Prediction and prevention of infectious complications in children with cancer

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Chapter 5

Prophylactic antibiotics for preventing early Gram-positive central venous catheter infections in oncology patients, a Cochrane systematic review

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Abstract

Background: Long-term tunnelled central venous catheters (TCVC) are increasingly used in oncology patients. Despite international guidelines on sterile insertion, appropriate catheter maintenance and use, infections are a frequent complication of TCVC. These infections are mostly caused by Gram-positive bacteria. The aim of this review is to evaluate the efficacy of antibiotics in the prevention of early TCVC infections.

Methods: We searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Register up to July 2003. Reference lists from relevant articles were scanned and conference proceedings were hand searched. Outcome parameters: the main outcome was documented Gram-positive bacteremia in patients with a TCVC. Selection criteria: randomized controlled trials (RCT) evaluating prophylactic antibiotics prior to insertion of the TCVC, and RCT evaluating the combination of an antibiotic and heparin to flush the TCVC. Both pediatric and adult oncology patient trials were selected. Data collection & analysis: the trials identified were assessed and the data extracted independently by two reviewers and a quality assessment was carried out.

Main results: We included 9 trials with a total of 529 patients. Four trials reported on vancomycin/teicoplanin prior to insertion of the TCVC compared to no antibiotics. Five trials studied flushing of the TCVC with a vancomycin/heparin solution compared to heparin flushing only. Antibiotics prior to insertion of the catheter compared to no antibiotics showed a significant reduction in the number of Gram-positive TCVC infections with an Odds ratio of 0.46 (95% confidence interval 0.24-0.91). Flushing the TCVC with antibiotics and heparin compared to only heparin significantly decreased the number of TCVC infections with an Odds ratio of 0.43 (95% CI 0.21-0.87).

Conclusion: Both interventions (antibiotics prior to insertion of the catheter and flushing of the catheter with the combination of an antibiotic and heparin) significantly reduced the incidence of Gram-positive infections in TCVC. In oncology patients who need a TCVC and are at high risk for Gram-positive infections it is justified to use the above interventions.
Introduction

Patients treated for cancer need adequate venous access because of the frequent use of chemotherapy, requirements of intravenous fluids and blood products. To limit discomfort of short-term venous access long-term tunneled central venous catheters (TCVC) are used in more than two thirds of both pediatric and adult cancer patients. However, the use of TCVC is limited by the risk of blood clot formation as well as infectious complications. The risk of infection ranges from 1.4 to 2.2 infections per 1000 catheter days. This corresponds to about one third of patients experiencing an episode of infection while having the TCVC in place. The risk of infection is greatest during the first 100 days after placement of the TCVC. In the majority of the cases the causative agents are Gram-positive organisms (70%), followed by Gram-negative organisms (15%), and fungi or anaerobic organisms (both 7%).

Early catheter infections (defined as infections that develop within 45 days after placement of the catheter) are mostly due to organisms from the skin at the insertion site, whereas after 45 days the catheter hub becomes a far more important source of infection. 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. Despite international guidelines on catheter insertion and handling, developed by the Hospital Infection Control Practices Advisory committee, about 15-20% of patients with a TCVC develop early infections. It has been shown that the incidence of Gram-positive infections is increasing, mainly coagulase negative staphylococci. Therefore, prophylactic antibiotics covering Gram-positive organisms might decrease catheter-related infections. Antibiotics can be introduced for this goal 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.

Several trials have evaluated the beneficial effects of these strategies, however results have been conflicting. Therefore we performed a Cochrane systematic review, to assess the effectiveness of prophylactic antibiotics to reduce early Gram-positive catheter related infections. The importance of this time-span allows us to cover the induction period of chemotherapy. The time-period that many manipulations of the TCVC are necessary because of the intensity of the chemotherapy. Both internal and external tunnelled central venous catheters could be included in the review.

Methods

Search

A literature search was performed using MEDLINE and EMBASE from 1966-2003 and the CENTRAL(Cochrane library) issue 2, 2003. We used the following terms:
Broviac OR Port-a-cath OR Port OR Portacath OR Hickman OR exp catheterization,central venous OR Tunnelled central venous catheter
AND:
prophylactic antibiotics OR vancomycin OR teicoplanin OR antibiotics
AND exp oncology OR cancer OR malignancy OR neoplasm OR leuk(a)emia OR carcinoma
AND
infection.exp OR infection prevention OR infection control OR bacter(a)emia OR sepsis
AND
The sensitive methodology filter of the Cochrane handbook for RCT
Additional trials not registered in MEDLINE or the Cochrane Library were identified by scanning the reference lists of the found articles.

Inclusion and exclusion criteria
We included all randomized controlled trials (RCTs) that compared antibiotics to no antibiotics prior to insertion of the catheter, and all RCT that compared the antibiotic/heparin flush technique to flushing with heparin only to reduce Gram-positive infections related to the catheter. Trials were included considering oncology patients (both adults and children) undergoing chemotherapy who had a tunneled central venous catheter inserted, and who were likely to become neutropenic. In reviewing the papers both adults and children were included, as the adult patient is comparable to the pediatric patient in the development of TCVC infections. We excluded trials if patients had an infection prior to insertion of the catheter, or if they received continuous intravenous antibiotics before and after insertion of the catheter.

Data-extraction
Two reviewers (MvdW, JW) independently abstracted the following data: year of publication, characteristics of the patients, including age and type of malignancy, type of catheter inserted, number of patients in each arm. Life-span of the catheter, number of catheter related infections, number of catheter related bacteremia's, time to first catheter related infection, culture method (quantitative or qualitative), type of organism cultured (Gram-positive, Gram-negative, fungal), outcome of the infection that was defined as improvement of the patient and clearing of the organism on antibiotics only or removing the catheter. Definitions used for catheter related infections were defined according to the Hospital Infection Control guidelines i.e. isolation of
the same organism from percutaneous blood culture and from one of the following: exudate at
the catheter exit site, a semiquantitative catheter segment culture (requiring removal of the
catheter), or a blood-culture from the TCVC lumen with a recovery of at least five fold higher
colony count than from the peripheral blood. Catheter-related infection could also be defined
when there was a temporal succession of catheter flushing, onset of chills, fever and a positive
blood culture, or if the culture from the TCVC was positive 2 hours earlier than the culture from
the peripheral blood, this method is called differential time to positivity and makes use of
continuous blood-culture monitoring. A tunnel infection was defined if a spreading cellulitis
was present over the tunnel tract of the subcutaneous tunnelled catheter. There are signs of
inflammation and tenderness to palpation over the tunnel tract.
Disagreements were resolved between the 2 reviewers by discussion.

Quality assessment
The quality-list of Tulder 13 was used. The Tulder criteria consist of 17 items assessing both
internal and external validity, including allocation generation and concealment, blinding of the
patient and of the outcome-assessor, method of analysis (intention to treat), number of drop-
outs, follow-up including the end-point of the study and description of the statistics.
Outcome and analyses:
The primary outcome was bacteremia due to central venous catheter infections. We measured
the number of patients with catheter-related bacteremia compared to the total number of
patients. If necessary these data were extracted from the raw data. The secondary outcome
was the number of tunnel-infections reported. The trials were divided into two groups which
were analysed separately.
1: prophylaxis of antibiotics at insertion of the central venous catheter versus no prophylaxis
2: vancomycin/heparin flush technique versus only heparin flush technique
The analyses performed were:
1: The number of patients with catheter-related bacteremia in the group who received antibiotics
prior to insertion compared to the number of patients with catheter-related bacteremia in
the group who did not receive antibiotics.
2: The number of patients with catheter-related bacteremia in the group flushing the catheter
with a vancomycin/heparin solution compared to the number of patients with catheter-
related bacteremia in the group flushing the catheter only with heparin.

Statistics
Dichotomous data were analyzed calculating the Odds ratio for each trial with the uncertainty
in each result being expressed using 95% confidence intervals (CI). A standard meta-analysis
was performed where all individual trials were weighted by the inverse of the variance. (The
software used was The Cochrane Reviewmanager 4.1) Throughout the review a fixed effect
model was used. Trials were pooled if there was clinical homogeneity, in therapy given and outcome looked at. A random effect model was used if the included trials were heterogenous in design, intervention and study population. Heterogeneity (degree of difference between the results of different trials) was calculated with the chi square test of heterogeneity. The outcome considered was the number of patients with catheter-related bacteremia compared to the total number of patients. Pooling was only considered if ≥ 3 trials were present in the same group.

Results

We scanned the abstracts of 33 articles retrieved from the literature search. A total of 14 trials were evaluated for inclusion, of which 5 were excluded (Table 3). Three trials were excluded because the results were analysed retrospectively 14-16 and 2 because non-tunneled catheters were studied 17,18 (Table 3). Of the 9 trials included, 4 addressed the administration of antibiotics prior to insertion of the catheter (Table 1) 11,19,21, and 5 addressed flushing the catheter with the combination of vancomycin and heparin (Table 2) 22-26. In total 588 patients were included in the 9 trials. Four trials were done in adults (n=252) 11,19,21, three in children (n=192) 24-26, and two combined children and adults (n=144) 22,23. In all trials single or double lumen external tunneled central venous catheters were used. Seven trials included both patients with solid tumours and hematological malignancies and in 2 trials only patients with hematological malignancies were included 11,19. In 7 trials qualitative culture methods were used to define catheter related bacteremia, in 2 quantitative methods 24,26. No additional trials were obtained from the conference proceedings.

Quality-assessment

In 5 trials the method of blinding was adequately described, whereas in 4 trials investigators were not adequately blinded 11,19,21,25 (Table 1 and 2). In 6 trials randomization procedures were adequate, in 3 semi-randomization methods were used. In one these patients were initially randomised to vancomycin treatment or not, but later all patients received treatment 21. Therefore we only used the first part of the study (i.e. when randomization was performed) in our analysis. In the second study an open randomization was performed and the study was stopped at interim analysis 19. The third study did not specify how patients were randomized 11. In one study no intention to treat analysis was applied 20.

Outcome and analysis

Intravenous antibiotics at TCVC insertion

Of the 4 trials that evaluated the efficacy of antibiotics prior to the insertion of the TCVC, 2 studied teicoplanin 11,19 and 2 studied vancomycin before insertion of the catheter 11,19. Since we aimed to review the prevention of Gram-positive TCVC infections and both vancomycin and
Prophylactic antibiotics for preventing early Gram-positive central venous catheter infections in oncology patients

teicoplanin are glycopeptides, that are equally active against Gram-positive bacteria we felt it was acceptable to pool the data of these 4 trials.

In all trials the number of patients, the number of TCVC’s inserted as well as the number of catheter-related bacteremia’s in the treatment group and the control group were given. The follow-up time of all trials did not exceed 30 days. Since there was heterogeneity in the patient groups of the trials (p=0.06) mainly caused by the study of Ljungman et al., who studied a large group of allogenic bone-marrow transplant patients, who were already given TMP/SMZ (trimethoprim/sulphamethoxazole) one week prior to insertion of the catheter, we analysed the pooled data after exclusion of this study. This resulted in a more homogenous group of trials with a p-value for test of heterogeneity of 0.11. There were 17 patients with a Gram-positive bacteremia in the group who received prophylaxis (n=95) and in the control group there were 30 patients with a Gram-positive bacteremia (n=92). There was a significant benefit for the use of antibiotics prior to insertion of the catheter. The pooled OR was 0.46 (95% CI 0.24-0.91) (Fig 1).

No analysis on decreasing tunnel-infections was done, since only 2 trials reported on this item. In the first study by Ranson et al., patients were stratified in hematological patients and patients with solid tumours. In the first group vancomycin resulted in a reduction of 10% in the occurrence of tunnel-infections, whereas in the latter group no tunnel-infections occurred. In the second trial trial of Lim the same trend was observed, with an absolute reduction of 7%.

Figure 1: Pooled data of the three trials administering antibiotics prior to insertion of the catheter. The number of patients in the treatment group is presented with a Gram-positive catheter related infection and the number of patients with a catheter related infection in the control-group is given. The OR and 95% CI are represented.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranson 1990</td>
<td>9/36</td>
<td>9/36</td>
<td>26.58</td>
<td>1.00</td>
<td>[0.34, 2.91]</td>
</tr>
<tr>
<td>Lim 1993</td>
<td>7/43</td>
<td>16/45</td>
<td>51.55</td>
<td>0.35</td>
<td>[0.13, 0.97]</td>
</tr>
<tr>
<td>Vassilomaniakis 1995</td>
<td>1/16</td>
<td>5/11</td>
<td>21.88</td>
<td>0.08</td>
<td>[0.01, 0.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>95</td>
<td>92</td>
<td>100.00</td>
<td>0.46</td>
<td>[0.24, 0.91]</td>
</tr>
</tbody>
</table>

Total events: 17 (Treatment), 30 (Control)

Test for heterogeneity: Chi² = 4.43, df = 2 (P = 0.11)

Test for overall effect: Z = 2.23 (P = 0.03)

0.1 0.2 0.5 1 2 5 10  
Favors treatment Favors control
Table 1: Trials using antibiotics prior to insertion of the catheter

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patients</th>
<th>Intervention</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim 1993&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Adult oncology patients Hematological disorders (n=88)</td>
<td>Teicoplanin 400 mg within 2 hours before insertion catheter versus control</td>
<td>B</td>
</tr>
<tr>
<td>Ljungman 1997&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Adult oncology patients BMT and leukaemia (n=66)</td>
<td>Teicoplanin 400 mg within 2 hours before insertion catheter and 24 hours after insertion versus control</td>
<td>B</td>
</tr>
<tr>
<td>Ranson 1990&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Adult oncology patients 2 groups (n=48) acute leukaemia and BMT (n=50) solid tumour pts</td>
<td>Vancomycin 500 mg 30 min prior to insertion and 500 mg 2 hours after insertion versus placebo</td>
<td>A</td>
</tr>
<tr>
<td>Vassilomaniakis 1995&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Adult oncology patients (n=30) solid tumours, (n=10) leukemia/lymphoma</td>
<td>Vancomycin 500 mg within 1 hour prior to insertion catheter and 500 mg 6 and 12 hrs later versus control</td>
<td>B</td>
</tr>
</tbody>
</table>

Table 2: Trials using the vancomycin/heparin flush technique

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patients</th>
<th>Intervention</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barriga 1997&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Adult and pediatric pts Mainly leukaemia (n=83)</td>
<td>Daily flushing of the catheter with 5 ml V/H solution (vanco-25 mcg/ml, hep-25U/ml) versus only H solution</td>
<td>A</td>
</tr>
<tr>
<td>Daghistani 1996&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Adult and pediatric pts Mainly leukaemia (n=61)</td>
<td>Daily flushing of the catheter with 5 ml V/A/H (vanco 25 mcg/ml, hep 100 U/ml, amikin 25mcg/ml) solution versus only H solution</td>
<td>A</td>
</tr>
<tr>
<td>Henrickson 2000&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Pediatric oncology pts Leukaemia/ BMT and solid tumours(n=126)</td>
<td>Daily flushing of the catheter with 5 ml V/H solution (vanco 25 mcg/ml, hep 10 U/ml) versus only H solution</td>
<td>A</td>
</tr>
<tr>
<td>Rackoff 1995&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Pediatric oncology patients, leukaemia, lymphoma and neuroblastoma (n=55)</td>
<td>Daily flushing of the catheter with 3 ml s V/H solution (vanco 25 mcg/ml, hep 100 U/ml) versus only H solution</td>
<td>A</td>
</tr>
<tr>
<td>Schwartz 1990&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Pediatric oncology patients mainly leukaemia (n=45)</td>
<td>Daily flushing of the catheter with 5 ml s V/H solution (vanco 25 mcg/ml, hep 10 U/ml) versus only H solution</td>
<td>A</td>
</tr>
</tbody>
</table>

Heparin/vancomycin flush technique after CVC insertion

The data of the 5 trials using vancomycin/heparin flush method compared to only heparin flush method (control) were pooled. All these trials were done in pediatric oncology patients. In this group of trials the follow-up time was longer than in the previous group. The flush method was used throughout the life-span of the catheter and, the mean time the CVC was inserted was 250 days per patient in all trials. There was no heterogeneity in the patient groups included.
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<table>
<thead>
<tr>
<th>Blinding</th>
<th>Intention to treat</th>
<th>Treatment Group Gram+CRS</th>
<th>Control group Gram+CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>A</td>
<td>7/43</td>
<td>16/45</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>2/33</td>
<td>0/32</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>9/36</td>
<td>9/36</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>1/16</td>
<td>5/11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blinding</th>
<th>Intention to treat</th>
<th>Treatment Group Gram+CRS</th>
<th>Control group Gram+CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>7/39</td>
<td>16/44</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>3/34</td>
<td>2/30</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>1/28</td>
<td>7/64</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>2/28</td>
<td>1/27</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>0/21</td>
<td>6/24</td>
</tr>
</tbody>
</table>

(p=0.32). In the patients who received flushing of the catheter with an antibiotic and heparin there were 13 patients with a Gram-positive bacteremia (n=150) and in the control group there were 32 patients with a Gram-positive bacteremia (n=189). Using the fixed model this resulted in a significant reduction of Gram-positive catheter related bacteremia’s using the flush method. An OR of 0.43 (95% CI 0.21-0.87) was found (Fig 2).

As it is of interest to know the catheter related infection rate in the first 30 days after insertion
Table 3: Excluded trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Sibai 1987</td>
<td>146 patients with malignant disease received 160 Hickman catheters</td>
<td>70 patients received prophylactic antibiotics during and after insertion of the catheter. 91.5% of these pts received vancomycin. catheter-infection-rate dropped from 0.50 to 0.25 per 100 days</td>
</tr>
<tr>
<td>Dawson 2000</td>
<td>143 pediatric oncology patients, 176 TCVC</td>
<td>Intervention: Cephalothin 100 mg/kg iv or vancomycin 20-25mg/kg prior to insertion. Rate of infections &lt;30 days dropped 40%</td>
</tr>
<tr>
<td>Rubie 1994</td>
<td>163 pediatric patients with cancer had 180 subcutaneous ports inserted</td>
<td>Because of increased CNS catheter related infections care and maintenance of the ports was changed from only flushing with heparin to a V/H solution (50 mcg/ml V and 100U/ml H). The staphylococcus sepsis rate dropped from 31% to 4%</td>
</tr>
<tr>
<td>Carratella 1999</td>
<td>120 adult oncology patients mainly leukaemia patients who had non-tunnelled catheters inserted</td>
<td>When patients were neutropenic the treatment group received a V/H solution (25 mcg/ml V,10U/ml H.2.5 ml) dwell for 1 hour every second day. Control group received only heparin solution The catheter related sepsis rate dropped from 7% to 0%</td>
</tr>
<tr>
<td>Raad 1998</td>
<td>26 patients with melanoma on IL-2 treatment received non-tunnelled catheters</td>
<td>Prophylactic antibiotics given were novobiocin 500 mg + rifampin 300 mg. Catheter related, bacteremia decreased from 41% to 6%</td>
</tr>
</tbody>
</table>

Figure 2: Pooled data of the five trials flushing the catheter with an antibiotic and heparin. The number of patients in the treatment group is presented with a Gram-positive catheter related infection and the number of patients with a catheter related infection in the control-group is given. The OR and 95% CI are represented.

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz 1990</td>
<td>0/21</td>
<td>6/24</td>
<td>23.53 0.07 [0.00, 1.26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rackoff 1995</td>
<td>2/28</td>
<td>1/27</td>
<td>3.74 2.00 [0.17, 23.44]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daghistani 1996</td>
<td>3/34</td>
<td>2/30</td>
<td>7.67 1.35 [0.21, 8.71]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barriga 1997</td>
<td>7/39</td>
<td>16/44</td>
<td>48.81 0.38 [0.14, 1.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henrickson 2000</td>
<td>1/28</td>
<td>7/64</td>
<td>16.26 0.30 [0.04, 2.58]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>150</td>
<td>189</td>
<td>100.00 0.43 [0.21, 0.87]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 13 (Treatment), 32 (Control)
Test for heterogeneity: Chi² = 4.67, df = 4 (P = 0.32)
Test for overall effect: Z = 2.36 (P = 0.02)

of the catheter we attempted to extract these data from the raw data. Only two trials allowed us to deduct these figures from the Kaplan-Mayer curves given. Schwartz et al 26 showed 1 bacteremic episode in the control-group, none in the treatment group in the first 50 days. In addition Henrickson et al 24 showed 7 bacteremic catheter related episodes in the control-group compared to one in the treatment group.
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Reason for exclusion

Antibiotic use and duration at the discretion of the attending physician, results retrospectively analyzed.

No randomization done. Intervention period was compared to pre-intervention period

Not randomized. A change of policy over time Results retrospectively analyzed.

Non-tunneled catheters used And a flush solution that was allowed to dwell

Non-tunneled catheters and the antibiotics were administered within 48 hours of receiving the central line, not before insertion

Discussion

Infections due to Gram-positive organisms in oncology patients have increased over the past years. Colonization of central venous catheters with Gram-positive organisms can occur at the insertion-site and these organisms can become invasive when patients are neutropenic and immune suppressed. Therefore preventive strategies must reduce colonization of the insertion site and decrease spread both extraluminal from the skin and intraluminal from the hub to the catheter tip.\textsuperscript{10} The main preventive strategy remains adequate education in care and maintenance of the catheter. Education of parents and care-givers about the handling of the catheters has been shown to reduce catheter-related infections.\textsuperscript{27,28} In addition it has been shown that the number of care takers that manipulates the TCVC should be minimized in order to reduce infectious complications. The most important preventive measure is careful handwashing\textsuperscript{9}. To reduce the extraluminal spread of Gram-positive organisms via the insertion-site antibiotic prophylaxis at the time of catheter-placement has been evaluated in a number of trials. Because of controversial results of these trials however, this has not lead to recommendation of the use of prophylactic antibiotics in most guidelines.\textsuperscript{5,9,10} These guidelines however have been based on heterogeneous patients groups including neonates and patients who are on total parenteral nutrition for other reasons than cancer. In this systematic review we only included trials in oncology patients in need of a tunneled central venous catheter inserted for chemotherapy,
bloodproducts and fluids. Study design and methodology of the 4 included trials were sufficient and of these the data of 3 trials could be pooled. We found a significant reduction (OR = 0.46: 95% CI 0.24-0.91) of Gram-positive catheter related infections with the use of vancomycin or teicoplanin before insertion of the catheter. This OR indicates that in a unit with a baseline incidence of tunneled catheter related sepsis (TCRS) that ranges from 10% to 30% the number needed to treat (NNT) to prevent 1 TCV infection ranges from 10 to 18 patients. It is justifiable to administer antibiotics prior to insertion of the catheter in high risk patients. The short prophylaxis will limit the emergence of resistant strains.

To reduce the intraluminal spread of Gram-positive organisms via the hub of the catheter the effect of antibiotic flushing of the catheter was evaluated. The most important step is the care in accessing the hub. The hub should be disinfected before access. More frequent catheter-hub manipulation increases the risk of contamination. Therefore, it is recommended to minimize the number of times per day to handle the catheter-hub. Flush solutions should contain heparin to prevent thrombotic events. The efficacy of adding vancomycin to the flush solution to decrease Gram-positive catheter related infections in oncological patients has not been clearly established so far. In vitro trials have proven that the combination of heparin and vancomycin 25 mcg/ml is stable and active. In the second part of this systematic review we aimed to answer the question if the vancomycin/heparin flush technique can decrease Gram-positive catheter related infections in oncology patients with a tunneled CVC.

Design and methodology of the 5 included trials that have evaluated this were sufficient to pool and analyze the data. We found that vancomycin/heparin flush technique is effective in reducing TCRS (OR 0.43, 95% CI 0.21-0.87) The number needed to treat to prevent 1 catheter-related sepsis is 13 with an infection rate of 30% and 23 with an infection rate of 10%. The fear for resistant strains does not seem justified as the dose of vancomycin is so low that it will not distribute systemically. The possibility exists to develop super infections with Gram-negative organisms and fungal organisms, therefore the advice of the authors is to take the TCRS rate into account before considering to flush the tunneled central venous catheter with an antimicrobial agent.

Implications for practice

We feel that a selection of patients with a high base-line risk for infection (i.e. hematologic 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 the use of antibiotics prior to insertion of the central venous catheter, or flushing the central venous catheter with a combination of an antibiotic and heparin.
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Reference List


