

Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients (Review)

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ABSTRACT

Background

Long-term tunnelled central venous catheters (TCVCs) are increasingly used when treating oncology patients. Despite international guidelines on sterile insertion, appropriate catheter maintenance and use, infections still a complication of TCVC. These infections are mainly caused by Gram-positive bacteria. Antimicrobial prevention strategies aimed at these micro-organisms could potentially decrease the majority of TCVC infections. The aim of this review was to evaluate the efficacy of antibiotics in the prevention of early TCVC infections.

Objectives

To determine the efficacy of administering antibiotics prior to insertion of a TCVC with or without vancomycin/heparin flush technique in the first 45 days after insertion of the catheter to prevent Gram-positive catheter-related infections in oncology patients.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) to July 2006. MEDLINE (1966 to 2006) and EMBASE (1966 to 2006). Reference lists from relevant articles were scanned and conference proceedings were hand searched. The authors of eligible studies were contacted to obtain additional information.

Selection criteria

We selected RCTs which administered prophylactic antibiotics prior to insertion of the TCVC, and RCTs using the combination of an antibiotic and heparin to flush the CVC in oncology patients (both adults and children).

Data collection and analysis

The studies identified were assessed and the data extracted independently by the two authors. Authors were contacted for details of randomization, and a quality assessment was carried out. The analysis was carried out using the standard Cochrane software package, RevMan 4.2.

Main results

We included nine trials with a total of 588 patients. Four reported on vancomycin/teicoplanin prior to insertion of the TCVC compared to placebo, and five trials reported on antibiotic flushing combined with heparin, compared to heparin flushing only. The overall effect of administering an antibiotic prior to insertion of the catheter decreases the number of Gram positive TCVC infections (odds ratio [OR] = 0.42, 95% confidence interval (CI) 0.13 to 1.31), this effect is not significant.

Flushing the TCVC with antibiotics and heparin proved to be beneficial (OR = 0.43, 95% CI 0.21 to 0.87). For intraluminal colonization the baseline infection rate is 15% which leads to a number needed to treat (NNT) of 13 (95% CI 5 to 23).

Authors' conclusions

Flushing of the catheter with a vanco/heparin lock solution leads to a positive overall effect. Depending on the baseline TCVC infection rate it is justified to flush the catheter with a combination of an antibiotic and heparin, if the catheter related infection-rate is high.

PLAIN LANGUAGE SUMMARY

Oncology patients require venous access during chemotherapy, therefore central venous catheters (CVCs) are frequently inserted. Chemotherapy duration will often last from six months to two years so a long-term tunnelled central venous catheter (TCVC) is used. Despite standard protocols for insertion and maintenance of these catheters infections do occur. It is therefore necessary to find alternative ways to prevent such infections.

This review first focussed on randomized controlled trials (RCTs) on administering antibiotics prior to insertion of the catheter. The results show that it is not beneficial to give an antibiotic prior to insertion of the catheter. The second focus of the review was RCTs flushing the newly inserted catheter with a combination of a low dose vancomycin and heparin. The results show that it is beneficial to flush the catheter with the combination of vancomycin and heparin, but only for high-risk patients where this intervention minimizes the risk of introducing microbial resistance.

BACKGROUND

Patients treated for cancer need adequate venous access because of the frequent administration of chemotherapy, requirements of intravenous fluids, blood products etc. To limit discomfort of short-term venous access long-term tunnelled catheters are used in more than two thirds of pediatric and adult cancer patients (Groeger 1993; Ingram 1991; Simon 2006). However, the use of long-term tunnelled catheters is limited by the risk of blood clot formation as well as infection. This risk ranges from 1.4 (Bagnall-Reeb 2004; Press 1984; Schinabeck 2003) to 2.2 (Groeger 1993; Sarper 2006) infections per 1000 catheter days. The duration of antimicrobial therapy for the treatment of these infections ranges from 7 to 21 days. Success rates of 60% to 91% have been reported, although often the device has to be removed (Bagnall-Reeb 2004). About one third of patients experience an episode of infection while having the TCVC in place. The organisms cultured are Gram-positive organisms (70%) mainly coagulase negative staphylococci, *Staphylococcus aureus* and *enterococci*, Gram-negative organisms (15%) mainly *E coli* and fungal organisms (8%) mainly *Candida* species, and anaerobic organisms (7%) (O'Grady 2002).

The adherence to and colonization of TCVC with micro-organisms is facilitated by the formation of a very thin biofilm inside the catheter lumen. This process is influenced by several factors such as the production of fibroglycocalyx (extracellular slime) by coagulase negative staphylococci. In addition, the host reaction to the TCVC results in the formation of a thrombin sleeve rich in clotting factors such as fibronectin, fibrinogen, and fibrin which contributes to the formation of the biofilm (Bagnall-Reeb 2004; Darouiche 1999). This means that adequate antibiotic treatment may lead to resolution of the TCVC infection only in certain cases (i.e. when caused by coagulase negative staphylococci) whereas in

other cases (i.e. when caused by *Pseudomonas*, *Staphylococcus aureus*, or fungi) this will be much more difficult to clear and therefore removal of the catheter is necessary (Simon 2006).

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

Early catheter infections (infections that develop within 45 days after placement of the catheter) are mostly due to organisms from the skin insertion site. After 45 days the catheter hub becomes a far more important source of infection (Abbas 2004; Shaul 1998). Because of the increased chance of early catheter infections within days of placement, internal guidelines were developed to prevent these infections, such as:

- a) aseptic technique of insertion of the catheter
- b) protocols for care and handling of the catheter
- c) adequate information to all who handle the catheter
- d) restriction on the number of interruptions of the catheter (the number of times per day one is allowed to open the catheter, to give medication or to draw blood)

Despite international guidelines that have been developed by Hospital Infection Control Practices Advisory committee (CPAC 1990; O'Grady 2002) about 15 to 20% early TCVC infections are still seen. It has been shown (Donowitz 2001; Lim 1993) that the incidence of Gram-positive infections is increasing. The increase is probably due to two factors:

- 1) an increase in the use of CVCs (mainly Hickman/Broviac catheters).

2) the use of high-dose chemotherapy, which destroys the normal mucosal protective barriers of the upper respiratory tract and the gastrointestinal tract.

Reduction of Gram-positive infections by introducing antibiotics at an early stage may be effective to decrease specific catheter-related bloodstream infections. Antibiotics can be introduced in two ways, either prior to the insertion of the catheter, or by flushing the catheter with a combination of an antibiotic and heparin during the life-span of the catheter.

The risk of infections is lower in internal CVCs (ports) than in external devices (Broviac or Hickman). However, it has been shown that this difference only becomes significant after more than one year of catheter use and therefore data on different tunnelled CVC types were pooled in this analysis. The risk of infection is greatest during the first 100 days after placement (Abbas 2004; Salzman 1995).

This review assesses the effectiveness of prophylactic antibiotics in the prevention of early Gram-positive catheter related infections, when the risk of infections is highest. The importance of the first 45 days allows the authors to cover the induction period of chemotherapy. This is the time-period that many manipulations of the TCVC are necessary because of the intensity of chemotherapy, for this reason both internal and external TCVCs are included in the review.

In reviewing the papers both adults and children were included, as the adult patient is comparable to the paediatric patient as far as interpreting infections in central venous catheters.

OBJECTIVES

To determine the efficacy of administering antibiotics prior to insertion of a TCVC with or without vancomycin/heparin flush technique in the first 45 days after insertion of the catheter to prevent Gram-positive catheter-related infections in cancer patients.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

- RCTs comparing placebo versus antibiotics prior to insertion of the TCVC to reduce Gram-positive infections related to the TCVC.
- RCTs comparing the heparin flush technique versus the antibiotic/heparin flush technique to reduce Gram-positive infections due to TCVC related infections
- RCTs combining the two interventions

Types of participants

Patients with cancer (both adults and children) who had a TCVC inserted and were likely to receive chemotherapy causing episodes of neutropenia, with an increased risk of infection.

Types of intervention

- Drug interventions
- Administering antibiotics prior to TCVC insertion
- Adding an antibiotic to the normal heparin flush technique

Types of outcome measures

The major outcome indicator is bacteraemia due to TCVC infections.

Proxy measures will be the frequency of exit-site infections and tunnel-infections.

The time frame for assessment of outcomes within a study should have been stated (establishing when the catheter related infection occurred from the time of insertion).

Definitions (Mermel 2001; O'Grady 2002):

Infections related to the catheter should be defined as follows:

*exit-site infections: Evidence of cellulitis around the exit site, diagnosis can be made by inspection. If quantitative culturing in the laboratory is present then quantitative culturing of the skin or of the subcutaneous catheter segment may be helpful. An exit site infection may occur with or without a bloodstream infection.

*tunnel infection: This involves spreading cellulitis overlying the tunnel tract of subcutaneously tunneled catheters. There are signs of inflammation along the tunnel tract and there is tenderness to palpation over the tunnel tract

Definite catheter infection:

* Isolation of the same organism from percutaneous blood culture and from one of the following:

- a) exudate at the catheter exit site
- b) a semiquantitative catheter segment culture (but this requires catheter removal)
- c) quantitative blood culture with recovery of at least five fold higher colony count from blood obtained through the catheter than from a percutaneous blood culture.

* Catheter-related infection can also be defined when there is a temporal succession of catheter flushing, onset of chills and fever and a positive blood culture, then this is highly suggestive of a catheter related infection

In addition, a short time to positivity of the blood culture is suggestive of a catheter related infection, this method makes use of continuous blood-culture monitoring and compares the differential time to positivity for qualitative cultures of blood samples drawn from the catheter and a peripheral vein.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Gynaecological Cancer Group methods used in reviews.

The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library to July 2006. MEDLINE and EMBASE search was done for the years 1966 to 2006.

Search terms: 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 (catheterisation central venous) OR (tunnelled central venous catheter) OR TCVC OR (catheterization central venous) OR (catheterization, central venous) OR catheter OR catheter*

AND ((antibiotics) OR (antibiotic*) OR (prophylactic antibiotics) OR (prophylactic antibiotic*) OR (vancomycin OR teicoplanin))

AND (cancer OR cancer* OR oncolog* OR oncology OR oncolo* OR neoplasm OR neoplasms OR neoplas* OR carcinoma OR carcinomas OR carcinom* OR tumour OR tumours OR tumor OR tumors OR tumor* OR tumour* OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo* OR hematologic neoplasms OR hematologic malignancy OR hematolog* OR hematooncolo* OR hemato oncolo* OR hemato-oncolo* OR bone marrow transplantation OR bone marrow transplant* OR leukemia OR leukaemia OR lymphoma OR malignancy OR malignan* OR metastases OR metastasis OR metastatic OR metasta* OR pediatric oncology OR paediatric oncology)

AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized controlled trials[mh]) OR (random allocation[mh]) OR (double-blind method[mh]) OR (single-blind method[mh]) OR (clinical trial[pt]) OR (clinical trials[mh]) OR (clinical trial[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw]) AND (mask*[tw] OR blind*[tw])))) OR (placebos[mh] OR placebo*[tw]) OR (random*) OR (research design[mh:noexp]) OR (comparative study[mh]) OR (evaluation studies[mh]) OR (follow-up studies[mh]) OR (prospective studies[mh]) OR (control*[tw]) OR (prospectiv*[tw]) OR (volunteer[tw])) NOT (animals[mh] NOT human[mh]))

Information about trials not registered in MEDLINE or the Cochrane Library was located by scanning the reference lists of the found articles.

In addition we handsearched the following conference proceedings: SIOP 1995-2005 (International Society for Paediatric Oncology), MASCC (Multinational Association of Supportive Care in Cancer) 1995-2005, ASCO (American Society of Clinical Oncology) 1995-2005, ICAAC (Interscience Conference of Antimicrobial agents and Chemotherapy) 1995-2005.

METHODS OF THE REVIEW

Identification of studies meeting the eligibility criteria were performed independently by two authors (MvdW,JvW). Decisions on which trials to include was based on the methods section of the trial. Data-extraction included, the patient group involved, the intervention described, the outcome assessed, and the analysis done.

The methodological quality was initially performed using the Jadad criteria. (blinding of randomization, inclusion and exclusion criteria, intervention performed, and outcome looked at), thereafter scored using the van Tulder criteria (van Tulder 1997), including assessment of the quality of randomization, blinding and analysis. Authors were contacted for additional information where necessary. Disagreements were resolved by discussion between the authors.

Allocation concealment was assessed using the scale set out in the Cochrane Collaboration Handbook.

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

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

(C) Inadequate: when alternation, date of birth, case record, day of the week, enrolment order etc were used, or when an open system of random numbers or assignment were used.

The studies were divided into two groups which were analysed separately;

(1) prophylaxis of antibiotics at insertion of the TCVC versus no prophylaxis

(2) vancomycin/heparin flush technique versus only heparin flush technique

Statistics

The outcomes were weighted by inverse variance. Besides the fixed effect model the random effect model was used to calculate the effects because the included studies were heterogenous in design, intervention and study population. The number of catheter related infections was used as the primary endpoint. Results are presented with 95% CIs. Heterogeneity will be assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the I^2 statistic. In the absence of significant heterogeneity ($I^2 < 50\%$), a fixed effects model will be used for the estimation of treatment effects. The outcome considered was the number of patients with catheter related bacteraemia compared to

the total number of patients. Pooling was only considered if >3 trials were present in the same group.

DESCRIPTION OF STUDIES

We identified the abstracts of 40 potentially relevant trials. Of these 20 were excluded because of the use of iv antibiotics for five days before insertion of the catheter, and because of the use of antibiotic lock therapy. We identified 20 studies for possible inclusion of these 11 studies were excluded. Two studies were excluded because they involved only neonates (Garland 2005; Ocete 1998) four studies were excluded because non-tunneled catheters were used (Carratala 1999; Chatzinikolaou 2003; Hanna 2004; Raad 1998) and five studies were excluded because they were not adequately randomized or had no adequate control group assigned (Al Sibai 1987; Chatzinikolaou 03a; Dawson 2000; Fourcade 2001; Rubie 1995).

Of the nine included studies, four addressed the administration of antibiotics prior to insertion of the catheter (Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995), and five studies addressed flushing the catheter with the combination of vancomycin and heparin (Barriga 1997; Daghistani 1996; Henrickson 2000; Rackoff 1995; Schwartz 1990). The total number of patients in the nine included studies was 588, four studies were done in adults (252 patients), three studies in children ($n = 192$), and two trials combined children and adults ($n = 144$). In all trials single or double lumen external tunneled central venous catheters were used. Seven trials included both patients with solid tumours and haematological malignancies and two trials only included patients with haematological malignancies (Lim 1993; Ljungman 1997).

No extra information was obtained from the conference proceedings.

METHODOLOGICAL QUALITY

In five studies the method of blinding was adequately described (Barriga 1997; Daghistani 1996; Henrickson 2000; Ranson 1990; Schwartz 1990) and four studies were not adequately blinded (Lim 1993; Ljungman 1997; Rackoff 1995; Vassilomaniakis 1995). Initially in one study randomization was performed but later all patients were included in the experimental group. In our analysis we only used the first part of the study when randomization was performed (Vassilomaniakis 1995). In the second study an open randomization was performed and the study was stopped at interim analysis (Ljungman 1997). Due to the poor internal validity of the latter study in comparison to the three other studies included two analyses are presented.

Eligibility criteria

All studies described the eligibility criteria sufficiently. All the studies excluded patients already receiving vancomycin, or other systemic antibiotics and selective gut decontamination use was allowed (that is the use of oral antibiotics starting before a neutropenic episode is expected in which the potentially pathogenic aerobic organisms are eliminated without affecting the non-pathogenic anaerobic organisms). One study only included patients not neutropenic at the start of the study. The others did not specify this aspect at the start of the study but specified that these patients would become neutropenic due to their disease. All paediatric studies specified children to be less than 20 years of age. All studies specified the catheter used (in all studies a Hickman catheter was used, double or single-lumen)

Treatment allocation:

In six out of nine studies the treatment allocation was concealed (Grade A as described in the methodological quality of the studies). Two studies used a quasi-randomization method (Grade B, Lim 1993; Vassilomaniakis 1995), and one study did not specify the method of randomization (Ljungman 1997). In all studies the index intervention and control intervention was explicitly described. In three out of nine trials the participants were not blinded to the treatment (Lim 1993; Ljungman 1997; Vassilomaniakis 1995). In four out of nine trials the outcome assessor was not blinded to the intervention (Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995). In two out of nine trials the outcome measures were not clearly stated (Ranson 1990; Vassilomaniakis 1995).

See additional tables for the criteria list for the assessment of the methodological quality of included studies (van Tulder 1997) Table 01 gives these criteria, Table 02 the internal validity scores and Table 03 the external validity scores.

RESULTS

Comparison 1: The four studies evaluating antibiotic prophylaxis before insertion of the central venous catheter were pooled (Lim 1993; Ljungman 1997; Ranson 1990; Vassilomaniakis 1995). In two studies teicoplanin but not vancomycin was used as the intervention before insertion of the catheter (Lim 1993; Ljungman 1997). Since we aimed to review the prevention of Gram-positive TCVC infections and both vancomycin and teicoplanin are glycopeptides, that are active against Gram-positive bacteria we felt it was felt acceptable to pool these data.

The odds ratio under a fixed effect model was 0.55 (95% CI 0.29 to 1.04). Because of heterogeneity the random effect model was applied resulting in an OR of 0.54 (95% CI 0.17 to 1.74).

These results show that this intervention does not give a significant decrease in the number of catheter related infections. However the studies are very heterogenous, therefore pooling of the four trials is not acceptable $I^2 = 60.8\%$.

This heterogeneity is mainly caused by the study of Ljungman (Ljungman 1997). They studied a large group of allogeneic bone-marrow transplant patients who were already given trimethoprim/sulphamethoxazole one week prior to the insertion of the catheter. If this study is excluded and the 3 trials are pooled, there were 17 patients with a Gram positive bacteraemia in the group who received prophylaxis ($n = 95$) and in the control group there were 30 patients with a Gram-positive bacteraemia $I^2 = 54.2\%$, heterogeneity is present but just acceptable to pool the data. The odds ratio under a fixed effect model was 0.46 (CI 0.24 to 0.91), because of heterogeneity a random effect model should be applied resulting in an odds ratio of 0.42 (CI 0.13 to 1.31). The overall effect of decreasing Gram-positive catheter related bacteraemia by giving antibiotic prophylaxis before insertion of the catheter is not significant.

Comparison 2: The five studies using vanco/heparin flush method compared to heparin only flush (control) were pooled (Barriga 1997; Daghistani 1996; Henrickson 2000; Rackoff 1995; Schwartz 1990) There was no heterogeneity in the patient groups included ($p = 0.32$, $I^2 = 14.3\%$). All were oncology patients who needed chemotherapy, mainly children.

Using the fixed effect model there was a significant reduction of Gram-positive catheter related bacteraemia's using the flush method. In 13/150 patients who received vancomycin/heparin flush method a bacteraemia developed whereas this occurred in 32/189 of patients treated with heparin flush only (OR of 0.43 (95% CI 0.21 to 0.87)). If the risk of a catheter related sepsis is 10% then the NNT to prevent one catheter related infection will be 17, if this risk is 20% then the NNT is 9. The overall effect favours treatment with an antibiotic in the flush solution to prevent catheter related infections, although the base-line risk of catheter related infection rate is of importance.

DISCUSSION

1: To assess the effect of antibiotics before insertion of the catheter. Study design and methodology of the four included studies were sufficient to pool and analyze the data. The study of Vassilomanakis 1995 was the most difficult to interpret because of the initial randomization followed by treating all participants with antibiotics before insertion of the catheter. Because of heterogeneity between the trials we used the random effect model. The OR did not show a significant result (0.43 CI 0.13 to 1.31), therefore there is no evidence to administer antibiotics prior to insertion of the catheter to prevent Gram-positive infections.

2: To assess the effect of antibiotic flushing of the catheter. Design and methodology of the five included studies were sufficient to pool and analyze the data. Two studies (Rackoff 1995; Schwartz 1990) had relatively small groups of patients. Henrickson 2000 and Barriga 1997 and Daghistani 1996 included larger

groups of patients. The combined overall EER(= experimental event rate) and the CER (control event rate) were 8.6% and 16.9% respectively. Barriga 1997 pointed out that intraluminal colonization of central venous catheters with microorganisms probably occurs mainly during non-neutropenic episodes, whereas during neutropenia other sources of infection play a major role, like the gastro-intestinal tract. Depending on the incidence of TCRS (ranging from 5 to 15%) the NNT ranges from 13 to 23 patients.

In both cases vancomycin/teicoplanin prior to insertion of the central venous catheter and vancomycin/heparin flushing of the central venous catheter may develop the problem of bacterial resistance to vancomycin. With the doses flushed this seems unlikely as the dose is so small it does not distribute systemically (25 microgram/ml using 3 mls) and the vancomycin is confined to the lumen of the TCVC and skin organisms are not exposed.

AUTHORS' CONCLUSIONS

Implications for practice

The prophylactic vancomycin lock solution is beneficial in preventing Gram-positive tunnelled catheter related infections but the analyses should be considered with care due to the small number of studies. We feel that a selection of patients with a high baseline risk for infection (i.e. haematological patients receiving induction chemotherapy, patients who are neutropenic at the time of insertion of the catheter and patients undergoing a bone-marrow transplant) will benefit from flushing the central venous catheter with a combination of an antibiotic and heparin.

Implications for research

As indicated it would be useful to know in which risk groups one would implement the interventions. Although some of the included studies stratified risk groups, none analyzed these separately because of small numbers.

A multicentre RCT addressing the question of whether the above interventions are justified in the specific risk groups is of extreme importance.

The future direction could be coating of long term TCVCs with antibiotics compared to the above interventions to decrease Gram-positive catheter related infections, or the use of other interventions such as the ethanol-lock solution.

POTENTIAL CONFLICT OF INTEREST

None known.

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T A B L E S**Characteristics of included studies**

Study	Barriga 1997
Methods	double blind randomization
Participants	N=83 adult and paediatric patients various malignancies, mainly leukemia, 143 febrile episodes recorded
Interventions	vanco vs heparinflush (25 ug/ml vanco and 25 units/ml hep
Outcomes	*bacteraemia *Vanco-sensitive organism bacteraemia
Notes	a difference was stated in neutropenia and nonneutropenia
Allocation concealment	A – Adequate

Study	Daghistani 1996
Methods	double blind randomization
Participants	N=61 adult and paediatric patients various malignancies
Interventions	vanco+amikin heparin flush (25 ug/ml vanco, 25 ug/ml amikin and 100 units/ml hep) versus Hep
Outcomes	*catheter related sepsis *cellulitis
Notes	the only study in which amikin was added
Allocation concealment	A – Adequate

Study	Henrickson 2000
Methods	double blind randomization

Characteristics of included studies (Continued)

	stratified for riskgroups
Participants	n=126 paediatric patients (44% ALL, 40% solid, 7 % BMT) There were 153 assessable TCVC
Interventions	vanco versus heparin flush(25 ug/ml vanco and 100 units/ml hep
Outcomes	*exit-site infection *bacteraemia *time to first infection
Notes	the third group included vanco-heparin ciprofloxacin quantitative cultures were done
Allocation concealment	A – Adequate

Study **Lim 1993**

Methods	method of randomization not clear
Participants	N=88 adult oncology patients, haematological malignancies baseline characteristics reported- no sign.difference
Interventions	teicoplanin before insertion 400 mgr before insertion catheter vs control
Outcomes	*soft-tissue infection *catheter related sepsis
Notes	all episodes of CRS occurred in patients who were neutropenic
Allocation concealment	B – Unclear

Study **Ljungman 1997**

Methods	method of randomization not clear
Participants	N=66 adult oncology patients, BMT and leukemia patients
Interventions	teicoplanin prior to insertion and 24 hrs after insertion
Outcomes	*bacteraemia *exit-site infection
Notes	At interimanalysis the preset efficacy could not be met therefore stop study
Allocation concealment	B – Unclear

Study **Rackoff 1995**

Methods	double blind randomization
Participants	n=55 paediatric patients, one centre (total group was 63 patients , 8 were receiving TPN Analysis was done on the oncology patients only
Interventions	vanco versus heparin flush (25 ug/ml vanco and 100 units/ml heparin)
Outcomes	*bacteraemia with a vanco sensitive organism *time to first infection
Notes	
Allocation concealment	A – Adequate

Study **Ranson 1990**

Methods	double blind randomization
Participants	N=98 adult patients A) N=48 and 35 catheters, acute leukemia and BMT)

	B) N= 50 and 37 catheters (solid tumor)
Interventions	vancomycin vrs control (2 doses one prior to insertion, one after positioning of the catheter 500 mg vanco)
Outcomes	*catheter related sepsis in first 30 days *tunnel sepsis *CNS bacteraemia
Notes	
Allocation concealment	A – Adequate

Study	Schwartz 1990
Methods	Double blind randomization
Participants	n=45 paediatric patients
Interventions	vancomycin versus heparin flush(25 ug/ml vanco and 100 units/m
Outcomes	*bacteraemia (quantitative culture) *time to first inf.
Notes	statistics on the number of children not catheters quantitative blood cultures
Allocation concealment	A – Adequate

Study	Vassilomaniakis 1995
Methods	Randomization by cards in closed envelopes,
Participants	N=40 adult patients
Interventions	vancomycin vs control (vanco in 3 doses of 500 mg 1 hr prior to insertion, 6 and 12 h afterwards)
Outcomes	*exit-site infection *cvc related bacteraemia *Gram+infections
Notes	only initially randomized
Allocation concealment	B – Unclear

Vs = versus

CRS = Catheter related sepsis

BMT = Bone marrow transplant

TCVC = Tunneled central venous catheter

TPN = total parenteral nutrition

CVC = central venous catheter

Characteristics of excluded studies

Study	Reason for exclusion
Al Sibai 1987	146 patients with malignant disease received 160 Hickman catheters. 70 of these patients received prophylactic antibiotics during and after insertion of the catheter. The catheter infection rate dropped from 0.5-0.25 per 100 days. Excluded because the antibiotic use and duration was at the discretion of the attending physician, and the results were retrospectively analysed.
Carratala 1999	Adult haematology patients with non-tunneled CVC's received 10U heparin per ml (n=57) or 10U heparin+ 25 microgr. vancomycin per ml (n=60) allowed to dwell in catheter 1 hour every 2 days. Catheter related bacteraemia in 7% of patients in control group, and 0% in experimental group (p=0.05).

Characteristics of excluded studies (Continued)

Mainly excluded because non-tunnelled catheters.

Chatzinikolaou 03a	Prospective cohort study. M-EDTA was used as lock solution in indwelling ports in 14 children. No catheter related infections were observed. In 48 control patients locked with heparin 10 port infections were observed. Not included because cohort study
Chatzinikolaou 2003	Hemodialysis catheters in patients with cancer. 66 patients impregnated catheter with minocycline and rifampin and 64 nonimpregnated catheters. 0 catheter related infections in the impregnated group and 7 in the nonimpregnated group duration catheter 8 days. Excluded because this concerns non-tunnelled catheters. And duration of insertion is short.
Dawson 2000	143 paediatric oncology patients, with 176 TCVC. Intervention Cephalothin 100 mg/kg iv or vancomycin 20-25 mg/kg iv prior to insertion of the catheter. Rate of infections <30 days dropped 40% No randomization performed and intervention period was compared to pre intervention period
Fourcade 2001	Prospective cohort study using antibiotic-lock technique to prevent bacteraemia in chronic hemodialysis catheters. The incidence of bacteraemia dropped from 4.6 per 1000 catheter days to 0.88 per 1000 catheter days no RCT, comparison with historical control, non-tunnelled catheters.
Garland 2005	Prospective RCT in critically ill neonates. Vanco lock solution was used in 42 infants and heparin lock in 43 infants. Two patients in the vanco/heparin lock group developed a catheter related infection, 13 patients in the control group developed a catheter related infection RR 0.13 (0.01-0.57) highly significant, duration catheter 20 days. Excluded because it concerns non tunnelled catheters and done in neonates, which is not the appropriate group for our inclusion criteria
Hanna 2004	Prospective RCT at MC Anderson in cancer patients, 356 catheters placed, 182 impregnated with Minocyclin and rifampin, 174 non-impregnated. Mean duration of the catheter 66 days. 3 catheter related infections in the MR group and 14 in the non impregnated group, highly significant. Not included because these are non-tunnelled catheters and baseline risk for these catheters is higher than the tunnelled catheters. And our inclusion criteria were a newly inserted tunnelled central venous catheter.
Ocete 1998	Single centre trial 2 groups control group - 61 newborns and experimental group 85 newborns, all receiving a central catheter (umbilical artery, umbilical vein and/or silastic). The study group received prophylactic vancomycin 25 ug/ml. All patients received parenteral nutrition. Results CNS 21/61 in the control group and 19/85 in the vancomycin group (p<0.05). The patient group is not the group studied in this review. Methods of the study poor. Not specified how often the prophylactic vanco is given. Clinical criteria were used to determine if the neonate was infected, then peripheral and central cultures were done. Not specified if quantitative or qualitative cultures were done. Trial not blinded, no tunnelled catheters used, no appropriate patient group
Raad 1998	Crossover study: 26 patients with melanoma on IL2 treatment enrolled. All patients received a double lumen non-tunneled silicone catheter in subclavian vein. Patients randomized to receive prophylactic antibiotics novobiocin 500 mg + rifampin 300 mg orally. Significant results 41% in control group catheter related bacteraemia and 6% in experimental group, excluded because of non-tunnelled catheters Very specific group with high incidence of infection, not representing the group aimed at in this Cochrane review.
Rubie 1995	163 paediatric patients with cancer had 180 subcutaneous ports inserted. Over time a change of policy was made from only flushing with heparin to a V/H solution. The infection rate dropped from 31% to 4% This study is not randomised, and the results were retrospectively analysed

ADDITIONAL TABLES

Table 01. Criteria list for the assessment of methodological quality of included studies

Item ID	Description	Implementation
patient selection		
a	Were the eligibility criteria specified?	Note: all criteria were scored yes(+),no(-) or don't know Patient inclusion/exclusion criteria must have been described appropriately according to the reviewer
b1	was a method of randomization applied?	A random (unpredictable) allocation must have been applied
b2	was the treatment allocation concealed	Allocation should have been performed by an independent person not responsible for determining eligibility for inclusion.
c	were the groups similar at baseline with regard to the most important prognostic indicators?	groups must be similar at baseline with regard to at least three of the four prognostic indicators of age sex duration of symptoms and value of main outcome measures
intervention		
d1	was the experimental intervention explicitly described	adequate description of the experimental intervention so that treatment can be replicated
d2	was the control intervention explicitly described	adequate description of the control intervention so that treatment can be replicated
e	were co-interventions avoided or similar for all groups	co-interventions should either have been avoided in the trial design or be similar in the 2 groups
f	was the patient blinded for the intervention	adequate information about blinding must have been provided
outcome measurement		
g	was the outcome assessor blinded to the intervention?	Adequate information about blinding must have been provided
h	were the outcome measures relevant?	at least one of the following outcome measures must be included: catheter related sepsis, exit infections, tunnel infections and time to first infection
i	were complications described?	any adverse events should be noted
j	was the drop-out loss to follow up described and acceptable?	included patients who did not complete the follow up period or were not included in the analysis should be described, if the percentage of drop outs is less than 20% then a ' + ' is scored
k	was a follow up measurement performed	outcome assessment after randomization
l	was the timing of the outcome similar for all groups?	Timing of outcome assessment should have started from the moment of treatment allocation and be identical for all intervention groups and all important outcome measures
statistics		
m	was the sample size described for each group?	sample size should have been presented for each group at randomization and for the most important outcome

Table 01. Criteria list for the assessment of methodological quality of included studies (*Continued*)

Item ID	Description	Implementation
		measures
n	did the analysis include an intention to treat analysis	for all randomized patients the most important moments of effect measurement should have been reported
o	were point estimates and measures of variability presented for the primary outcome measures?	For continuous data mean, median, standard deviation with 95 % confidence interval should be presented. For nominal and ordinal outcomes the number of patients to whom the outcome measure applies and the total number of patients must be presented.

Table 02. internal validity scores(b1,b2,c,e,f,g,j,l,n)

reference	b1	b2	c	e	f	g	j	l	n
Vassilomaniakis 1995	+	-	+	+	-	-	+	+	+
Ranson 1990	+	+	+	+	+	+	+	+	+
Lim 1993	+	-	+	+	-	+	+	+	+
Barriga 1997	+	+	+	+	+	+	+	+	+
Rackoff 1995	+	+	+	+	+	+	+	+	+
Schwartz 1990	+	+	+	+	+	+	+	+	+
Henrickson 2000	+	+	+	+	+	+	+	+	+
Daghistani 1996	+	+	+	+	+	+	+	+	+
Ljungman 1997	+	-	-	-	-	-	+	+	+

Table 03. External Validity (a, d1, d2, h, i, k, m,o)

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

ANALYSES

Comparison 01. vancomycin versus control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
02 catheter related sepsis	4	215	Odds Ratio (Fixed) 95% CI	0.57 [0.31, 1.03]

Comparison 02. vancomycin flush versus heparin flush

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 catheter related sepsis	5	339	Odds Ratio (Fixed) 95% CI	0.43 [0.21, 0.87]
02 catheter-related sepsis in first 50 days	3	223	Odds Ratio (Fixed) 95% CI	0.52 [0.14, 1.90]

Comparison 03. vancomycin/teicoplanin versus control

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 analysis of vancomycin/teicoplanin prior to insertion catheter excluding Lungman study, outcome CRS	3	187	Odds Ratio (Fixed) 95% CI	0.46 [0.24, 0.91]

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Catheterization, Central Venous [*adverse effects]; Gram-Positive Bacterial Infections [*prevention & control]; *Neoplasms [therapy]; Randomized Controlled Trials

MeSH check words

Humans

COVER SHEET

Title	Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients
Authors	van de Wetering MD, van Woensel JBM
Contribution of author(s)	MD van de Wetering- reference search, article retrieval, assessment of studies for inclusion/exclusion, data-extraction analysis, manuscript preparation. J van Woensel - reference search, assessment of studies for inclusion/exclusion, data extraction, reviewing of manuscript.
Issue protocol first published	2002/2
Review first published	2003/3
Date of most recent amendment	14 November 2006
Date of most recent SUBSTANTIVE amendment	09 November 2006
What's New	Updating the search from July 2001 to July 2006 revealed no new RCTs in tunnelled central venous catheters. However, the improved method of testing heterogeneity I, has resulted in a change to the conclusions.

Vanco prophylaxis at insertion of the catheter is not beneficial.
 Flushing the catheter is beneficial in high risk patients.
 In the excluded studies some new RCTs have been included. These were all RCTs with non-tunnelled central venous catheters.

Date new studies sought but none found 01 September 2006

Date new studies found but not yet included/excluded Information not supplied by author

Date new studies found and included/excluded 08 September 2006

Date authors' conclusions section amended 19 September 2006

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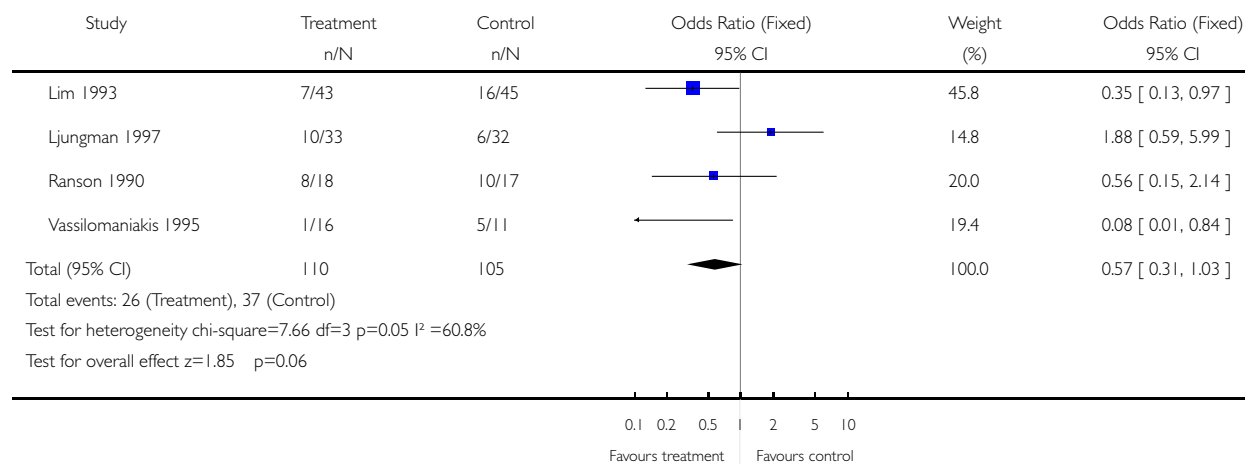
GRAPHS AND OTHER TABLES

Analysis 01.02. Comparison 01 vancomycin versus control, Outcome 02 catheter related sepsis

Review: Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients

Comparison: 01 vancomycin versus control

Outcome: 02 catheter related sepsis

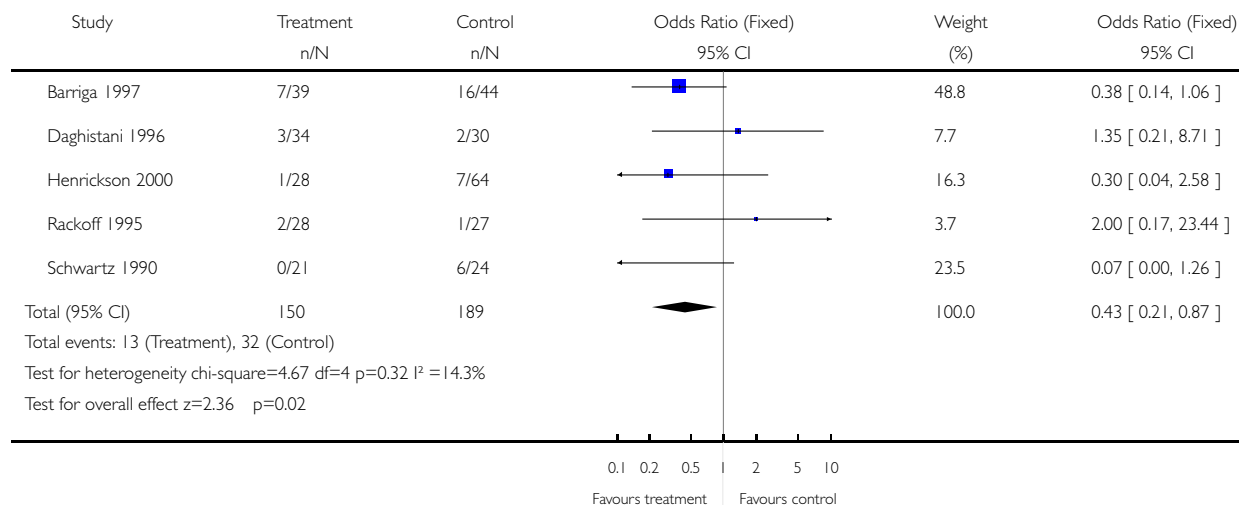


Analysis 02.01. Comparison 02 vancomycin flush versus heparin flush, Outcome 01 catheter related sepsis

Review: Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients

Comparison: 02 vancomycin flush versus heparin flush

Outcome: 01 catheter related sepsis

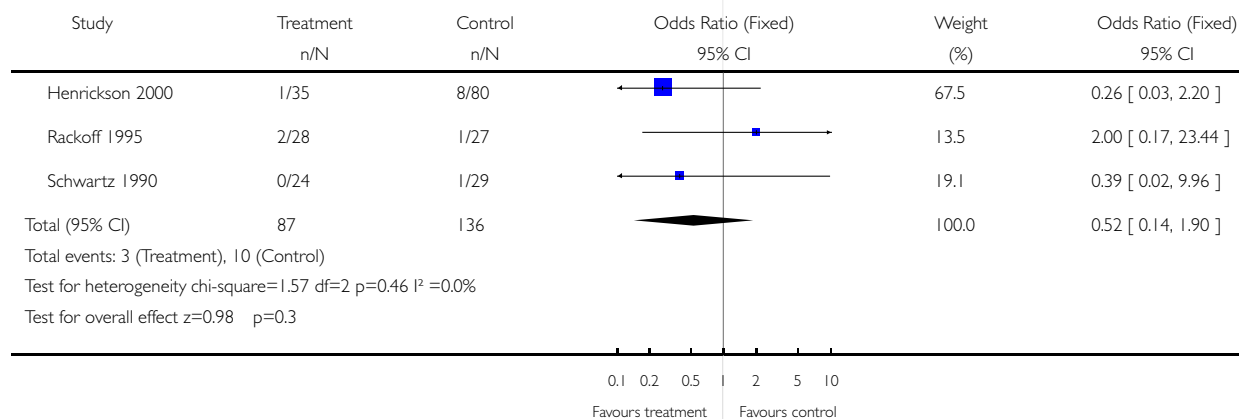


Analysis 02.02. Comparison 02 vancomycin flush versus heparin flush, Outcome 02 catheter-related sepsis in first 50 days

Review: Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients

Comparison: 02 vancomycin flush versus heparin flush

Outcome: 02 catheter-related sepsis in first 50 days



Analysis 03.01. Comparison 03 vancomycin/teicoplanin versus control, Outcome 01 analysis of vancomycin/teicoplanin prior to insertion catheter excluding Lungman study, outcome CRS

Review: Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients

Comparison: 03 vancomycin/teicoplanin versus control

Outcome: 01 analysis of vancomycin/teicoplanin prior to insertion catheter excluding Lungman study, outcome CRS

