Thrombotic and infectious complications of central venous catheters in patients with hematological malignancies

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Central venous catheters (CVCs) have considerably improved the management of patients with hematological malignancies, by facilitating chemotherapy, supportive therapy and blood sampling. Complications of insertion of CVCs include mechanical (arterial puncture, pneumothorax), thrombotic and infectious complications. CVC-related thrombosis and infections are frequently occurring complications and may cause significant morbidity in patients with hematological malignancies. CVC-related thrombosis and infections are related and can therefore not be seen as separate entities. The incidence of symptomatic CVC-related thrombosis had been reported to vary between 1.2 and 13.0% of patients with hematological malignancy. The incidence of CVC-related bloodstream infections varies between 0.0 and 20.8%. There is need for a specific approach regarding diagnosis and treatment of CVC-related thrombosis and infection with specific attention to the preservation of the catheter. Since data on CVC-related infections and thrombosis in hematological patients have been obtained mainly from retrospective studies of small sample size, prospective, randomized studies of prophylactic measures concerning CVC-related thrombosis and infection are warranted.

Key words: central venous catheter-related infections, central venous catheter-related thrombosis, hematological malignancies

introduction

Central venous catheters (CVCs) are frequently used in patients with a hematological malignancy in order to administer chemotherapy, stem cell infusions, blood products, medication, parenteral hyperalimentation as well as for blood sampling.

Reported complications consist of mechanical complications during or directly after the insertion (arterial puncture, hematoma and pneumothorax) and long-term complications such as infection and thrombosis [1]. CVC-related thrombosis and infections result in patient morbidity, significant increases in the length of hospitalization and medical care costs [2, 3].

Many studies have addressed the incidence and associated risk factors of CVC-related infections and thrombosis in patients with solid tumors, but only few data are available on hematological patients. These patients may differ from patients with solid tumors with respect to more severe and prolonged thrombocytopenia and leucopenia [4, 5]. Thrombocytopenia is associated with a trend for reduced risk of thrombotic complications [4], but might increase the risk of bleeding and perhaps contraindicate the use of antithrombotic prophylaxis. Patients with severe and sustained neutropenia are at high risk of infectious complications.

Since CVC-related thrombosis and CVC-related infections cannot be seen as separate entities, this review focuses on the epidemiology, pathogenesis, diagnosis, prevention and treatment of both CVC-related thrombosis and CVC-related infections in patients with a hematological malignancy.

CVC-related thrombosis

CVC-related thrombosis may be asymptomatic and demonstrated by screening diagnostic imaging or present with symptoms. An asymptomatic CVC-related thrombosis is found in 1.5–34.1% of patients with a hematological malignancy (see Table 1). About two-thirds of all thromboses are clinically silent. The presence of asymptomatic thrombosis increases the risk of developing symptomatic thrombosis 7-fold compared with negative Doppler ultrasound findings (RR 6.8; 95% CI 2.3–20.2) [6].

Symptomatic CVC-related thrombosis is defined as thrombosis objectified by diagnostic imaging upon overt symptoms and signs and is found in 1.2–13.0% of patients with a hematological malignancy (see Table 1).
The observed incidence of CVC-related thrombosis varies considerably among the different studies, reflecting differences in type of CVCs, study design and duration, study population and sensitivity of the examination procedures.

The incidence of CVC-related thrombosis seems to be higher in older studies compared with more recent studies which may be explained by improvements in CVC insertion technique and/or improvements in the biocompatibility of the CVCs. Currently used CVCs are composed of silicon or polyurethane and are less often associated with local thrombosis than the CVCs made of polyethylene [7].

Symptoms of CVC-related thrombosis vary widely and consist of swelling or pain of arm/neck/head, headache, numbness of the extremity, erythema of the extremity, phlegmasia, venous distension and jaw pain. The median number of days between line insertion and CVC-related thrombosis is 16–23 [4, 6, 8–10].

CVC-related thrombosis may have serious complications. The catheter is located deep in the mediastinum and thrombosis may be clinically silent until late in its course. Pulmonary embolism occurs in 15–25% of patients with a symptomatic CVC-related thrombosis [11, 12], postphlebitic syndrome arises in 14.8% of patients with an upper-extremity deep vein thrombosis [13] and there is an increased risk of CVC-related infection [14–16].

Asymptomatic thrombosis may be clinically important. A strong association between asymptomatic CVC-related thrombosis and catheter complications like occlusion of the CVC and CVC-related infection has been reported [14, 15].

Pathogenesis and risk factors for CVC-related thrombosis

The pathogenesis of CVC-related thrombosis is multifactorial. Vessel damage, a major component of Virchow’s triad, plays an important role. Vessel damage can be caused by a variety of factors such as mechanical injury of the venous endothelium by the catheter during insertion, the number of vein punctures [17] and irritation of the vessel wall by chemotherapeutic agents [18, 19].

After the insertion of a CVC, a fibrin sheath can form around the CVC. The development of a CVC-related sleeve has been reported to occur in up to 47% of patients with CVCs [20, 21]. The catheter sleeve is an adherent coating of fibrin and collagen that may envelope the CVC. This fibrin sleeve is in itself a benign complication, but can cause catheter malfunction, facilitates the development of infection and may lead to mural thrombosis. Mural thrombosis can cause subtotal stenosis or occlusion of the venous lumen and may lead to clinically manifest thrombosis or associated complications. Mural thrombosis is often found near the entry site of the CVC into the vessel or at the junction of the large veins.

There are several risk factors for CVC-related thrombosis, such as CVC biocompatibility, catheter tip position, side of insertion, puncture site of insertion, thrombophilic abnormalities and CVC-related infections. The position of the catheter tip in the vascular system is an important risk factor for the development of CVC-related thrombosis. The incidence of CVC-related thrombosis is higher...
in patients in whom the catheter tip is placed in the innominate vein or proximal superior vena cava as compared with the distal superior vena cava/right atrial junction [22, 23]. Tesselaar et al. [24] showed a 2.6-fold higher risk when the catheter was located in the superior vena cava compared with the right atrium. The risk of CVC-related thrombosis was 8-fold higher for arm ports than for chest ports.

The side of insertion and puncture site of insertion are other important risk factors. Tesselaar et al. [24] showed left-sided placement to be associated with a 3.5-fold increased risk for CVC-related thrombosis compared with right-sided placement. In children with acute lymphoblastic leukemia, left-sided CVCs were also associated with an increased incidence of CVC-related thrombosis. Patients with a CVC in the subclavian vein had a 44% (22 of 50) incidence of CVC-related thrombosis compared with a 20% (7 of 35) incidence in patients with a jugular vein CVC ($P = 0.025$) [25]. A possible explanation for all this lies in the anatomy of the upper body venous system. In comparison with the right side, the left brachiocephalic vein is longer and has a more horizontal course, leading to a sharper angle into the superior vena cava. Compared with jugular CVCs, subclavian CVCs follow an even sharper curve into the central venous system, resulting in wall adherence. The CVC enters where the vein passes between the clavicle and the first rib, which may cause vein compression and kinking of the CVC [25].

Whether the factor V Leiden mutation should be regarded as an increased risk factor is still not established. In one study patients with the factor V Leiden mutation had a 7.7-fold increased risk of CVC-related thrombosis after an allogeneic bone marrow transplantation. [26]. Van Rooden et al. [27] also found an increased relative risk of 2.6 (CI 95% 1.9–3.8) for CVC-related thrombosis in the factor V Leiden mutation group. Two other studies, however, showed no significant contribution of factor V Leiden on the development of CVC-related thrombosis [24, 28].

CVC-related infections contribute to the pathogenesis of thromboembolic complications [16, 29, 30]. Van Rooden et al. reported in a prospective study in a population of hematological patients an increased risk of CVC-related thrombosis in patients with a CVC-related infection compared with those without infection (relative risk 17.6; 95% CI 4.1–74.1) [29].

diagnosis of CVC-related thrombosis

Contrast venography is considered the gold standard in detecting upper limb-venous thrombosis (UL-VT). Routine application, however, is limited due to its invasive nature and the use of a contrast medium. Compression ultrasound (CUS) with Doppler and color imaging is more easily applicable for the detection of thrombosis and is therefore more widely used.

In a systematic review of studies on the diagnosis of suspected UL-VT a sensitivity of CUS ranging from 56% to 100% and a specificity ranging from 94% to 100% has been reported [31]. CUS in experienced hands can be regarded as a sufficient diagnostic tool in patients in whom a CVC-related thrombosis is suspected clinically. If the CUS is negative in a patient with a high clinical suspicion of CVC-related thrombosis, a contrast venography should be performed.

is antithrombotic prophylaxis indicated?

It is still a matter of debate whether antithrombotic prophylaxis in hematological patients with a CVC is indicated and if so, which type of drug is recommended. It is estimated that currently <10% of hemato-oncological patients with CVCs receive any kind of systematic prophylaxis [32, 33]. Many physicians are reluctant to prescribe anticoagulant prophylaxis for the prevention of CVC-related thrombosis because of a low expected incidence of clinically manifest thrombosis and a presumed high risk of bleeding in these often thrombocytopenic patients [32, 33]. The use of antithrombotic prophylaxis has been evaluated mainly in patients with solid tumors; only limited evidence-based data are available in patients with hematological malignancies. Only a few prospective, well-conducted, randomized studies of prophylactic strategies in hematological patients have been performed.

In a well-conducted, randomized double blind trial, Cougan et al. [34] found that the administration of warfarin 1 mg daily did not reduce the incidence of symptomatic CVC-related thrombosis in a patient population with mostly hematological malignancies. Major limitations of their study were the unexpectedly low incidence of thrombosis (only 11 symptomatic CVC-related thromboses in 255 patients) and the timing of starting warfarin (study drug was always administered after CVC insertion and may have been started up to 72 h later).

Another prospective randomized controlled trial has been published comparing continuous intravenous unfractionated heparin (UFH) with normal saline solution as a continuous infusion in patients with a hematological malignancy. CVC-related thrombosis occurred in 1.5% of the CVCs inserted in patients of the heparin group, and in 12.6% of the control group ($P = 0.03$). Two patients in the heparin group and three patients in the control group experienced severe bleeding ($P = 0.18$) [35]. Dillon et al. [36] showed in a prospective, randomized study which included patients ≤21 years of age with an implantable port or tunneled catheter that flushing the CVC with urokinase every 2 weeks resulted in fewer occlusive events than flushing with heparin (23% versus 31%; $P = 0.02$). A number of non-randomized studies of pharmacologic prophylaxis in hematological patients have been carried out.

In an attempt to reduce CVC-related thrombosis 108 consecutive patients with hematological malignancies were started on minidose warfarin (1 mg warfarin daily) at the time of line insertion. Five (5%) of the 108 patients developed a CVC-related thrombosis. A major drawback in this study was the use of a historic control group of 115 consecutive patients who had not received warfarin. In this control group 15 patients (13%) developed a CVC-related thrombosis. The difference between the groups was statistically significant ($P = 0.03$) [10].

In a retrospective study with minidose warfarin three CVC-related thromboses were observed in 254 CVCs. Four episodes of bleeding were seen. It was therefore concluded that minidose warfarin is effective and safe to use for preventing CVC-related thrombosis. Unfortunately also in this study an adequate control group was not included [37].
Lagro et al. [9] found no effect using prophylactic nadroparin on the incidence of CVC-related thrombosis in 382 patients receiving a stem cell transplantation. Their study however, has a retrospective design and the patients only received nadroparin for the first 6–10 days after insertion of the CVC. Since CVC-related thrombosis is observed at a median of 16–23 days after insertion of the CVC, the time course of nadroparin administration may have been too short.

Due to the lack of well-designed, prospective studies, the optimal antithrombotic prophylaxis in patients with hematological malignancies remains a matter of debate. Further prospective, well-conducted, randomized studies of prophylactic strategies are clearly warranted.

treatment of CVC-related thrombosis
The aims of treatment of CVC-related thrombosis are to reduce the mortality and morbidity from the acute event and to reduce late complications.

The management of patients who develop a CVC-related thrombosis is not standardized. Treatment strategies consist of thrombolytic therapy, initiation of systemic anticoagulation, removal of the catheter or both.

In non-hematological patients with a CVC-related thrombosis the preferred treatment is the combination of a low molecular weight heparin (LMWH) followed by oral anticoagulation for at least 3–6 months [38, 39]. No prospective, randomized studies have been published on this subject.

The management of thrombosis in hematological and often thrombocytopenic patients is difficult because LMWH and oral anticoagulant are relatively contraindicated because of the high risk of major bleeding.

There is only limited information on the treatment of CVC-related thrombosis in hematological patients. No randomized trials have been published on this subject in the literature.

In a retrospective study the treatment and outcome of 112 cancer patients with a CVC-related thrombosis was reported. Treatment consisted of anticoagulation (n = 39), anticoagulation with CVC removal or replacement (n = 22), other therapy (n = 7) or no therapy (n = 8). Regardless of the intervention, no patients had a major adverse outcome such as pulmonary emboli, vascular compromise of a limb or death. Only four patients did not have resolution of their presenting symptoms, all of whom were treated with line replacement [40].

Whether a CVC-related thrombosis necessitates the removal of the CVC remains unclear. The decision of removal is usually left to the discretion of the attending physician. Kovacs et al. [41] recently assessed in a prospective cohort study the safety and effectiveness of a management strategy for CVC-related thrombosis in cancer patients consisting of dalteparin and warfarin without the need for removal of the CVC. There were no episodes of recurrent venous thrombo-embolism and three (4%) major bleeds in 74 cancer patients. No lines were removed due to infusion failure or recurrence/extenson of thrombosis.

Prophylaxis can preserve the life span of a CVC with a CVC-related thrombosis. Lee et al. [17] did not find a statistically significant difference in catheter life span between cancer patients who did not have CVC-related thrombosis and cases with a CVC-related thrombosis who were treated with anticoagulation. However, their results should be interpreted with caution because there were only 19 cases of CVC-related thrombosis and they did not control for the use of anticoagulation in their study.

The safety of LMWH in the treatment of CVC-related thrombosis has been reported in the literature in five patients undergoing bone marrow transplantation. No hemorrhagic complications were seen in these five patients with protracted thrombocytopenia [42].

No randomized comparison of thrombolytic therapy with heparin has been performed in hematological or non-hematological patients with a CVC-related thrombosis. In a retrospective, non-randomized analysis of 95 patients with a subclavian vein thrombosis systemic thrombolysis was compared with anticoagulant therapy. Systemic thrombolysis was associated with an acceptable primary technical success rate, but a rather high frequency of bleeding complications (21% versus none in the group of anticoagulants only) [43].

The conventional therapy for a blocked CVC resulting from catheter tip occlusion or catheter sleeve occlusion is local thrombolytic therapy with a low dose of single or repeated bolus or urokinase, streptokinase or tissue plasminogen activator. This therapy restores catheter patency in most patients, providing the CVC is well positioned [44, 45].

There is no consensus regarding the treatment of asymptomatic thrombosis. Since unrecognized thrombosis may be clinically important [15] further prospective studies are needed to determine whether the treatment of asymptomatic thrombosis will prevent occlusion of the CVC or CVC-related infection.

CVC-related infections
CVC-related infections can be divided into catheter colonization, exit-site infection, tunnel infection and bloodstream infection [46].

The prevalence of CVC-related bloodstream infections in hematological patients varies from 0.0% to 20.8%, depending on the patient and device characteristics and the definition used for a CVC-related bloodstream infection (see Table 2). Only a minority of these publications adhere to the US Hospital Infection Control Practices Advisory Committee (HICPAC) definitions for intravascular device-related infections [47].

The risk of infection is particularly high in neutropenic patients, patients undergoing myeloablative chemotherapy followed by autologous stem cell transplantation or patients with a CVC-related thrombosis [14, 48].

Pathogenesis and etiology of CVC-related infections
Following catheter insertion, a thrombin layer or sheath covers the external and the internal surfaces of the intravascular segment. This sheath, which is rich in host-derived proteins, such as fibrin, fibronectin, thrombospondin and laminin,
promotes adherence of potential microbial pathogens to the surface. Furthermore, staphylococci, Candida and some other microbes produce a slimy material rich in exopolysaccharides, resulting in the formation of a microbial biofilm. This biofilm helps these organisms to adhere to and survive on the surfaces of foreign bodies in the bloodstream [49].

The organisms causing a CVC-related infection can gain access to the device through four different routes: invasion of the skin insertion site, contamination of the catheter hub, hematogenous spread from a distant site of infection or infusion of contaminated fluid through the device [46, 50].

For tunneled CVCs, contamination of the catheter hub is the most common route of infection. From the contaminated hub, the organisms migrate along the internal surface of the CVC, where they create a bloodstream infection. For short-term, non-tunneled catheters, skin contamination is the most likely route of infection, whereby organisms migrate along the external surface of the CVC and the intercutaneous and subcutaneous segments, leading to colonization of the intravascular catheter tip, which may lead to bloodstream infection [49, 50].

CVC-related infections in hematological patients are usually caused by coagulase-negative Staphylococcus (62.5%), Staphylococcus aureus (4.2%), Gram-negative bacilli such as Enterobacteriaceae, Escherichia coli and Pseudomonas spp. (29%) or Candida spp (4.2%) [8].

**Diagnosis of CVC-related infections**

Diagnosis of CVC-related infections is notoriously difficult. In daily care it may be difficult to discriminate between infection and contamination. Clinical studies are hampered because of the lack of a gold standard for the diagnosis. Clinical signs often are unreliable at indicating the presence of a catheter-related infection [51, 52]. Microbiological criteria are therefore essential.

The most common techniques based on removal of the CVC are Maki’s semi-quantitative culture and quantitative endoluminal cultures. Quantitative cultures of the catheter segment requires either flushing the segment with broth, or vortexing, or sonicating it in broth, followed by serial dilutions and surface plating on blood agar [53–55]. The most widely used method is the semi-quantitative method, in which the catheter segment is rolled across the surface of an agar plate and colony-forming units are counted after overnight incubation [56]. The major disadvantages of this roll plate method are that only the external surface of the CVC is cultured and the need for removal of the catheter. Since these catheters are often integral to patient care in hematological patients, this often requires re-insertion and exposing patients again to all risks related to this procedure. The semi-quantitative roll plate method is of limited usefulness in hematological patients with mostly long-term catheters, in which the internal surface is the predominant source of colonization and bloodstream infection.

Diagnostic methods in which the CVC is left *in situ* include paired quantitative blood cultures, paired qualitative blood cultures with a continuously monitored differential time to positivity or the endoluminal brush [46, 49, 57]. Quantitative blood cultures drawn from the CVC and concomitantly by venipuncture from a peripheral vein are time consuming and expensive. If the CVC is infected the blood drawn through it shows a 5-fold increase in the concentration of organisms compared with the blood drawn percutaneously from a peripheral vein. Safdar et al. [58] found in their meta-analysis a sensitivity of 87% and a specificity of 98% and concluded that paired quantitative blood cultures is the most accurate diagnostic method in patients with long-term CVCs.

The differential time to positivity (DTP) of paired CVC and peripheral blood cultures provides comparable sensitivity and

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**Table 2. Incidence of CVC-related bloodstream infections in hematological patients**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>No. CVCs</th>
<th>CVC-related bacteremia, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carratala et al.</td>
<td>1999</td>
<td>Prospective</td>
<td>57 heparin lock</td>
<td>4 (7.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 heparin–vancomycin lock</td>
<td>0</td>
</tr>
<tr>
<td>Nouwen et al.</td>
<td>1999</td>
<td>Prospective</td>
<td>48</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Lagro et al.</td>
<td>2000</td>
<td>Retrospective</td>
<td>390</td>
<td>46 (11.8)</td>
</tr>
<tr>
<td>Harter et al.</td>
<td>2002</td>
<td>Prospective</td>
<td>113 standard CVCs</td>
<td>10 (8.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120 silver-coated CVCs</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Karthaus et al.</td>
<td>2002</td>
<td>Prospective</td>
<td>178</td>
<td>17 (9.6)</td>
</tr>
<tr>
<td>Corteleazzi et al.</td>
<td>2003</td>
<td>Retrospective</td>
<td>150, also PICCS</td>
<td>16 (10.6)</td>
</tr>
<tr>
<td>Lordick et al.</td>
<td>2003</td>
<td>Prospective</td>
<td>43</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>Nosari et al.</td>
<td>2004</td>
<td>Retrospective</td>
<td>227</td>
<td>23 (10.1)</td>
</tr>
<tr>
<td>Abdelkefi et al.</td>
<td>2005</td>
<td>Prospective</td>
<td>102 (heparin group)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>102 (control group)</td>
<td>17 (16.6)</td>
</tr>
<tr>
<td>Corteleazzi et al.</td>
<td>2005</td>
<td>Prospective</td>
<td>458</td>
<td>21 (4.6)</td>
</tr>
<tr>
<td>Jaeger et al.</td>
<td>2005</td>
<td>Prospective</td>
<td>55 standard CVCs</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55 CH-SS CVCs</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Van Rooden et al.</td>
<td>2005</td>
<td>Prospective</td>
<td>105</td>
<td>14 (13.3)</td>
</tr>
</tbody>
</table>

PICCS: peripherally inserted central venous catheters.
CH-SS CVC: chlorhexidine and silver sulfadiazine impregnated central venous catheter.
acceptable specificity (85% and 81%, respectively), at no increased costs [58]. Abdelkafi et al. [59] showed that DTP is useful for the diagnosis of catheter-related bloodstream infection in hematopoietic stem cell transplant recipients (86% sensitivity and 87% specificity).

Both culture techniques require a blood sample to be drawn through the CVC lumen, but in 15–50% of cases this may not be achieved [57, 60]. The endoluminal brush has no such limitation and has a sensitivity of 100% and a specificity of 89% [57]. It is theoretically possible to induce a peripheral bacteremia by endoluminal brushing of colonized CVCs. Dobbins et al. [61] found no peripheral bacteremia either 1 min or 1 h post- brushing in any of eight cases with significant endoluminal colonization. Few studies have assessed the endoluminal brush and most of the studies identified were performed by the same group of investigators. Since important side-effects may theoretically occur, it is not a method that can be recommended without further study.

**prevention of CVC-related infections**

Since the microbes that colonize the catheter hub and the skin surrounding the insertion site are the source of most CVC-related infections, prevention of CVC-related infections focuses mainly on the essential measures of aseptic insertion technique and proper catheter care.

Full barrier precautions during insertion of the CVC (sterile gloves, long-sleeved sterile gown, mask, cap and large sterile sheet drape) substantially reduces the incidence of CVC-related bloodstream infections compared with standard precautions (sterile gloves and small drape) (0.8/1000 and 0.5/1000 catheter-days, respectively; \( P = 0.02 \)) [62].

Any attempt to reduce the routine number of CVC manipulations at any site could reduce the risk of CVC-related infections. Good training in catheter manipulations is probably one of the best methods for guarding against CVC-related bacteremias both in the hospital and at home. The presence of a specialized team of nurses committed to the care of CVCs or the knowledge of proper maintenance procedure techniques shared by all nurses are both effective approaches for the reduction of CVC-related infection incidence in hospitalized patients [47, 63].

Continuing quality improvement programs to assure compliance with catheter care guidelines significantly reduce primary bloodstream infection [47, 63]. Moller et al. [64] showed a reduction of >50% in the incidence rate of CVC-related infections with a systematic, individualized, supervised patient education program and self-care for the catheter.

To prevent CVC-related infections, antibiotic lock prophylaxis has been attempted by flushing and filling the lumen of the CVC with an antibiotic solution and leaving the solution to dwell in the lumen of the CVC. In 126 immunocompromised children the use of either vancomycin/ciprofloxacin/heparin (VCH) or vancomycin/heparin (VH) compared with heparin alone significantly increased the time to develop a CVC-related infection and decreased the amount of Gram-positive CVC-related infections (VH, \( P = 0.028; \) VHC, \( P = 0.022 \)) [65]. However, the Centers for Disease Control and Prevention guidelines recommend against prophylactic use of vancomycin because it is an independent risk factor for acquisition of vancomycin-resistant enterococci [66].

Systemic antibiotic prophylaxis at the time of CVC insertion in 65 neutropenic patients has not been shown to reduce the incidence of CVC-related bloodstream infection [67]. In another study a single dose of teicoplanin did decrease the risk of Gram-positive CVC-related infections in neutropenic patients. The benefit of prophylactic teicoplanin was observed particularly among patients who were already neutropenic at the time of catheterization [68]. In the study of Ljungman [67] only two patients were neutropenic at the time of CVC insertion which is a possible explanation for the observed difference.

Antiseptic-impregnated CVCs are effective in preventing CVC-related infections. In a meta-analysis Veenstra et al. [69] showed that short-term (<2 weeks) use of CVCs impregnated with chlorhexidine/silver sulfadiazine reduced the risk of CVC-related bloodstream infections by ~40%. This meta-analysis, however, was not limited to hematological patients.

Since most hematological patients have a CVC *in situ* for more than 2 weeks, antiseptic impregnated CVCs did not prove their interest in this patient population. In a prospective, randomized trial in 106 patients with severe neutropenia, CVC-related colonization and CVC-related bloodstream infections were observed less frequently in the study group with chlorhexidine and silver sulfadiazine impregnated CVCs compared with the control group using a standard uncoated CVC. The CVCs, however, were only *in situ* for a period of 2 weeks, which is a relatively short period of time for hematological patients [70]. Logghè et al. [71] showed that the use of antiseptic impregnated CVCs in hematological patients reduced neither the overall risk of CVC-related bloodstream infection, nor the CVC-related infection rate, nor the delay for the occurrence of infections. The CVCs were *in situ* for a mean of 20 days (SD 12 days). This finding probably reflects reduced antimicrobial activity of the CVC over time and a lack of protection from microbes invading the luminal surface of the CVC from contaminated hubs [71].

Significant controversy surrounds the usefulness of CVCs impregnated with antimicrobial agents for the prevention of CVC-related bloodstream infections [72–74]. McConnell et al. [74] reviewed 11 trials of antimicrobial impregnated CVCs versus uncoated CVCs and they concluded that there is a lack of solid evidence to support a benefit of antimicrobial impregnated CVCs in reducing the rate of CVC-related bloodstream infections. Others assert that there is a large body of evidence that demonstrates a powerful decrease in the risk of infection [72, 73].

In a recently published meta-analysis Falagas et al. [75] demonstrated that CVCs impregnated with rifampicin and monocyclic are safe and efficacious in reducing the rate of catheter colonization and CVC-related bloodstream infections. Most patients included in all reviews, however, were not hematological patients.

Hanna et al. [76] performed a prospective study in hematological patients with 356 CVCs who were randomized between non-impregnated CVCs and CVCs impregnated with minocycline/rifampin. Fourteen CVC-related bloodstream infections occurred in the non-impregnated CVCs and only
three occurred in the group with CVCs impregnated with minocycline/rifampin (8% compared with 1.6%; \( P = 0.003 \)). The mean duration of catheterization was, respectively, 63.01 ± 30.88 days and 66.21 ± 30.88 days.

Since CVC-related thrombosis and infection are interrelated, interventions designed to decrease fibrin deposition and thrombus formation have the potential to reduce CVC-related infections. Abdelkefi et al. [8] showed in a randomized study that the use of a continuous infusion of heparin significantly reduced the risk of CVC-related bloodstream infections.

### treatment of CVC-related infections

Patients with a CVC-related infection should be separated into those with complicated infections, into which there is septic thrombosis, endocarditis, osteomyelitis or possible metastatic seeding, and those with uncomplicated CVC-related infections in which there is no evidence of such complications. Patients with an uncomplicated CVC-related infection should receive 10–14 days of antimicrobial therapy. Relapse, continuous fever or bacteremia, despite removal of the catheter, is consistent with the suspicion of a persistent focus of infection. This implies prolonged (4–6 weeks) or modified antimicrobial treatment and an active search for metastatic abscess, septic thrombophlebitis or endocarditis.

If a patient has a removable CVC, the catheter should be removed. Because removal of a tunneled (and thus surgically implanted) CVC is often a management challenge, it is important to be sure that one is dealing with a true CVC-implanted CVC is often a management challenge, it is important to be sure that one is dealing with a true CVC-implanted CVC is often a management challenge, it is important to be sure that one is dealing with a true CVC-implanted

In the case of non-neutropenic CVC-related candidemia, the CVC should always be removed. Removal of the CVC is controversial in neutropenic patients since a gastrointestinal source is common. Duration of antifungal treatment for candidemia should be at least 14 days after the last positive blood culture result and resolution of signs and symptoms of infections or resolved neutropenia [46, 79].

### relationship between CVC-related infections and thrombosis

There is accumulating evidence showing that CVC-related thrombosis and infection are interrelated and can therefore not be seen as separate entities. There seems to be a bi-directional relationship [14, 29, 30].

A major contributing factor in both CVC-related thrombosis and CVC-related infection might be fibrin sheath formation around the external portion of the catheter and within the catheter lumen [80].

The composition of CVC-related thrombi consists of several proteins such as fibrin, fibronectin, collagen, laminin and several types of immunoglobulins. Microorganisms, especially \( S. \) aureus and \( S. \) epidermidis, easily adhere to thrombin sheaths [80, 81]. These microorganisms are able to produce a coagulase enzyme that enhances the thrombogenic process.

There is sufficient evidence that thrombosis affects inflammation in more ways. Activated coagulation proteases interact with protease-activated receptors which are believed to play a role in translating coagulation products in inflammatory signals. Thrombin induces upregulation of various proinflammatory cytokines in vitro [82–84].

Lordick et al. [14] detected a CVC-related infection in 14 of 43 hemato-oncological patients. In 12 of the 14 patients with a CVC-related infection a CVC-related thrombosis preceded the CVC-related infection.

After an episode of CVC-related infection, the risk of clinically manifest thrombosis is markedly increased. In a group of patients with a CVC-related infection, the frequency of subsequent clinically manifest thrombosis was 44% (11 of 25 patients), compared with 3% in patients without CVC-related infection (2 of 80 patients). This yields a relative risk of 17.6. The absolute risk of developing a clinically manifest thrombosis increased with the severity of infection: a 57% thrombosis risk was observed after an episode of CVC-related bloodstream infection, compared with 27% in patients with a positive lock fluid culture [29].

CVC-related infection might induce an inflammatory response which can result in activation of coagulation, due to tissue factor-mediated thrombin generation, downregulation of physiological anticoagulant mechanisms and inhibition of fibrinolysis. This could induce thrombus formation which may further promote catheter colonization, bacterial biofilm growth and eventually bloodstream seeding [83, 84].

Since CVC-related thrombosis and infection are interrelated, interventions designed to decrease fibrin deposition and thrombus formation have the potential to reduce CVC-related infections. In a randomized study the use of a continuous infusion of low-dose unfractionated heparin (100 U/kg per day) to prevent CVC-related thrombosis and CVC-related bloodstream infection in patients with hematological disease was investigated. CVC-related bloodstream infection occurred...
in 6.8% (7 of 102 CVCs) of those in the heparin group and in 16.6% (17 of 102 CVCs) of those in the control group (P = 0.03). CVC-related thromboses were observed more frequently in the control group (10 of 102) than in the heparin group (2 of 102) (P = 0.017). Severe bleeding was experienced by four patients in the heparin group and five patients in the control group (P = 0.2) [8].

Urokinase administration every 2 weeks significantly affected the rate of occlusive and infectious events in children with a CVC compared with heparin administration [36].

In hemodialysis the use of trisodium citrate 30% was compared with unfractionated heparin 5000 U/ml for catheter locking. The risk reduction for CVC-related bacteremia was 87% for tunneled cuffed CVCs (P < 0.01) and 64% for untunneled CVCs (P = 0.05) [85]. This effect warrants further investigation in hematological patients.

conclusions

CVC-related thrombosis and infections are frequently occurring complications and may cause significant morbidity in patients with hematological malignancies. CVC-related thrombosis and infection are related and can therefore not be seen as separate entities.

There is need for a specific approach regarding diagnosis and treatment of CVC-related thrombosis and infection with specific attention to the preservation of the catheter.

It is clear that the prevention of CVC-related infections and thrombosis is of utmost importance and will help to decrease patient suffering as well as the costs of patient management. Since the fibrin sleeve has been implicated as a major contributing factor in both CVC-related thrombosis and CVC-related infection, interventions designed to decrease fibrin deposition seems to be the future.

Since data on CVC-related infections and thrombosis in hematological patients have been obtained mainly from retrospective studies of small sample size, prospective, randomized studies of prophylactic measures concerning CVC-related thrombosis and infection are warranted. Many topics remain unsolved and there is still an urgent need for effective, cheap and easy to implement preventive measures.

references


70. Jaeger K, Zier S, Juttner B et al. Reduction of catheter-related infections in neutropenic patients: a prospective controlled randomized trial using...
a chlorhexidine and silver sulfadiazine-impregnated central venous catheter. Ann Hematol 2005; 84: 258–262.


