, showed that higher concentrations of heparin were compatible with a wider range of antibiotic concentrations. Two of the cohort studies presented in Table 2 reported CVC malfunction due to antibiotic lock treatment (Bernardi 2005; Jones 1993; Jones 1996 (the Jones studies described the same cohort)). Bernardi 2005

mentioned CVC obstruction in one participant after treatment with teicoplanin/heparin locks. This CVC obstruction was resolved with urokinase flushes. Jones 1996 reported CVC malfunction in six of 97 participants, but did not specify the type of malfunction (occlusion, tearing, dislocation, precipitation). However, the number of CVC complications reported in the studies included in this review is still lower than the incidence of CVC complications reported in three prospective observational studies of people without lock treatments (Adler 2006; Cesaro 2004; Fratino 2005). These numbers suggest that CVC complications may have been under-reported in the included lock treatment trials.

Lock treatment studies should use uniform definitions adapted to paediatric practice for CVC-related infections. As many hospitals do not have the facilities needed for quantitative techniques and because withdrawal of peripheral blood cultures in children with CVCs is not desirable, we should accept other non-quantitative definitions for the diagnosis of CVC-related infections in children. Currently, the Infectious Diseases Society of America (IDSA) recommends semi-quantitative or quantitative blood cultures for the diagnosis of CVC-related infections (Mermel 2001; Mermel 2009). However, only one of the studies included in our analyses (La Quaglia 1994) defined CVC-related infections by quantitative measures such as differential time-to-positivity (DTTP) or the number of colony forming units from CVC cultures exceeding the number cultured from peripheral cultures (Table 1), but the report contained no data describing peripheral blood cultures. In addition to clinical symptoms suggesting CVC-related infections, collection of at least two central blood cultures could further substantiate the diagnosis of a CVC-related infection (Simon 2006). However, other sources of the infection, such as the skin or gut, cannot be ruled out with this definition (Costa 2004).

Finally, antibiotic resistance is a significant problem, especially in oncology where patients are immunocompromised, often need antibiotic treatments and spend many days in hospitals at risk of encountering multi-resistant pathogens. An advantage of antibiotic lock treatment over systemic antibiotics is the possibility of high local dosage without exposure to high systemic concentrations, thereby reducing antibiotic resistance. Nevertheless, despite these lower systemic concentrations, antibiotic lock treatments might still induce antibiotic resistance. New studies have therefore explored alternative lock solutions such as ethanol and taurolidine (Bradshaw 2008; Dümichen 2012; Oliveira 2012; Sanders 2008; Torres-Viera 2000). Neither lock solution has known microbial resistance and both have shown activity against Gram-positive, Gram-negative rods and fungals (Chaudhury 2012; Chu 2012; Qu 2009; Rane 2012). Nevertheless, as pathogens and resistance patterns differ between patient groups, hospitals and countries, the optimal lock treatment should be determined by the pathogens cultured.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence which supports the use of urokinase and ethanol lock treatments in addition to systemic antibiotics for tunnelled CVC-related infections in children with cancer, compared to systemic antibiotics alone. However, it should be noted that 'no evidence of effect', as demonstrated in this review, is not the same as 'evidence of no effect'. Based on the currently available evidence we are not able to give recommendations for clinical practice.

No eligible randomised or controlled clinical trials addressed the other comparisons in which we were interested: one lock treatment versus another without systemic antibiotics, lock treatment versus systemic antibiotics alone, and one lock treatment versus another with concomitant systemic antibiotics. No conclusions can therefore be drawn about their efficacy in treating tunnelled CVC-related infections in children with cancer.

Implications for research

More high quality research is needed before we can draw definitive conclusions about the efficacy of lock treatments for tunnelled CVC-related infections in children with cancer. Future studies should preferably be randomised controlled trials, performed in homogeneous study populations (e.g. by diagnosis or type of CVC), with long enough follow-up to detect recurrent infections. As few cases have described haemodynamic instability or CVC malfunction after lock procedures, future studies should closely monitor safety and perform interim analyses. The definition of CVC-related infections should be adapted to children, and should be based on clinical presentation and blood cultures. The number of participants should be sufficient to obtain the power needed for reliable results. However, the number of participants needed to achieve enough power for a statistically significant result in randomised supportive care studies is often far beyond the number of patients locally available. International co-operation is therefore essential within paediatric oncology research.

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CHARACTERISTICS OF STUDIES

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

Atkinson 1998

Methods	Single-centre RCT conducted in Los Angeles, USA.
Participants	63 children with cancer and tunnelled CVCs with a CVC-related infection (for the exact definition of CVC-related infections in this study see Table 1) and without a gross thrombus of fibrin within or attached to the CVC. Thrombus and fibrin deposits were investigated with a dye study injection of the CVC. Not all children received chemotherapy; the exact number is not reported. Type of CVCs; 11 single-lumen Broviac (7 intervention, 4 control), 41 double-lumen Broviac (18 intervention, 23 control) and 11 porth-á-cath (8 intervention, 3 control). Underlying diseases: 5 neuroblastoma (3 intervention, 2 control), 9 haemophilia (4 intervention, 5 control), 11 brain tumours (8 intervention, 3 control), 4 lymphomas (2 in each group), 11 ALL (4 intervention, 7 control), 8 ANLL (2 intervention, 6 control), 7 sarcomas (5 intervention, 2 control), 8 other (not further specified; 5 intervention, 3 control).
Interventions	Urokinase locks and concomitant systemic antibiotics (n = 33, intervention group) versus systemic antibiotics only (n = 30, control group). Lock treatment: intraluminal boluses of urokinase (Abbokinase Open-Cath, Abbott laboratories, Chicago IL) were instilled after at least 24 hours of systemic antibiotics. Children received 2 x 5000 IU boluses of urokinase administered 12 hours apart via each lumen of the catheter to dwell for one hour. The choice of antibiotics was adjusted by the treating physician according to the sensitivities of the organisms that had been cultured.

Atkinson 1998 *(Continued)*

Outcomes	(1) Number of children cured of their CVC-related infection. (2) Number of days until first negative blood culture (defined as time from initiation of antibiotic therapy to negative catheter culture). (3) Premature removal of the CVC (defined as the number of catheters requiring removal because of persistent clinical or culture-documented (i.e. culture positive for more than 72 hours beyond study entry) catheter sepsis). Children in both groups were monitored from the day of study entry with daily blood cultures drawn from all lumens of the catheters. They were also monitored for clinical signs of clearance or persistence of the infection including resolution of fever and leukocytosis.
Notes	A maximum of 17 participants with non-malignant disease could have been included in this study (i.e. 9 with haemophilia; for 8 other participants their underlying disease was not mentioned in the article). Not all participants received chemotherapy. The urokinase lock group contains fewer children (n = 8) with haematologic malignancies than the systemic antibiotics alone group (n = 15). Quote: "Study follow-up was completed when negative culture results were obtained and clinical signs resolved or when a failure was declared and the catheter removed". No further information regarding follow-up was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was performed by the pharmacist who also supplied the urokinase for injection" Comment: the sequence generation was probably done randomly, as this is the purpose of randomisation; however a description of the method of randomisation is missing.
Allocation concealment (selection bias)	Unclear risk	The method of randomisation was not specified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome assessment of all included participants for all outcome measures investigated.
Selective reporting (reporting bias)	Low risk	Complete outcome reporting of all included participants for all outcome measures investigated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open-label: neither participants nor personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open-label: outcome assessors were not blinded for any outcome evaluated.

Dannenberg 2003

Methods	CCT conducted in a single centre in Germany.

Dannenberg 2003 *(Continued)*

Participants	28 children with cancer with a CVC-related infection (for the exact definition of CVC-related infections in this study see Table 1). All were treated with chemotherapy. No information on the presence of a thrombus in the CVC was provided. Types of CVCs: double-lumen or triple-lumen Broviac catheters (possibly one triple-lumen catheter was used; not stated in which treatment group it might have been included). Underlying disease: 9 ALL (6 intervention, 3 control), 2 AML (one in each treatment group), 3 neuroblastoma (2 intervention, 1 control), 4 osteosarcoma (1 intervention, 3 control), 2 Ewing sarcoma (one in each treatment group), 1 Hodgkin lymphoma (intervention), 2 medulloblastoma (both intervention), 1 rhabdomyosarcoma (intervention), 1 schwannoma (control), 1 PNET (control), 1 nephroblastoma (control) and 1 ependymoma (control).
Interventions	Ethanol locks and systemic antibiotics (n = 15, intervention group) versus systemic antibiotics alone (n = 13, control group). Participants were treated between January 2000 and December 2001. The systemic antibiotics alone were standard care until the second half of 2000. The ethanol lock and systemic antibiotics treatment became standard policy during 2001. So in the second half of 2000 both interventions were used. Three children were treated in both treatment arms for different infectious episodes. However, we have only included the results of the first episode for each child in the analyses. Lock treatment: each port was alternately locked for three days with 2.3 ml of a 74% ethanol solution for 20 - 24 hours. The solution was then flushed through to prevent clotting inside the catheter. Systemic antibiotics were started concomitantly (initially empiric, and specific after antibiogram).
Outcomes	(1) Number of children cured of their CVC-related infection. (2) Number of children experiencing a recurrence of their CVC-related infection. (3) Premature removal of the CVC (defined as catheter removal because of infection).
Notes	The ethanol lock group contained more children (n = 8) with haematologic malignancies than the systemic antibiotics alone group (n = 4). Follow-up period consisted of "the subsequent leukopenic periods or within 4 weeks of finishing treatment".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	CCT, so no randomisation was performed. Quote: "Until the second half of the year 2000, all children who had a documented positive blood culture received systemic antibiotic therapy alone, whereas the ethanol-lock technique became standard procedure in our management plan during 2001." Comment: In the second half of 2000 participants were allocated to both the experimental and the control arm. The procedure for this selection was not specified. Also three children were treated in a different arm when presenting with a recurrence of the infection.
Allocation concealment (selection bias)	High risk	CCT, so no randomisation was performed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete reporting for all outcomes investigated.

Dannenberg 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	Complete reporting for all outcome measures investigated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors (for any outcome investigated).

La Quaglia 1994

Methods	RCT conducted in a single centre in the USA.
Participants	41 children undergoing chemotherapy with tunnelled external CVCs and CVC-related sepsis (for the exact definition of CVC-related infections in this study see Table 1). The presence of a thrombus in the CVC was not assessed for all participants; the presence of a thrombus was not an exclusion criterion. Types of CVCs: all Hickman catheters. Underlying diseases: 6 neuroblastoma (4 intervention, 2 control), 16 ALL/AML/monosomy 7/aplastic anaemia (9 intervention, 7 control), 8 osteosarcoma/chondrosarcoma/Ewing's sarcoma (4 in each treatment group), 3 rhabdomyosarcoma (1 intervention, 2 control), 4 hepatoblastoma/Wilms' tumour/germ cell tumour (2 in each treatment group), 4 non-Hodgkin's lymphoma/brain tumour (3 intervention, 1 control).
Interventions	Urokinase locks and systemic antibiotics (n = 23, intervention group) versus systemic antibiotics alone (n = 18, control group). All participants were started with broad-spectrum antibiotics at diagnosis (usually ticarcillin/clavulanate (300 mg/kg/d) and gentamicin (2 mg/kg loading and 5 mg/kg/d every 6 to 8 hours thereafter)). When the diagnosis of CVC-related sepsis was established, participants were randomised to receive urokinase (25,000 U/cm^3/catheter lumen) or a similar volume of placebo every 12 hours for a total of four doses. The study drug was instilled by a slow push from a syringe, then aspirated after 1 hour.
Outcomes	(1) Number of children cured of their CVC-related infection. (2) Number of children experiencing a recurrence of their CVC-related infection. (3) Number of days until first negative blood culture. (4) Premature removal of CVC (defined as removed during study because of infection). (5) ICU admission. (6) Sepsis.
Notes	A maximum of 16 children with non-malignant disease could have been included in this study (i.e. monosomy 7 and aplastic anaemia), but all participants included in this study received chemotherapy. It was unclear if the number of haematological malignancies was comparable between the treatment groups. Trial prematurely stopped because of results futility analysis and haemodynamic instability after flushing of catheters in both study groups. Follow-up duration not specified.

La Quaglia 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was conducted by the central pharmacy". Comment: the method of randomisation was not described and it is therefore unclear if sequence generation was random.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was conducted by the central pharmacy" Comment: the method of randomisation was not described and it is therefore unclear if allocation was concealed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome assessment in all included patients for all outcomes investigated.
Selective reporting (reporting bias)	Low risk	Reporting on all findings for all outcome measures investigated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the pharmacy dispensed the study drug in numbered vials, the contents of which were unknown to the medical staff". Comment: Although it is not mentioned if participants were blinded, it is very unlikely the participants were aware of the group they were allocated to, since the study was double-blind and the drug was dispensed in numbered vials. We have assumed they were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded (for all outcomes evaluated). Quote: "the pharmacy dispensed the study drug in numbered vials, the contents of which were unknown to the medical staff".

RCT: randomised controlled trial; USA: United States of America; CVC: central venous catheter; ALL: acute lymphoblastic leukaemia; ANLL: acute non-lymphocytic leukaemia; IL: Illinois; ICU: intensive care unit; IU: international unit; CCT: controlled clinical trial.

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

Study	Reason for exclusion
Abdelkefi 2007	(1) Study group consisted mainly of adults. (2) Investigates prevention of CVC-related infections. (3) Coated CVCs.
Abdelkefi 2008	(1) Study group consisted mainly of adults. (2) Investigates prevention of CVC-related infections. (3) Coated CVCs.
Akyüz 2010	Investigates prevention of CVC-related infections, with taurolidine locks.
Al-Hathal 1989	Observational study of CVC-related complications; lock treatments not evaluated.
Albanese 1993	Review of CVCs in children with cancer.

Study	Reason for exclusion
Anoop 2009	Review of the role of ALT in the treatment of CVC-related infections.
Aquino 2002	Investigates prevention of CVC-related infections.
Arora 2010	(1) Investigates prevention of CVC-related infections. (2) Systematic review.
Ascher 1993	(1) Case report. (2) Urokinase flushes with systemic antibiotics.
Ashkenazi 1992	Observational study of risk factors for mortality due to bacteraemia and fungaemia in childhood.
Atay 2004	Systemic antibiotic treatment of CVC-related infection; lock treatments not evaluated.
Attal 1991	(1) Adult study population. (2) Investigates prevention of Gram-positive infections. (3) Systemic antibiotic treatment; lock treatments not evaluated.
Averbuch 2008	(1) Systemic antibiotic treatment; lock treatments not evaluated. (2) Retrospective study.
Backeljauw 1991	(1) Case report. (2) Treatment of CVC-related thrombus.
Bagnall-Reeb 1990	Observational study of CVC-related complications; lock treatments not evaluated.
Ball 1993	Systemic antibiotic treatment; lock treatments not evaluated.
Barriga 1997	Prevention of CVC-related infections.
Berger 2004	Systemic antibiotic treatment; lock treatments not evaluated.
Beutel 2005	Review of diagnosis and treatment of CVC-related infections.
Boughton 1989	(1) Systemic antibiotic treatment; lock treatments not evaluated. (2) Febrile neutropenic participants.
Butt 2004	(1) Adult study population. (2) Observational study of CVC-related infections; lock treatments not evaluated.
Castagnola 2001	(1) Case report. (2) Observational study of bacillus sphaericus bacteraemia.
Castagnola 2010	Investigates diagnosis of CVC-related infections.
Cesaro 2009	Investigates prevention of CVC-related complications.
Chamberlain 2005	(1) Systemic antibiotic treatment; lock treatments not evaluated.

Study	Reason for exclusion
	(2) Audit investigating treatment of febrile neutropenia.
Chatzinikolaou 2003	Investigates prevention of CVC-related infections.
Chen 2009	(1) Diagnosis of CVC-related infections. (2) Study group consisted mainly of adults.
Chen 2011	(1) Adult study population. (2) Observational study of CVC-related infections; lock treatments not evaluated.
Cherif 2004	(1) Systemic antibiotic treatment; lock treatments not evaluated. (2) Adult study population. (3) Febrile neutropenic patients.
Cherrick 1995	(1) Case report. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Chiu 1998	Observational study of bacteraemia in children with neutropenic fever.
Daghistani 1996	Investigates prevention of CVC-related infections.
Dias 2008	(1) Investigates an outbreak of *Pseudomonas putida* and *Stenotrophomonas maltophilia* infections associated with contaminated heparin catheter-lock solution. (2) Heterogeneous treatments; 27 different treatment regimens.
Dillon 2004	Investigates prevention of CVC-related complications.
Doganis 2007	Observational study of CVC-related infections; lock treatments not evaluated.
Douard 1991	(1) Investigates diagnosis of CVC-related infections. (2) Heterogeneous group, including selected cases treated with ALT and systemic antibiotics (n = 2) or ALT alone (n = 3).
Dunn 2008	Children with malignancies were not included in this study.
Elting 1990	Observational study of *Xanthomonas* and non-aeruginosa *Pseudomonas* species.
Giacchino 2007	Systemic antibiotic treatment; lock treatments not evaluated.
Haffar 1984	Children with malignancies were not included in this study.
Haimi-Cohen 2001	Pharmacokinetics study.
Handrup 2010	Observational study of CVC-related infections; lock treatments not evaluated.
Henrickson 2000	Investigates prevention of CVC-related infections and thrombotic events.
Jones 2001	Investigates prevention of CVC-related infections and thrombotic events.
Kalmanti 2002	Investigates prevention of CVC-related complications.

Study	Reason for exclusion
Kaplan 2003	Systemic antibiotic treatment; lock treatments not evaluated.
Kefeli 2009	Investigates prevention of CVC-related complications.
Kethireddy 2008	(1) Investigates prevention of CVC-related complications. (2) Meta-analysis.
Ketley 1995	(1) Study group consisted mainly of adults. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Kinsey 1998	Systemic antibiotic treatment; lock treatments not evaluated.
Lee 2005	Systematic review.
Ley 1996	(1) Adult study population. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Menichetti 1990	(1) Adult study population. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Norville 2006	Observational study of hub colonisation; lock treatments not evaluated.
O'Brien 1988	(1) Study group consisted mainly of adults. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Paulus 2005	Systemic antibiotic treatment; lock treatments not evaluated.
Raad 1997	(1) Adult study population. (2) Investigates prevention of CVC-related infections. (3) Coated CVCs.
Raad 2003	(1) Study group consisted mainly of adults. (2) Systemic antibiotic treatment; lock treatments not evaluated.
Reilly 2004	Observational study of atypical mycobacterial infections in children.
Riikonen 1993	Observational study in children with CVCs and febrile neutropenia.
Rubin 1999	Observational study of treatment of CVC-related infections; lock treatments not evaluated.
Russell 1990	Observational study of CVC-related complications; lock treatments not evaluated.
Ruud 2006	Investigates prevention of CVC-related thrombosis.
Safdar 2007	(1) Adult study population. (2) Observational study of polymicrobial bloodstream infections.
Safdar 2006	(1) Adult study population

Study	Reason for exclusion
	(2) Investigates prevention of CVC related infections, with vancomycin lock or flush solutions
Sanchez-Munoz 2005	Adult study population.
Scheinemann 2010	Diagnosis of CVC-related infections.
Schierholz 2010	(1) Adult study population. (2) Investigates prevention of CVC-related infections. (3) Coated CVCs.
Schmid 1991	(1) Mainly adult study population. (2) Observational study of CVC-related complications; lock treatments not evaluated.
Schwartz 1990	Investigates prevention of CVC-related infections.
Shivnan 1991	Investigates prevention of CVC-related infections.
Simon 1994	(1) Mainly adult study population. (2) Observational study of treatment of CVC-related infections; lock treatments not evaluated.
Simon 2006	Review.
Simon 2008a	Investigates prevention of CVC-related infections with taurolidine-citrate lock solution.
Simon 2008b	(1) Review. (2) Investigates prevention of CVC-related complications.
Smith 1989	Systemic antibiotic treatment; lock treatments not evaluated.
Snaterse 2010	(1) Investigates prevention of CVC-related infections. (2) Review.
Souza Dias 2008	Treatment of colonised CVCs; lock treatments not evaluated.
Stoneham 2007	Diagnosis of CVC-related infections.
Tobiansky 1997	Observational study of CVC-related complications in children with and without cancer; lock treatments not evaluated.
Viscoli 1988	Review.
Wiener 1992	Observational study of CVC-related complications; lock treatments not evaluated.
Wiernikowski 1991	Investigates prevention of CVC colonisation.

ALT: antibiotic lock treatment; CVC: central venous catheter

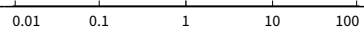
DATA AND ANALYSES

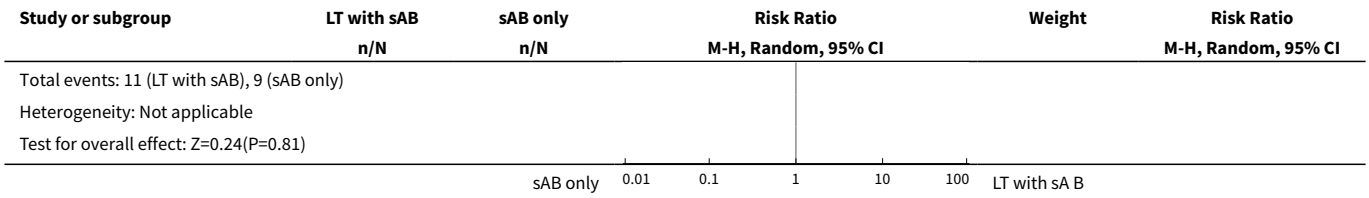
Comparison 1. Lock treatment with systemic antibiotics versus systemic antibiotics alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants cured from CVC-related infection	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Data extracted from RCTs (urokinase lock)	2	104	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.79, 1.32]
1.2 Data extracted from CCT (ethanol lock)	1	28	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.66, 1.70]
2 Number of participants with a recurrence of the CVC-related infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Data extracted from RCT (urokinase lock)	1	41	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.44, 2.47]
2.2 Data extracted from CCT (ethanol lock)	1	28	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.27, 2.79]
3 Premature CVC removal	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Data extracted from RCTs (urokinase lock)	2	104	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.54, 1.72]
3.2 Data extracted from CCT (ethanol lock)	1	28	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.06, 12.52]
4 ICU admission (urokinase lock)	1	41	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.05, 11.67]
5 Sepsis (urokinase lock)	1	41	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.18, 3.43]

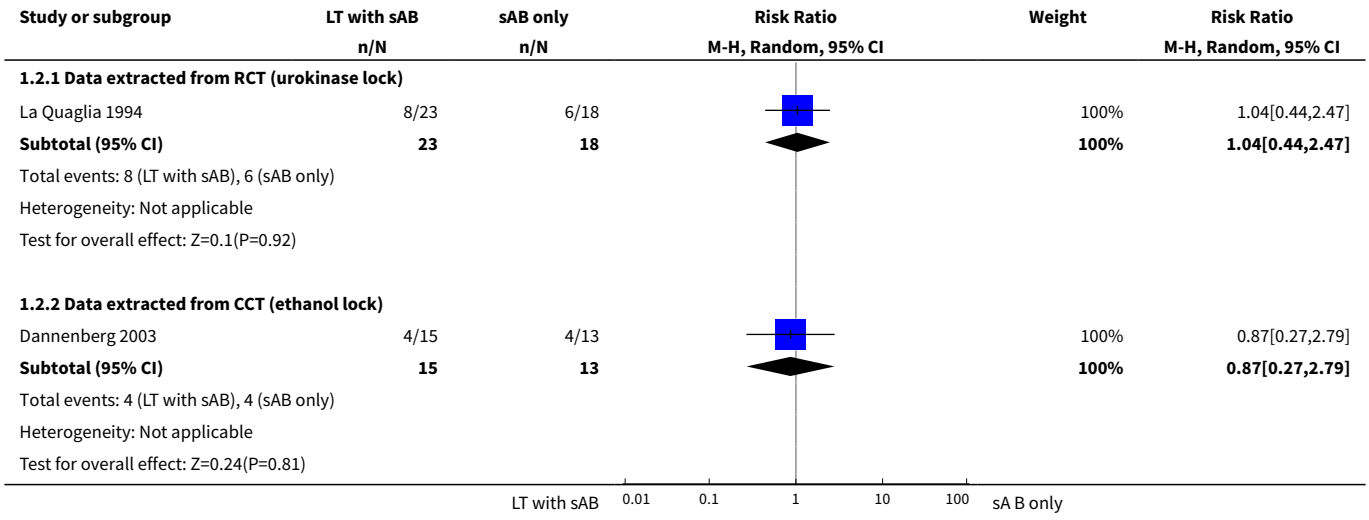
Analysis 1.1. Comparison 1 Lock treatment with systemic antibiotics versus systemic antibiotics alone, Outcome 1 Number of participants cured from CVC-related infection.

Study or subgroup	LT with sAB n/N	sAB only n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Data extracted from RCTs (urokinase lock)					
Atkinson 1998	24/33	21/30		66.52%	1.04[0.76,1.42]
La Quaglia 1994	15/23	12/18		33.48%	0.98[0.63,1.52]
Subtotal (95% CI)	**56**	**48**		**100%**	**1.02[0.79,1.32]**
Total events: 39 (LT with sAB), 33 (sAB only)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					
1.1.2 Data extracted from CCT (ethanol lock)					
Dannenberg 2003	11/15	9/13		100%	1.06[0.66,1.7]
Subtotal (95% CI)	**15**	**13**		**100%**	**1.06[0.66,1.7]**

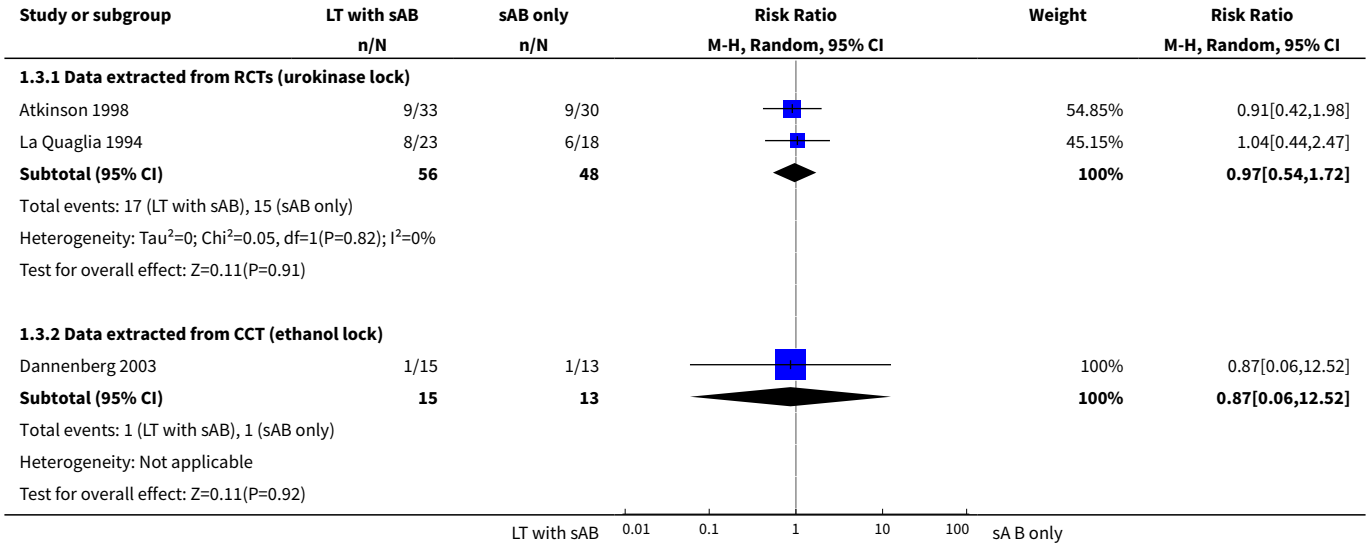




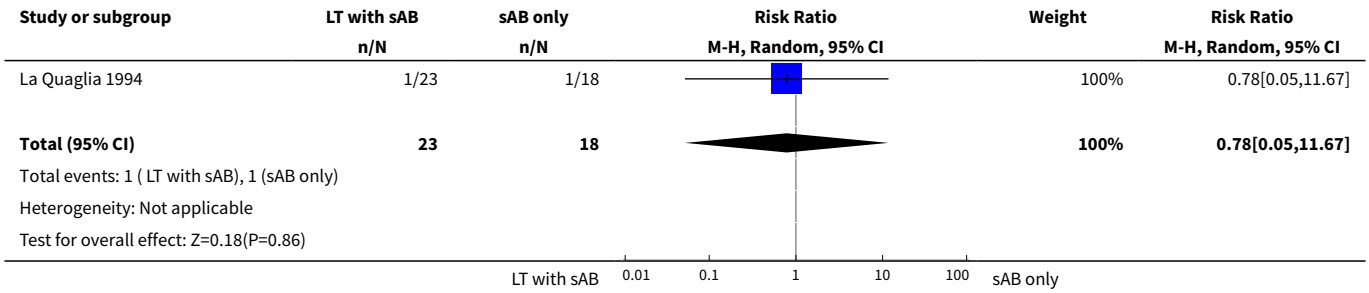
Analysis 1.2. Comparison 1 Lock treatment with systemic antibiotics versus systemic antibiotics alone, Outcome 2 Number of participants with a recurrence of the CVC-related infection.



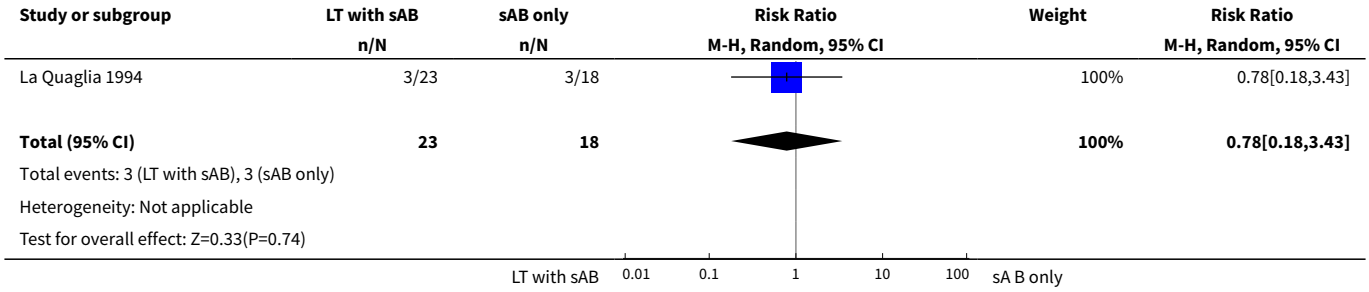
Analysis 1.3. Comparison 1 Lock treatment with systemic antibiotics versus systemic antibiotics alone, Outcome 3 Premature CVC removal.



Analysis 1.4. Comparison 1 Lock treatment with systemic antibiotics versus systemic antibiotics alone, Outcome 4 ICU admission (urokinase lock).



Analysis 1.5. Comparison 1 Lock treatment with systemic antibiotics versus systemic antibiotics alone, Outcome 5 Sepsis (urokinase lock).



ADDITIONAL TABLES

Table 1. Definitions of CVC-related infections

Study	Definitions of CVC related infections
Atkinson 1998	Blood cultures drawn from the line positive for infection in the absence of any other source of infection including tunnel infections.
Dannenberg 2003	1) Bacteraemia: positive blood culture from the catheter and fever or a rise of infectious laboratory findings. 2) Sepsis: positive blood culture from the catheter and a least five of the following eight symptoms; fever/hypothermia, chills, tachycardia/bradycardia, tachypnoea, hypotonia, prolonged capillary refill time, oliguria, or altered mental status.
La Quaglia 1994	CVC-related sepsis was defined by quantitative cultures, i.e. 1) negative peripheral blood cultures, with simultaneous 1000 or more CFUs cultured from the CVC; or 2) CFUs from the catheter exceeded those from the peripheral blood by a factor of 10 or more.

CVC: central venous catheter; CFU: colony-forming units

Table 2. Cohort studies to identify adverse events (no control group present)

Study	Patients	Interventions	Outcomes
Barbaric 2004	42 children with cancer (including one with thalassaemia) with tunnelled CVC-related infections	Other lock treatment and systemic antibiotics: After 48 hours of systemic antibiotics, if positive blood cultures persisted; 2M HCL locks were administered, three times for ten minutes. No information was provided on type of antibiotic agents and dosage. We assume they all received systemic antibiotic treatment.	28/42 children cured, 14/42 CVCs removed. Quote: "The most common reason for removal was the recurrence of positive blood cultures involving at least one of the initially cultured organisms". Two CVCs were removed because of mechanical complications (one CVC rupture and one extravasation of infusing fluids). Quote: "Because CVC removal occurred for reasons unrelated to sepsis, those two episodes were considered not evaluable and were excluded from subsequent analyses". Comment: it is unclear if these CVC complications occurred during or after HCl administration. No adverse events occurred.
Bernardi 2005	11 children with cancer with a (tunnelled) CVC-related infection.	Antibiotic lock treatment: ALT with vancomycin, vancomycin + amikacin, amphotericin B (2.5 mg/ml), teicoplanin (10 - 40 mg/ml) or ciprofloxacin, for at least 12 - 24 hours, 5 - 10 days. In 9 of 11 children the CLC 2000 connector was used, and the other two received ALT with heparin. No information was provided on dosage other than what we report here.	10 of 11 infectious episodes were cured. In one child the CVC was removed because fever persisted and another blood culture became positive. Adverse events were not reported. CVC malfunction: in one child (without a CLC 2000 connector, treated with teicoplanin and heparin) the ALT solution precipitated, which was solved with urokinase flushes.
Cesaro 2007	Nine children with cancer with Broviac-Hickman CVCs using a CLC 2000 connector device, treated for recurrent bloodstream infections (n = 4) or CVC colonisation (n = 5).	Antibiotic lock treatment and systemic antibiotics: ALT with concomitant systemic antibiotic treatment. ALT consisted of vancomycin (5 mg/ml), amikacin (5 mg/ml), teicoplanin (10 - 40 mg/ml) or amphotericin B (2.5 mg/ml), dwell period at least 12 - 24 hours, for 5 - 14 days. No information was provided on systemic antibiotic treatment.	All nine infectious episodes were cured initially. Three CVCs were removed; two because of fever of unknown origin (91 and 145 days after ALT) and one because of a sepsis caused by *Trichoderma sp*. 71 days after ALT for a CVC-related infection with a different pathogen (*Staph. epidermidis)*. No adverse events and no CVC malfunctioning occurred.
Jones 1993	59 episodes of blood culture positive sepsis in 45 children with cancer with tunnelled CVCs. Please note that Jones 1996 describes the same study.	Other lock treatment and systemic antibiotics: Systemic antibiotic treatment with concomitant 1 - 2 ml urokinase locks (Abbokinase; Abbott, Chicago), left to dwell for one hour, for 2 days. No information was provided on systemic antibiotic treatment.	All infectious episodes initially responded; three children developed recurrent sepsis and required CVC removal. In total, eight CVCs were removed. Reasons for removal: two exit site infections, three sepsis recurrence, and three other: two elective removals and one because of CVC malfunction (not further specified). No adverse events occurred.

Table 2. Cohort studies to identify adverse events (no control group present) *(Continued)*

Jones 1996	154 episodes of bacteraemia or candidaemia in 97 participants (including 11% with non-malignant haematologic conditions) with 110 tunnelled CVCs. Please note that Jones 1993 describes the same study.	Other lock treatment and systemic antibiotics: Systemic antibiotic treatment with concomitant 1 ml urokinase locks (5000 IU/ml), repeated 12 - 24 hours later. If the blood culture remained positive another course of the urokinase protocol was given. No information was provided on systemic antibiotic treatment and the duration of lock treatment.	In 12 of 154 episodes, blood cultures remained positive: in two children CVCs were removed, ten children were treated with a second course of urokinase and seven became negative in second instance. The remaining three CVCs were removed. Of the 142 episodes in which the bacteraemia was initially cleared (after the first course of urokinase) or in the seven episodes cleared in second instant (after the second course), 24 CVCs were removed for the following reasons: exit site infection (n = 3), child or physicians wish (n = 8), mechanical complications (n = 6), death of the child as a result of progression of malignant disease (n = 6) or end of treatment (n = 1). Mechanical complications were not further specified. 15 of 125 episodes recurred within 5 - 51 days after antibiotic treatment for the original infection was concluded. No adverse events occurred. CVC malfunction occurred in six children.
McCarthy 1995	19 episodes of Gram positive cocci CVC-related infections in 11 children with cancer.	Antibiotic lock treatment alone: 15 episodes in nine children with negative peripheral blood cultures and neutrophil count > 1.5 x 10^9/L were treated with 66 mg or 145 mg (adjusted to catheter size) teicoplanin (Targocid 400 mg/3 ml, Marion Merrell Dow) locks. Locks were replaced every 24 hours, mean treatment duration 6 days (range 4 - 9 days). One CVC-related infection recurred and was treated in lock treatment and systemic antibiotics group. Antibiotic lock treatment and systemic antibiotics: 4 episodes in three children with CVC-related infections and either a positive peripheral blood culture or a neutrophil count less than 1.5 x 10^9/L were treated with teicoplanin locks (as described above) and concomitant systemic antibiotics.No information was provided on systemic antibiotic treatment.	Three of nine children in the antibiotic lock group alone experienced a recurrence of the CVC-related infection and one of two in the antibiotic lock and systemic antibiotics group. None of the CVCs was removed because of infections. No adverse events or CVC malfunction occurred.
Plourde 2011 Preliminary data; abstract only	80 children with cancer with CVC-related infections	Other lock treatment only: Retrospective study, investigating 70% ethanol locks, four hours daily for 1 - 11 days. 39 children received ethanol locks. We assume participants were given concomitant systemic antibiotics. However, this was not specified in the report. Treatment without lock:	36 of 169 infections (21.3%) were described as treatment failures, 6.5% occurred in the other lock treatment group, 14.7% in the treatment without lock group. Number of children with recurrent infections was not specified in the report.

Table 2. Cohort studies to identify adverse events (no control group present) *(Continued)*

		41 children received no ethanol lock treatment. We assume participants were given concomitant systemic antibiotics. However, this was not specified in the report.	Adverse events and CVC malfunction were not reported.
Rao 1992	11 children with cancer with CVC-related infections	Antibiotic lock treatment alone: Eight episodes in six children with negative peripheral blood cultures and neutrophil count > 1.5 x 10^9/L were treated with 40 mg Amikacin locks (amikacin sulphate paediatric injection 100 mg 2 ml^{-1}, Bristol Myers). One episode was a recurrence of an episode treated in the control group. Also, one participant in the intervention group experienced a recurrence and was subsequently treated in the intervention group. Lock duration not specified. Antibiotic lock treatment and systemic antibiotics: Six episodes in five children with CVC-related infections and either a positive peripheral blood culture or a neutrophil count less than 1.5 x 10^9/L were treated with amikacin locks and concomitant systemic antibiotics. No information was provided on type of antibiotic agents used for systemic treatment, dosage and lock duration.	One child out of six in the antibiotic lock alone group experienced a recurrence of the CVC-related infection and one out of five in the lock and systemic antibiotics group. Adverse events and CVC malfunction were not reported.
Yazici 2007 Preliminary data; abstract only	33 episodes of CABSI in 22 children with cancer	Antibiotic lock treatment and systemic antibiotics: Systemic antibiotics with concomitant antibiotic lock treatment, containing vancomycin, teicoplanin, meropenem, teicoplanin with aminoglycoside or amphotericin B. Dose and lock duration not specified.	25 of 33 episodes were cured. Quote: "Device removal and recurrent infections were detected in five patients. Two patients died, with progressive disease and sepsis." Further specification not reported. Adverse events and CVC malfunction were not reported.

CVC: central venous catheter; CABSI: CVC-associated blood stream infection; HCL: hydrochloric acid; ALT: antibiotic lock treatment; IU: international unit

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Antibiotic lock** the following text words were used:

ethanol lock or citrate lock or taurolidine lock or taurolock or urokinase or lock solution or flush solution or flush or flushing or flush* OR antibiotic or antibiotics or antibiotic* OR lock or locks or locking or lock* OR lock therapy or lock treatment or lock regimen or lock technique OR antibiotic lock or antibiotic locks or antibiotic-lock or antibiotic-locks or antibiotic locking or antibiotic-locking OR antibiotic lock treatment OR ALT

2. For **Catheter** the following text words were used:

central venous catheter OR central venous catheters OR central venous catheter* OR CVCs OR catheter-related infections OR catheter related complications OR broviac OR port-a-cath OR port acath OR port a cath OR hickman OR infuse a port OR catheterisation central venous OR tunnelled central venous catheter OR TCVC OR catheterization central venous OR peripherally inserted central catheter OR picc OR central venous line OR central venous device OR central venous access device OR CVAD OR CVC OR Indwelling Catheter OR Indwelling Catheters OR In-Dwelling Catheters OR In Dwelling Catheters OR In-Dwelling Catheter OR Venous Reservoirs OR Venous Reservoir OR Implantable Catheters OR Implantable Catheter OR Vascular Access Ports OR Vascular Access Port OR Intra-Arterial Lines OR Intra Arterial Lines OR Intra-Arterial Line OR Arterial Lines OR Arterial Line OR implantable port OR implantable ports OR implantable catheter OR implantable catheters OR totally implantable access port OR totally implantable access ports OR TIAP OR TIAPs

3. For**Infection** the following text words were used:

sepsis OR bacteremia OR bacteremias OR bacteraemia OR infection OR infections OR line infection OR line infections OR bloodstream infection OR bloodstream infections OR infectious diseases OR Pyemia OR Pyemias OR Pyohemia OR Pyohemias OR Pyaemia OR Pyaemias OR Septicemia OR Septicemias OR Septicaemia OR Septicaemias OR Severe Sepsis OR catheter-related bloodstream infection OR catheter-related bloodstream infections OR CRBSI OR CRBSIs OR catheter-related bacteremia OR catheter-related bacteremias OR catheter-related bacteraemia OR catheter-related bacteraemias OR BSI OR NSIs OR CABSI OR CABSIs OR catheter-associated bloodstream infection OR catheter-associated bloodstream infections OR catheter-related infections OR catheter related complications

4. For**Children** the following text words were used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

5. For **Childhood cancer** the following text words were used:

(leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR cancer or neoplasms or tumor or cancers or neoplasm or tumors)

6. For**Cancer** the following text words were used:

cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

Final search: 1 and 2 and 3 and 4 and (5 or 6)

The search was performed in title, abstract or keywords.

[*=one or more characters]

Appendix 2. Search strategy for PubMed

1. For **Antibiotic lock** the following MeSH headings and text words were used:

ethanol lock or citrate lock or taurolidine lock or taurolock or urokinase or lock solution or flush solution or flush or flushing or flush* OR antibiotic or antibiotics or antibiotic* OR lock or locks or locking or lock* OR lock therapy or lock treatment or lock regimen or lock technique OR antibiotic lock or antibiotic locks or antibiotic-lock or antibiotic-locks or antibiotic locking or antibiotic-locking OR antibiotic lock treatment OR ALT

2. For **Catheter** the following MeSH headings and text words were used:

central venous catheter OR central venous catheters OR central venous catheter* OR CVCs) OR (catheterization, central venous) OR (broviac OR port-a-cath OR port acath OR port a cath OR hickman OR infuse a port) OR (catheterisation central venous OR tunnelled central venous catheter OR TCVC OR catheterization central venous OR peripherally inserted central catheter OR picc OR central venous line OR central venous device) OR (central venous access device OR CVAD OR CVC) OR (catheters, indwelling[mh]) OR (Catheter, Indwelling OR Indwelling Catheter OR Indwelling Catheters OR In-Dwelling Catheters OR Catheter, In-Dwelling OR Catheters, In-Dwelling OR In Dwelling Catheters OR In-Dwelling Catheter OR Venous Reservoirs OR Reservoir, Venous OR Reservoirs, Venous OR Venous Reservoir OR Implantable Catheters OR Catheter, Implantable OR Catheters, Implantable OR Implantable Catheter OR Vascular Access Ports OR Access Port, Vascular OR Access Ports, Vascular OR Port, Vascular Access OR Ports, Vascular Access OR Vascular Access Port OR Intra-Arterial Lines OR Intra Arterial Lines OR Intra-Arterial Line OR Line, Intra-Arterial OR Lines, Intra-Arterial OR Arterial Lines OR Arterial Line OR Line, Arterial OR Lines, Arterial) OR implantable port OR implantable ports OR implantable catheter OR implantable catheters OR totally implantable access port OR totally implantable access ports OR TIAP OR TIAPs

3. For**Infection** the following MeSH headings and text words were used:

sepsis OR bacteremia OR bacteremias OR bacteraemia OR infection OR infections OR line infection OR line infections OR bloodstream infection OR bloodstream infections OR infectious diseases OR Pyemia OR Pyemias OR Pyohemia OR Pyohemias OR Pyaemia OR Pyaemias OR Septicemia OR Septicemias OR Septicaemia OR Septicaemias OR Severe Sepsis OR Sepsis, Severe OR catheter-related bloodstream infection OR catheter-related bloodstream infections OR CRBSI OR CRBSIs OR catheter-related bacteremia OR catheter-related bacteremias OR catheter-related bacteraemia OR catheter-related bacteraemias OR BSI OR NSIs OR CABSI OR CABSIs OR catheter-associated bloodstream infection OR catheter-associated bloodstream infections OR catheter-related infections OR catheter related complications

4. For**Children** the following MeSH headings and text words were used:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

5. For**Childhood cancer** the following MeSH headings and text words were used:

(((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

6. For **Cancer** the following MeSH headings and text words were used:

cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

Final search: 1 and 2 and 3 and 4 and (5 or 6)

[mh = MeSH term; *=one or more characters;RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for Embase/Ovid

1. For**Antibiotic lock** the following Emtree terms and text words were used:

1. (ethanol lock or citrate lock or taurolidine lock or taurolock).mp.
2. exp UROKINASE/ or urokinase.mp.
3. (lock solution or flush solution).mp.
4. exp flushing/
5. (flush or flushing or flush$).mp.
6. exp antibiotic agent/

7. (antibiotic or antibiotics or antibiotic$).mp.
8. (lock or locks or locking or lock$).mp.
9. (lock therapy or lock treatment or lock regimen or lock technique).mp.
10. (antibiotic-lock or antibiotic-locks or antibiotic locking or antibiotic-locking).mp.
11. (antibiotic lock or antibiotic locks).mp.
12. (antibiotic lock treatment or ALT).mp.
13. or/1-12

2. For **Catheter** the following Emtree terms and text words were used:

1. (broviac or port-a-catch or port acatch or port a catch or portacatch or port or port-a-cat or portacat or hickman or infuse a port).mp.
2. exp central venous catheter/
3. (central venous catheter or central venous catheters or central venous catheter$).mp.
4. CVCs.mp.
5. exp central venous catheterization/
6. (central venous catheterization or central venous catheterisation).mp.
7. (tunnelled central venous catheter or TCVC).mp.
8. (peripherally inserted central catheter or PICC).mp.
9. (central venous line or central venous device).mp.
10. (central venous access device or CVAD or CVC).mp.
11. exp indwelling catheter/
12. (indwelling catheter or indwelling catheters or in-dwelling catheter or in-dwelling catheters).mp.
13. (venous reservoir or venous reservoirs).mp.
14. (implantable catheter or implantable catheters).mp.
15. (vascular access port or vascular access ports).mp.
16. (intra-arterial line or intra-arterial lines or intra arterial line or intra arterial lines).mp.
17. (arterial line or arterial lines).mp.
18. (implantable port or implantable ports).mp.
19. (implantable catheter or implantable catheters).mp.
20. (totally implantable access port or totally implantable access ports or TIAP or TIAPs).mp.
21. or/1-20

3. For **Infection** the following Emtree terms and text words were used:

1. sepsis.mp. or exp SEPSIS/
2. exp BACTEREMIA/ or bacteremia.mp.
3. (bacteremias or bacteraemia).mp.
4. exp INFECTION/ or exp BLOODSTREAM INFECTION/
5. (infection or infections or line infection or line infections or bloodstream infection or bloodstream infections).mp.
6. infectious diseases.mp.
7. (Pyemia or Pyemias or Pyohemia or Pyohemias or Pyaemia or Pyaemias or Septicemia or Septicemias or Septicaemia or Septicaemias or Severe Sepsis).mp.
8. (catheter-related infections or catheter related complications).mp.
9. catheter-related bloodstream infection.mp. or exp catheter infection/
10. (catheter-related bloodstream infections or CRBSI or CRBSIs).mp.
11. (catheter-related bacteremia or catheter-related bacteremias or catheter-related bacteraemia or catheter-related bacteraemias or BSI or NSIs).mp.
12. (catheter-associated bloodstream infection or catheter-associated bloodstream infections or CABSI or CABSIs).mp.
13. or/1-12

4. For **Children** the following Emtree terms and text words were used:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant$ or newborn$ or (new adj born$) or baby or baby$ or babies or neonate$ or perinat$ or postnat$).mp.
6. (child$ or (school adj child$) or schoolchild$ or (school adj age$) or schoolage$ or (pre adj school$) or preschool$).mp.
7. (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp.
8. (minors$ or (under adj ag$) or underage$ or juvenil$ or youth$).mp.
9. (puber$ or pubescen$ or prepubescen$ or prepubert$).mp.
10. (pediatric$ or paediatric$ or peadiatric$).mp.

11. (school or schools or (high adj school$) or highschool$ or (primary adj school$) or (nursery adj school$) or (elementary adj school) or (secondary adj school$) or kindergar$).mp.
12. or/5-11
13. 4 or 12

5. For **Childhood cancer** the following Emtree terms and text words were used:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

6. For **Cancer** the following Emtree terms and text words were used:

1. (cancer or cancers or cancer$).mp.
2. (oncology or oncolog$).mp. or exp oncology/
3. (neoplasm or neoplasms or neoplasm$).mp. or exp neoplasm/
4. (carcinoma or carcinom$).mp. or exp carcinoma/
5. (tumor or tumour or tumor$ or tumour$ or tumors or tumours).mp. or exp tumor/
6. (malignan$ or malignant).mp.
7. (hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo$).mp. or exp hematologic malignancy/
8. or/1-7

Final search: 1 and 2 and 3 and 4 and (5 or 6)

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; / = Emtree term; $=one or more characters ; RCT = randomized controlled trial; CCT = controlled clinical trial;]

CONTRIBUTIONS OF AUTHORS

Reineke Schoot and Marianne van de Wetering designed the study and wrote the protocol. They developed the search strategy (together with the Trials Search Coordinator of the Cochrane Childhood Cancer Group) and they identified the studies meeting the inclusion criteria (both by initial screening and thereafter). Reineke Schoot searched for unpublished and ongoing studies. Reineke Schoot and Marianne van de Wetering performed the data extraction and 'Risk of bias' assessment of the included studies. They analysed the data and interpreted the results. They wrote and revised the review.

Elvira van Dalen and Heleen van Ommen critically reviewed the protocol. Elvira van Dalen acted as third party arbitrator and performed the sensitivity analyses. Elvira van Dalen and Heleen van Ommen contributed to the interpretation of the results. They critically reviewed the review.

All authors approved the final version of the manuscript.

DECLARATIONS OF INTEREST

None known

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Internal sources

- Dutch Cochrane Centre, Netherlands.

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We extended our search, to include the conference proceedings of the American Society of Clinical Oncology, the Multinational Association of Supportive Care in Cancer, the American Society of Hematology and the International Society of Thrombosis and Haematology.

As well as RCTs and CCTs, we considered cohort studies for the assessment of adverse events. We modified our search strategy accordingly for PubMed and EMBASE, by removing the search terms for RCTs and CCTs.

Although heterogeneity was absent from all analyses we decided to use the random-effects model instead of the fixed-effect model for the estimation of treatment effects.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Anti-Infective Agents, Local [therapeutic use]; Catheter-Related Infections [*drug therapy]; Catheters, Indwelling [adverse effects]; Central Venous Catheters [*adverse effects]; Drug Therapy, Combination [methods]; Ethanol [therapeutic use]; Fibrinolytic Agents [therapeutic use]; Neoplasms [*therapy]; Randomized Controlled Trials as Topic; Urokinase-Type Plasminogen Activator [therapeutic use]

MeSH check words

Child; Humans