Prediction and prevention of infectious complications in children with cancer
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Addendum
Cochrane review chapter 5
PROPHYLACTIC ANTIBIOTICS FOR PREVENTING EARLY CENTRAL VENOUS CATHETER GRAM POSITIVE INFECTIONS IN ONCOLOGY PATIENTS

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ABSTRACT

Background
Long-term tunnelled central venous catheters (TCVC) are increasingly used in oncology patients. Despite guidelines on insertion, maintenance and use, infections remain an important complication. Most infections are caused by Gram-positive bacteria. Therefore antimicrobial prevention strategies aimed at these micro-organisms could potentially decrease the majority of the 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 MEDLINE, EMBASE, and CENTRAL up to July 2001. 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 randomized controlled trials giving prophylactic antibiotics prior to insertion of the TCVC, and trials using the combination of an antibiotic and heparin to flush the TCVC in oncology patients.

Data collection and analysis
Two reviewers independently assessed the studies for inclusion, extracted the data and assessed the quality.

Main Results
We included eight trials totalling 527 patients. Four reported on vancomycin/teicoplanin prior to insertion of the TCVC, and four reported on antibiotic flushing combined with heparin. The overall effect of an antibiotic prior to catheter insertion decreases the number of Gram-positive TCVC infections (odds ratio [OR] = 0.55, 95% confidence interval [CI] 0.29 to 1.04). Given an expected infection rate of TCVC during the first 45 days of up to 30% this OR implies that the number needed to treat (NNT) will be 10 (95% CI 4 to 13), this means vancomycin needs to be given to 10 patients to prevent one TCVC infection.

Flushing the TCVC with antibiotics and heparin proved to be beneficial (OR = 0.35, 95% CI 0.16 –to 0.77). For intraluminal colonization the baseline infection-rate is 15% which leads to a NNT of 13 (95% CI 5 to 23).

Reviewer's conclusions
Both interventions lead to a positive overall effect but should be considered with care due to the small number of studies. Depending on the baseline TCVC infection rate it is justified to administer antibiotics prior to the TCVC insertion or to flush the catheter with a combination of an antibiotic and heparin, if the catheter-related infection rate is high.

This review should be cited as:
BACKGROUND

Patients who are treated for cancer need adequate venous access because of the frequent use of chemotherapy, requirements of intravenous fluids, blood products etc. To limit discomfort of short-term venous access long-term tunneled catheters are nowadays used in more than two thirds of paediatric and adult cancer patients (Ingram 1991; Groeger 1993). However, the use of long-term tunneled catheters is limited by the risk of blood clot formation as well as infections. This risk ranges from 1.4 (Press 1984) to 2.2 (Groeger 1993) infections per 1000 catheter days. About one third of patients experience an episode of infection while having the TCV C in place. The organisms cultured are Gram-positive organisms (70%), Gram-negative organisms (15%) fungal organisms (8%) and anaerobic organisms (7%).

The adherence to and colonization of TCV C 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 TCV C 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 (Darouiche 1999). This means that adequate antibiotic treatment may lead to resolution of the TCV C 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.

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 TCV via the bloodstream) and contamination of the intravenous fluids given to the patient (for instance intravenous total parenteral nutrition) (Farr 1995).

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 (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) about 15-20% early TCV C infections are still seen. It has been shown (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 central venous catheters (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.

Therefore reduction of Gram-positive infections by introducing antibiotics in 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.

It is known that the risk of infections is lower in internal cvc's (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 tunneled cvc types were pooled in this analysis. The risk of infection is greatest during the first 100 days after placement (Salzman 1995; Wurzel 1988).

This systematic review assesses the effectiveness of prophylactic antibiotics in the prevention of early Gram-positive catheter related infections, when the risk of infections is greatest. The importance of the first 45 days allows us to cover the induction period of chemotherapy. This is the time-period that many manipulations of the TCV C are necessary because of the intensity of the chemotherapy. For this reason both internal and external tunneled central venous catheters could be 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 tunnelled central venous catheter 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

- Randomized controlled trials (RCTs) comparing placebo versus antibiotics prior to insertion of the catheter to reduce Gram-positive infections related to the catheter
- RCTs comparing the heparin flush technique versus the antibiotic/heparin flush technique to reduce Gram-positive infections due to catheter related infections
- RCTs combining the two interventions

Types of participants

Patients with cancer (both adults and children) who will have a tunnelled central venous catheter inserted and are likely to receive chemotherapy causing episodes of neutropenia, with increased risk of infection.

Types of intervention

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

Types of outcome measures

The major outcome indicator is bacteraemia due to central venous catheter infections. Proxy measures are the frequency of exit-site infections and tunnel-infections. The time frame for assessment of outcomes within a study should be stated, (establishing when the catheter related infection occurred from the time of insertion).

Definitions (Mermel 2001):

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 tunnelled 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 bloodculture 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 STRATEGY FOR IDENTIFICATION OF STUDIES

See: Cochrane Gynaecological Cancer Group search strategy

MEDLINE and EMBASE search was done for the years 1966-2000 and a search of CENTRAL on the Cochrane Library (Issue 4, 2000) was done.

Search terms: (Broviac OR Port-a-cath OR Hickman OR exp catheterization,central venous). AND (prophylactic antibiotics OR vancomycin OR teicoplanin) AND (exp oncolog? OR cancer OR malignancy OR neoplasm) AND
Identification of studies meeting the eligibility criteria was performed independently by two reviewers (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 assessed using the Jadad criteria, (blinding of randomization, inclusion and exclusion criteria, intervention performed, and outcome looked at), thereafter scored using the Tulder criteria (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 reviewers.

Allocation concealment was assessed using the scale set out in the Cochrane Collaboration Handbook for Reviewers (Cochrane Handbook).

Grade 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.

Grade 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.

Grade 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 with antibiotics at insertion of the central venous catheter 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% confidence intervals (CIs).

**METHODS OF THE REVIEW**

**DESCRIPTION OF STUDIES**

We identified 11 studies. Three studies were excluded. One study was excluded because it involved only neonates (Ocete 1998) and two studies were excluded because non-tunneled catheters were used (Raad 1998; Carratala 1999).

Of the eight included studies, four addressed the administration of antibiotics prior to insertion of the catheter (Vassiliomaniakis 1995; Lim 1993; Ranson 1990, Ljungman 1997), and four studies addressed flushing the catheter with the combination of vancomycin and heparin (Rackoff 1995; Schwartz 1990; Barriga 1997; Henrickson 2000). The total number of patients in the eight included studies was 527, four studies were done in adults (n=252), three studies in children (n=192), and one trial combined children and adults (n=83).

No extra information was obtained from the conference proceedings. In Table 04 all abstracts on central venous catheters and infection rates have been summarized to give information on the rates of infection in the different units. This may be important in interpreting the results of the included studies.
METHODOLOGICAL QUALITY

In six studies the method of blinding was adequately described and two studies were not adequately blinded. 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 five out of eight 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, Vassilomaniakis 1995; Lim 1993), 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 eight trials the participants were not blinded to the treatment (Vassilomaniakis 1995; Lim 1993; Ljungman 1997). In four out of eight trials the outcome assessor was not blinded to the intervention (Vassilomaniakis 1995; Ranson 1990; Lim 1993; Ljungman 1997). In two out of eight trials the outcome measures were not clearly stated (Vassilomaniakis 1995; Ranson 1990).

See additional tables for the criteria list for the assessment of the methodological quality of included studies (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 (Vassilomaniakis 1995; Lim 1993; Ranson 1990; Ljungman 1997). In two studies teicoplanin and 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 TCV C 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 0.28 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).

To interpret the results knowledge of the baseline infection rate of the TCV C is important. With this knowledge one can derive the number needed to treat from the odds ratio (Cochrane Handbook (appendix 8b)) if the catheter related infection rate approaches 15% an OR of 0.55 will give a NNT of 18 (this means vancomycin should be given to 18 patients to avoid one catheter related infection). If the catheter related infection rate is 30% vancomycin should be given to 10 patients to prevent one catheter related infection. The overall effect favours treatment with an antibiotic prior to insertion of the catheter, although the catheter related infection rate is of importance. Excluding the study of Ljungman because of poor internal validity, the OR under a fixed effect model was 0.46 (95% CI 0.24 to 0.91). The NNT will then range from eight to 20 patients.

Comparison 2: The four studies using vanco/heparin flush method compared to heparin only flush (control) were pooled (Schwartz 1990; Rackoff 1995; Barriga 1997; Henriksson 2000). There was no heterogeneity in the patient groups included. All were oncology patients who needed chemotherapy, mainly children.

Statistical results showed using the fixed effect model an OR of 0.35 (95% CI 0.16 to 0.77). Using the random effect model the OR was 0.39 (95% CI 0.16 to 0.95). 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 nine. The overall effect favours treatment with an antibiotic in the flush solution to prevent catheter related infections, although the 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. The combined overall EER (experimental event rate) and the CER (control event rate) were 14.8% and 24.6% respectively. Depending on the background tunneled catheter related infection rate that ranges from 10% to 30% the NNT will range from 10 to 18 patients.

If the risk of infection is high (for instance neutropenic patients and/or patients on induction therapy for haematological malignancies (cancer of the blood) one should consider giving antibiotics prior to insertion of the catheter. In this group of patients the skin insertion site is the source of introducing vancomycin-sensitive organisms (VCO). Prevention of infection at this level will decrease morbidity in these patients.

2: To assess the effect of antibiotic flushing of the catheter.
Design and methodology of the four included studies were sufficient to pool and analyze the data. Two studies (Schwartz 1990; Rackoff 1995) had relatively small groups of patients. Henrickson 2000 and Barriga 1997 included larger groups of patients. The combined overall EER (experimental event rate) and the CER (control event rate) were 8.6% and 18.8% 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). As for the antibiotic prior to insertion of the catheter, this involves only one or two doses, and if qualifying the definition that only certain patients will receive this treatment it does not imply a danger of developing resistance.

REVIEWER'S CONCLUSIONS

Implications for practice
Both interventions were effective in preventing Gram-positive tunneled catheter related infections but the analyses should be considered with care due to the small number of studies.

If the tunneled central venous catheter infection rate is expected to be high, then it can be justified to use antibiotics prior to insertion of the central venous catheter, or to flush 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. Therefore a multicentre RCT answering 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 longterm tunneled central venous catheters with antibiotics compared to the above interventions to decrease Gram-positive catheter related infections.

ACKNOWLEDGEMENTS

We wish to thank our funders for the research grant which made this systematic review possible. We would also like to thank Dr R. Scholten, epidemiologist at the AMC for reviewing the manuscript and assisting with the statistical part.

POTENTIAL CONFLICT OF INTEREST

None known
### TABLES

**Characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
<th>Allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barriga 1997</td>
<td>double blind randomization</td>
<td>n=83 adult and paediatric patients various malignancies, mainly leukaemia, 143 febrile episodes recorded</td>
<td>vanco vs heparin flush (25 ug/ml vanco and 25 units/ml heparin)</td>
<td><em>bacteraemia</em> <em>Vanco-sensitive organism bacteraemia</em></td>
<td>a difference was stated in neutropenia and nonneutropenia</td>
<td>A</td>
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<tr>
<td>Henriksen 2000</td>
<td>double blind randomization stratified for riskgroups</td>
<td>n=126 paediatric patients (44% ALL, 40% solid, 7% BMT) There were 153 assessable TCVC</td>
<td>vanco versus heparin flush(25 ug/ml vanco and 100 units/ml heparin)</td>
<td><em>exit-site infection</em> <em>bacteraemia</em> <em>time to first infection</em></td>
<td>the third group included vanco-heparin ciprofloxacin quantitative cultures were done</td>
<td>A</td>
</tr>
<tr>
<td>Lim 1993</td>
<td>method of randomization not clear</td>
<td>n=88 adult oncology patients, haematological malignancies</td>
<td>teicoplanin before insertion 400 mg before insertion catheter vs control</td>
<td><em>soft-tissue infection</em> <em>catheter related sepsis</em></td>
<td>all episodes of CRS occurred in patients who were neutropenic</td>
<td>B</td>
</tr>
<tr>
<td>Ljunghman 1997</td>
<td>method of randomization not clear</td>
<td>n=66 adult oncology patients, BMT and leukemia patients</td>
<td>teicoplanin prior to insertion and 24 hrs after insertion</td>
<td><em>bacteraemia</em> <em>exit-site infection</em></td>
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<tr>
<td>Study</td>
<td>Methods</td>
<td>Participants</td>
<td>Interventions</td>
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<tr>
<td><strong>Notes</strong></td>
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<td>At interim analysis the preset efficacy could not be met therefore study stopped</td>
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<td><strong>Allocation concealment</strong></td>
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<tr>
<td><strong>Rackoff 1995</strong></td>
<td>double blind randomization</td>
<td>n=55 paediatric patients, one centre (total group was 63 patients, 8 were receiving TPN Analysis was done on the oncology patients only</td>
<td>vanco versus heparin flush (25 ug/ml vanco and 100 units/ml heparin)</td>
<td>*bacteraemia with a vanco sensitive organism *time to first infection</td>
<td></td>
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</tr>
<tr>
<td><strong>Ransonn 1990</strong></td>
<td>double blind randomization</td>
<td>n=98 adult patients A) N=48 and 35 catheters, acute leukemia and BMT) B) N= 50 and 37 catheters (solid tumor)</td>
<td>vancomycin vs control (2 doses one prior to insertion, one after positioning of the catheter 500 mg vanco)</td>
<td>*catheter related sepsis in first 30 days *tunnel sepsis *CNS bacteraemia</td>
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<tr>
<td><strong>Schwartz 1990</strong></td>
<td>Double blind randomization</td>
<td>n=45 paediatric patients</td>
<td>vancomycin versus heparin flush(25 ug/ml vanco and 100 units/m</td>
<td>*bacteraemia (quantitative culture) *time to first inf.</td>
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<tr>
<td><strong>Notes</strong></td>
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<td>statistics on the number of children not catheters quantitative blood cultures</td>
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<tr>
<td><strong>Allocation concealment</strong></td>
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<tr>
<td><strong>Vassilomanakis 1995</strong></td>
<td>Randomization by cards in closed envelopes,</td>
<td></td>
<td></td>
<td>*exit-site infection *cvc related bacteraemia *Gram+infections</td>
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</table>
Note: only initially randomized

Allocation B
concealment

Vs = versus
CRS = Catheter related sepsis
BMT = Bone marrow transplant
TCVC = Tunneled central venous catheter
TPN = total parenteral nutrition
CVC = central venous catheter
vanco = vancomycin
hep = heparin
ALL = acute lymphoblastic leukaemia
mg = milligram(s)
ug = microgram(s)
ml = millilitre(s)
n = number of participants

Characteristics of excluded studies

Carratala 1999
Adult haematology patients with non-tunnelled CVC's received 10U heparin per ml (n=57) or 10U heparin+ 25 ug. 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).
Mainly excluded because non-tunnelled catheters.

Ooste 1998
Single centre trial 2 groups. Control group - 61 newborns, 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 was 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-tunnelled 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 8% in experimental group, excluded because of non-tunnelled catheters.
Vary specific group with high incidence of infection, not representing the group aimed at in this Cochrane review.

ADDITIONAL TABLES

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

<table>
<thead>
<tr>
<th>Item ID</th>
<th>Description</th>
<th>Implementation</th>
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<tbody>
<tr>
<td>patient selection</td>
<td>Were the eligibility criteria specified?</td>
<td>Patient inclusion/exclusion criteria must have been described appropriately according to the reviewer</td>
</tr>
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</table>

Note: all criteria were scored yes(+), no(-) or don't know
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

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

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

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 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 for 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)

<table>
<thead>
<tr>
<th>Reference</th>
<th>b1</th>
<th>b2</th>
<th>c</th>
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<tbody>
<tr>
<td>Vassilomaniakis 1995</td>
<td>+</td>
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</table>

180
Ranson 1990  +  +  +  +  +  +
Lim 1993  +  -  +  +  +  +
Barriga 1997  +  +  +  +  +  +
Rackoff 1995  +  +  +  +  +  +
Schwartz 1990  +  +  +  +  +  +
Henrickson 2000  +  +  +  +  +  +
Ljungman 1997  +  -  -  -  -  +

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

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Table 04 Abstracts congresses

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<th>ICAAC</th>
<th>ASCO</th>
<th>MASCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 O-54: Retrospective, 149 ports in 135 patients 8% infected, CNS majority of infections.</td>
<td>1995 J1: prospective 30 adults CVC inserted CNS isolated from 5 out of 30 catheter tips.</td>
<td>1995: 1723: Risk of sepsis associated with CVC in children with leukemia. The relative risk of fever and neutropenia is increased OR=1.3 (1.00-1.69)</td>
<td>1996 129: retrospective: In 101 patients 97 single lumen and 7 double lumen access ports implanted. 6 cases of infection.</td>
</tr>
<tr>
<td>1997 P-227: Retrospective. 51 catheters in 37 patients Clinically significant infection 12,2 per 1000 catheter days (CNS)</td>
<td>1995 J2: retrospective. 984 catheters in 837 patients. Infection 12.7% 1.26 per 1000 catheter days.</td>
<td>1995: 1791: complications of CVC. 273 devices The rate of catheter related infections was 15.8% (95% CI 11.6-20.6%) Most infections in leukemic patients who were neutropenic at time of insertion.</td>
<td>1996 56: descriptive: skin and catheter hub major sources of infection. CNS can be treated without catheter removal. Staph. aureus complications resulted in catheter removal.</td>
</tr>
<tr>
<td>1997 O-65: prospective randomized trial. Telcoptalin induction ALL 25 patients, 25 patients no telcoptalin, no difference in gram-positive organisms</td>
<td>1995 J10: 151 patients were randomized to new hub connector n=78 or standard connector n=73 CNS infection exp arm 4% control arm 16%</td>
<td>1997: 292: Trends in bacteraemia in BMT patients. In 5 years there were 277 bacteraemic patients. 254 Gram positive most often CNS (53%)</td>
<td>1999: O-35: retrospective. 23 patients positive Staph. aureus. 22 had CVD, 195 patients CNS positive, 135 had a CVD. Study meant to give insight into distribution of Staphylococcal infections.</td>
</tr>
</tbody>
</table>
complications 2.8 per 1000 catheter days. CRS in 10 cases, majority CNS infections. devices were removed. 7 due to infections.

bacteraemia had Taurolin installed. Clinical signs of bacteraemia disappeared, blood cultures negative.

1998 U-98: retrospective 502 catheters in 388 pts, 1996 J-103: continuous peroperative complications in leukemia 2.5% and in solid tumours 0.8%

2000 P-313: retrospective 32 catheters CRS 8.2 per 1000 catheter days, in 55% CNS.

References to studies included in this review

Barriga 1997 (published data only)

Henrickson 2000 (published data only)

Lim 1993 (published data only)

Ljungman 1997 (published data only)

Rackoff 1995 (published data only)

Ranson 1990 (published data only)

Schwartz 1990 (published data only)

Vassilomanakis 1995 (published data only)
References to studies excluded from this review

Carratala 1999


Ocete 1998


Raad 1998


Additional references

Cochrane Handbook


CPAC 1990


Darouiche 1999


Farr 1995


Groeger 1993


Ingram 1991


Mermel 2001


Press 1984


Salzman 1995


Shaul 1998


Tuider 1997


Wurzel 1988
GRAPHS

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<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size (95% CI)</th>
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<td>01 vancomycin versus control</td>
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<tr>
<td>02 catheter related sepsis</td>
<td>4</td>
<td>252</td>
<td>Odds Ratio (Fixed) 95% CI</td>
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<td>02 vancomycin flush versus heparin flush</td>
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<td>01 catheter related sepsis</td>
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<td>275</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>0.35 [0.16, 0.77]</td>
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<td>03 vancomycin/teicoplanin versus control</td>
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<td>01 analysis of vancomycin/teicoplanin prior to</td>
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<td>187</td>
<td>Odds Ratio (Fixed) 95% CI</td>
<td>0.46 [0.24, 0.91]</td>
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<td>insertion catheter excluding Liungman study,</td>
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<td>outcome CRS</td>
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</table>

COVER SHEET

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

Reviewer(s)
van de Wetering MD, van Woensel JBM

Contribution of reviewer(s)
contact reviewer: M.D. van de Wetering- reference search, article retrieval, assessment of studies for inclusion/exclusion, data-extraction analysis, manuscript preparation.
co-reviewer: J. van Woensel - Reference search, assessment of studies for inclusion/exclusion, data extraction, reviewing of manuscript.

Issue protocol first published
2001/4

Issue review first published
2003/2

Date of most recent amendment
31 July 2001
Prophylactic antibiotics or catheter flushing with vancomycin and heparin may help cancer patients at high risk of catheter-related infections.

Patients with cancer often need to be given drugs and other treatments intravenously, so are frequently fitted with long-term tunneled catheters. Infections sometimes occur. Evidence from randomised controlled trials shows it...
may be useful to give prophylactic antibiotics prior to catheter insertion or to flush the catheter with combined vancomycin and heparin, but microbial resistance may occur unless this practice is limited to high-risk patients.

**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:** Human

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**GRAPHS**

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

<table>
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<tr>
<th>Study</th>
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Test for heterogeneity chi-square=6.57 df=3 p=0.0988
Test for overall effect=-1.85 p=0.08

Favours treatment  | Favours control

.1  .2  1  5  10

186
### 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

<table>
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Test for heterogeneity chi-square=3.19 df=3 p=0.3528
Test for overall effect=-2.61 p=0.009

Favours treatment Favours control

### Review: Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients
### Comparison: 03 vancomycin/bacloplatin versus control
### Outcome: 01 analysis of vancomycin/bacloplatin prior to insertion catheter excluding Liiungman study, outcome CR5

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Test for heterogeneity chi-square=4.43 df=2 p=0.1093
Test for overall effect=-2.23 p=0.03

Favours treatment Favours control