

## Infectious Complications of Central Venous Catheters Increase the Risk of Catheter-Related Thrombosis in Hematology Patients: A Prospective Study

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### A B S T R A C T

#### Purpose

We studied whether the risk of central venous catheter (CVC)-related thrombosis increased after an episode of CVC-related infection in patients undergoing intensive chemotherapy. Secondly, we determined whether thrombosis can be predicted or excluded by CVC lock fluid surveillance cultures.

#### Patients and Methods

In a prospective setting, 105 consecutive patients were carefully examined for CVC-related infection and thrombosis. In all patients, microbial surveillance cultures of CVC lock fluid were taken every other day. All patients with clinical suspicion of CVC-related thrombosis underwent Doppler ultrasound or additional venography.

#### Results

The cumulative incidence of CVC-related infection was 24% (25 of 105 patients). Clinically manifest thrombosis occurred in 13 (12%) of 105 patients. In patients with CVC-related infection, the risk of thrombosis increased markedly in comparison to those without infection (relative risk, 17.6; 95% CI, 4.1 to 74.1). In patients having two or more positive subsequent CVC lock fluid cultures with identical micro-organisms, 71.4% developed thrombosis, as compared with 3.3% in patients with negative or a single positive culture.

#### Conclusion

The risk of clinically manifest thrombosis is increased after an episode of CVC-related infection in patients undergoing intensive chemotherapy. Surveillance culturing of CVC lock fluid may be clinically useful in estimating the risk for thrombosis and the instigation of focused early intervention.

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### INTRODUCTION

In patients who undergo intensive chemotherapy or a stem-cell transplantation, central venous access is often needed. The use of a central venous catheter (CVC) may be complicated by thrombosis and associated complications such as pulmonary embolism, which may lead to premature removal of the CVC and anticoagulant treatment.<sup>1,2</sup> These patients, who often suffer from thrombocytopenia, are particularly vulnerable for bleeding complications.

An association of CVC-related infection with CVC-related thrombosis has been suggested previously.<sup>3-5</sup> However, the reported thrombotic events were subclinical and were often diagnosed at CVC removal. Whether CVC-related infection increases the risk of clinically manifest thrombosis while the CVC remains in place is unknown. It is highly relevant to investigate this association since early determination and intervention on the diagnosis of infection in these patients could lead to CVC salvage and may prevent thrombotic complications. We

undertook a prospective study to evaluate whether, and to what extent, CVC-related infection increases the risk of subsequent clinically manifest thrombosis. In addition, we assessed the predictive value of surveillance CVC lock cultures in the diagnosis of thrombosis, which gives information on the potential benefits of prevention of thrombotic complications.

## PATIENTS AND METHODS

### Patients and Study Design

This study was performed at the department of Hematology of the Leiden University Medical Center from October 2000 until May 2002, a tertiary referral center for hematologic disease in the Netherlands.<sup>6</sup> The study protocol was approved by the local medical ethical committee, and all participating patients gave written informed consent. All consecutive patients 16 years or older with a CVC inserted for over 48 hours were considered for enrollment.

CVCs were inserted via the subclavian or jugular vein and were used for administering cytotoxic drugs and supporting treatment (ie, fluids, blood products, parenteral feeding, and antimicrobial therapy). Nurses were allowed to withdraw blood from the CVC for diagnostic purposes and monitoring. The lumina of the CVC were rinsed daily with urokinase (3,750 U in 1.5 mL sodium chloride). The use of urokinase for the prevention of CVC-related complications was based on local experience (not yet published) as well as other studies, the data of which suggest that urokinase may reduce the risk of (serious) infectious CVC complication as compared with heparin or saline alone.<sup>7,8</sup> No antibiotic prophylaxis specifically for CVC-related infections were given. All patients were treated according to a local protocol to prevent infections with aerobic Gram-negative rods, *Viridans streptococci* and *Candida* spp.<sup>9</sup> Prophylactic treatment included neomycin (250 mg), polymyxin B (1.10<sup>6</sup> U) orally qd, pipemidic acid 400 mg orally bid, and amphotericin B 200/10 mg qd. After 10 days of treatment, the dosage of the regime was reduced (half of the dosage in mg), except for the pipemidic acid.

Patients with abnormal Doppler ultrasound findings (performed within 48 hours after insertion) were excluded if they had a previous CVC at the same insertion site or if they had a proven thrombosis at the same insertion site. Patients who were unable to undergo Doppler ultrasound were also excluded.

### Microbiologic Surveillance and Treatment

Starting the day after the insertion of the CVC, lock fluid was cultured routinely each second day as described previously.<sup>10</sup> If a surveillance CVC lock fluid culture yielded growth of micro-organisms (positive lock culture), lock cultures were drawn daily. At each episode of onset of fever (body temperature > 38.5°C) or other symptoms or signs of infection (hypotension, chills, hypothermia, unexplained tachycardia), blood cultures were drawn, at least one via the CVC and one by standard venipuncture. At least two blood cultures were drawn on each consecutive day in all patients with clinical symptoms or signs of infection, until a causative micro-organism was isolated. In the presence of clinical signs of inflammation at the insertion site (ie, erythema, exudation, tenderness, warmth, or swelling) swab cultures were taken. Catheter tip cultures were not performed routinely, but only to support the diagnosis of CVC-related infection. Micro-organisms were identified by current tests (DNase testing), additional commercial ID 32 STAPH biochemical test strips (API; bioMerieux, Lyon, France), and antimicrobial sensitivity patterns.

The criteria for establishing a diagnosis of CVC-related infection were adapted to previous studies.<sup>10,11</sup> Two entities were distinguished: "local CVC infection" and "systemic CVC-related infection" (Table 1).<sup>11</sup>

In case of a proven insertion site infection or CVC colonization, appropriate antimicrobial therapy was started. The CVC was left in place. If a single CVC lock fluid culture was positive, no treatment was started. In case of fever or other symptoms or signs of systemic infection, empirical therapy was started (ceftazidime 500 mg intravenously tid and teicoplanin 200 mg intravenously bid on day 1, qid on consecutive days). Empirical therapy was discontinued if blood cultures remained negative after 72 hours. If a systemic CVC-related septicemia was diagnosed, empirical therapy was adjusted to the most appropriate small-spectrum regimen.<sup>7</sup> The CVCs were not removed routinely.

### Outcome: CVC-Related Thrombosis

During admission, all patients were routinely examined each day for symptoms and signs of CVC-related thrombosis; pain, swelling, discoloration, visible collateral circulation, or CVC dysfunction. Discharged patients were seen once weekly at the outpatient clinic by attending physicians. Patients with a clinical suspicion of CVC-related thrombosis were referred to the department of Radiology for Doppler ultrasound. If Doppler ultrasound

**Table 1.** Definitions of the Different Types of CVC-Related Infection Adapted to Earlier Studies

	Descriptions
1. Local CVC infection	
A. Insertion site infection:	The CVC insertion site exhibits clinical signs of inflammation with the swab Gram stain > 20 micro-organisms per field of vision (1,000 ×) and a positive culture within 48 hours. The CVC lock fluid and blood cultures remain negative.
B. Significant CVC colonization:	At least two consecutive CVC lock cultures become positive within 48 hours or the CVC tip culture is positive. Blood cultures by venipuncture are negative; CVC drawn blood cultures may yield identical micro-organisms.
2. Systemic CVC-related infection	
CVC-related bacteremia:	Presence of fever (body temperature > 38.5°C) or clinical signs or symptoms of infection, and blood cultures are positive. The insertion-site swab, CVC tip culture, or a positive CVC lock culture yields growth of identical micro-organisms. A systemic CVC-associated infection with positive blood cultures* at least 24 hours after adequate antimicrobial therapy is considered as a major systemic CVC infection.
NOTE. Earlier studies include those by Guiot et al <sup>10</sup> and Raad et al. <sup>11</sup>	
Abbreviation: CVC, central venous catheter.	
*In case of coagulase-negative staphylococci, at least two drawn blood cultures are positive.	

findings appeared normal or were inconclusive, additional venography was performed. In addition, for this study, all patients with clinically suspected thrombosis were examined by an independent examiner who performed Doppler ultrasound. These examinations were coded and assessed by a panel of two blinded physicians experienced in Doppler ultrasound evaluation. If needed, a third expert opinion was asked. A diagnosis of thrombosis was made when Doppler ultrasound recordings were abnormal, or when normal or inconclusive by an abnormal venogram. Follow-up for CVC-related thrombosis took place until 6 weeks after CVC removal.

A diagnosis of CVC-related thrombosis was made according to predefined criteria. For veins accessible to insonation, the criteria of noncompressibility, visualization of echogenic intraluminal mass, and absence of respiratory variation (jugular, axillary, or subclavian vein) were used.<sup>12-15</sup> For veins inaccessible to direct insonation (middle part of the subclavian vein, brachiocephalic vein, and superior caval vein), the criterion of monophasic flow to detect occlusive thrombosis was used.<sup>16</sup> A diagnosis of thrombosis by contrast venogram was made in case of intraluminal filling defects of a venous segment (axillary, subclavian, brachiocephalic, or superior caval vein) or persistent nonfilling of a venous segment in the presence of collateral circulation.<sup>17</sup>

### Statistical Analysis

Cumulative incidences for infection and thrombosis were calculated as number of first events over the number of individuals at baseline, and Kaplan-Meier statistics were performed. Patients were censored if they died or reached the end of follow-up. Relative risks (RR) and 95% CIs were calculated and based on SEs for binominal distributions. The relation of infection and thrombosis was assessed by applying Fisher's exact test ( $P < .05$  was considered statistically significant).

## RESULTS

### Patients and CVC-Related Thrombosis

The main patient and CVC characteristics have been described in detail elsewhere.<sup>6</sup> Briefly, of 136 consecutive patients, 110 consented to participate. Two patients were excluded before the start of the study, and three patients were excluded from the analysis based on exclusion criteria. Ultimately, for 105 patients, complete data were obtained and evaluated. The main characteristics for these 105 patients are shown in Table 2. None of the pretreatment parameters in Table 2 predisposed for CVC-related infection or thrombosis.

In 25 patients, CVC-related thrombosis was clinically suspected on symptoms and signs. In 13 of these 25 patients, clinically manifest thrombosis was objectified (cumulative incidence, 12.4%; 95% CI, 6.1% to 18.7%). In the other 12 patients, thrombosis was excluded by diagnostic imaging. There was no disagreement between the real-time diagnosis and the diagnosis as judged by our blinded panel.

### CVC-Related Infection and Risk of Clinically Manifest Thrombosis

The cumulative incidences for CVC-related infections and the absolute and relative risks of subsequent clinically manifest thrombosis are summarized in Table 3. Overall,

**Table 2.** Baseline Characteristics of the Study Patients

	No. of Patients	%
Age, years		
Mean	48	
Range	16-77	
Central venous catheter in situ, days		
Mean	22	
Range	5-64	
Sex		
Male	63	60
Female	42	40
Disease		
Acute myeloid leukemia	46	43.8
Acute lymphoblastic leukemia	13	12.4
Lymphoma	13	12.4
Chronic myeloid leukemia	11	10.5
Multiple myeloma	11	10.5
Other	11	10.5
Therapy		
Intensive chemotherapy	48	45.7
Stem-cell transplantation		
Allogeneic	36	34.2
Autologous	21	20
Central venous catheter		
Double or trilumen	100	95.2
Subclavian vein	94	89.5
Left insertion side	71	67.7

CVC-related infection was observed in 25 of 105 patients (cumulative incidence, 23.8%; 95% CI, 15.7% to 32%). In 11 patients (10.5%) CVC-related infection was classified as a local CVC infection such as CVC colonization ( $n = 1$ ), a local insertion-site infection ( $n = 6$ ), or both ( $n = 4$ ) in the absence of associated bacteraemia. Swab and CVC lock-fluid cultures yielded mainly coagulase-negative staphylococci (CoNS;  $n = 6$ ) or multiple types of micro-organisms including CoNS ( $n = 3$ ). Other isolated pathogens were *Enterobacter* spp ( $n = 1$ ) and *Acinetobacter* spp ( $n = 1$ ). Another 14 patients (13.3%; 95% CI, 6.8% to 19.8%) suffered from systemic CVC-related infection. In these patients, blood cultures yielded CoNS ( $n = 10$ ), multiple types of micro-organisms including CoNS ( $n = 3$ ), and *Corynebacterium* spp ( $n = 1$ ).

In the group of patients with a CVC-related infection, the frequency of subsequent clinically manifest thrombosis was 44% (11 of 25 patients), compared with 3% thrombosis in the patients without CVC-related infection (two of 80 patients;  $P < .05$ ). This yields a relative risk of 17.6 (95% CI, 4.1 to 74.1). Our findings suggest that the absolute risk of clinically manifest thrombosis increases with the severity of infection since thrombosis was observed in 57.1% of patients with systemic CVC-related infection as compared with 27.3% in patients with a local CVC infection (Table 3).

The frequency of CVC-related infection in the group of patients with objectified CVC-related thrombosis was

**Table 3.** Observed Cumulative Incidences of CVC-Associated Infections and the Absolute and Relative Risks of Subsequent Clinically Manifest Thrombosis

	Patients		Risk of Thrombosis*	
	No.	%	Absolute Risk (%)	Relative Risk
No CVC-related infection	80	76.2	2.5	
CVC-related infection*				
Local CVC infection	11	10.5	27.3	10.9
Insertion-site			6	
CVC colonization			1	
Insertion site and CVC colonization			4	
Systemic CVC infection	14	13.3	57.1	10.4
Overall	25	23.8	44.1	17.6

Abbreviation: CVC, central venous catheter.

\*For definitions of CVC related infection, see Table 1.

higher than in the group of patients in whom thrombosis was clinically suspected but ruled out (84.6% v 16.7%), indicating that the observed association of infection with thrombosis was not affected by the knowledge of infection among attending physicians who had decided on referral for diagnostic imaging for thrombosis.

Fifteen patients had a systemic infection (14.3%; 95% CI, 7.6% to 21%) classified as unrelated to the CVC. Blood cultures in these patients yielded CoNS (n = 4), *Streptococcus* spp (n = 3), multiple types of micro-organisms (n = 3), *Candida albicans* (n = 2), or other micro-organisms (n = 3). Of these patients, only one suffered from clinically manifest thrombosis (6.7%).

#### Accuracy for CVC Lock Fluid Cultures to Predict Clinically Manifest Thrombosis

During follow-up, 30 of 105 patients had at least one positive surveillance CVC lock culture (28.6%). Of 13 patients with clinically manifest thrombosis, 11 had at least one prior positive culture (sensitivity, 84.6%; 95% CI, 65% to 100%). In 73 of 92 patients without clinically manifest thrombosis, a negative culture was obtained for a specificity of 79.3% (95% CI, 71.1% to 87.6%). Of 75 patients with serially negative CVC lock fluid cultures, thrombosis occurred in two (negative predictive value 97.3%, 95% CI, 93.7% to 100%), whereas 11 of 30 patients with a positive CVC lock fluid developed thrombosis (positive predictive value, 36.7%; 95% CI, 19.4% to 53.9%). If two or more subsequent positive cultures with identical strains of micro-organisms were used to predict symptomatic thrombosis, the positive predictive value increased to 71.4%, whereas the negative predictive value decreased only slightly (96.7%). As illustrated in Figure 1, the risk of thrombosis increased markedly in patients with two or more consecutive positive cultures, as compared with only one positive followed by negative cultures or consecutive negative cultures.

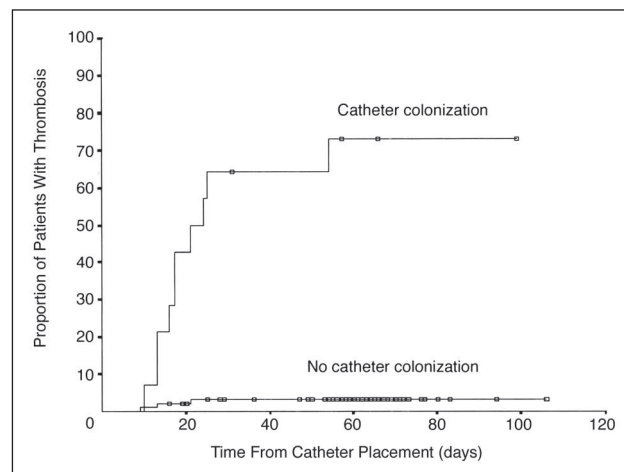
The time interval between the first positive surveillance culture and the clinical diagnosis in 11 patients with clinically

manifest thrombosis ranged from 1 to 39 days (mean, 9 days).

## DISCUSSION

In the present study, we show a clear temporal association of CVC-related infection and subsequent thrombosis. After an episode of CVC-related infection, the risk of clinically manifest thrombosis increased markedly (RR, 17.6). Besides, our findings suggest that the absolute risk of developing a symptomatic thrombotic event increases with the severity of CVC-related infection; a 57% thrombosis risk was observed after an episode of CVC associated septicemia, versus 27% in patients with a local CVC infection.

Previously, a direct association of CVC-related infection and thrombosis has been suggested in autopsy studies.<sup>3</sup> Reliable prospective data in which a direct relationship of CVC-related infection and thrombosis has been reported



**Fig 1.** The risk of clinically manifest thrombosis based on at least two surveillance central venous catheter lock fluid cultures.



are scarce.<sup>4,5</sup> In a study of critically ill patients (N = 208), the presence of subclinical thrombosis detected by routine Doppler ultrasound performed at CVC removal was associated with a three-fold increased rate of systemic CVC-related septicemia.<sup>4</sup> In hemato-oncology patients, only one small study (n = 42) has been performed, in which a direct association of infection and thrombosis was reported.<sup>5</sup> In this study, daily screening using ultrasound for (subclinical) thrombosis was used to estimate the risk of subsequent CVC-related infection. From 13 patients with documented subclinical thrombosis, CVC-related infection occurred in 12 (92%), whereas in 29 patients without thrombosis, the number of infections was only two (7%).<sup>5</sup> The main difference between our and these studies is that we have used clinically manifest thrombosis as the primary end point and that CVC-related infection was used as a parameter to predict symptomatic thrombotic events.

Based on our findings, as well as results from earlier studies, it could be argued that the relationship of thrombosis and infection is bi-directional. Thrombus formation, which is commonly observed after catheterization, may play an important role in the development of certain CVC-related infections.<sup>4,5,18,19</sup> The composition of CVC-associated thrombi consists of several proteins such as fibrin, fibronectin, collagen, laminin, and several types of immunoglobulins.<sup>20-22</sup> Micro-organisms, especially *Staphylococcus aureus* and certain types of CoNS, easily adhere to thrombin sheaths, which could explain the clinical observation of a close association of CVC infection and thrombosis.<sup>20-23</sup> Besides, CVC-related infection might induce an inflammatory response<sup>24</sup> that could induce or lead to further progression of excessive thrombus formation. Thrombosis and infection might also just be two separate entities occurring simultaneously in patients who are severely ill, but this hypothesis is not likely since the molecular basis of thrombosis suggests a direct relationship.<sup>20-24</sup> We can not, however, exclude that thrombosis may be induced by a local chemical phlebitis caused by antibiotics in patients treated for CVC infection.

From a clinical point of view, surveillance cultures of CVC lock fluid may be valuable to assess the risk of clinically manifest thrombosis in individual patients, particularly if this risk assessment is based on serially determined cultures. Such a strategy could allow early intervention in addition to adequate antimicrobial therapy. Timely CVC removal at the first sign of thrombosis or infection, or individualized

anticoagulant prophylaxis, may be beneficial. Such individualized risk assessment for clinically manifest thrombosis might be an alternative for routine anticoagulant prophylaxis in patients with CVCs, especially after intensive chemotherapy.<sup>25</sup> However, this study was an observational study, and whether early intervention would have changed clinical outcome and whether such a strategy is cost effective is unknown and should be investigated. Although anticoagulant prophylaxis is recommended in consensus guidelines, there is great reluctance among clinicians to prescribe anticoagulant prophylaxis routinely because of fear of bleeding complications and a low expected incidence of thrombosis.<sup>25-27</sup> In addition, since there seems to be a strong association of infection and thrombosis, the use of antibiotic impregnated CVCs may be of clinical benefit as well. However, the outcome of intervention(s) based on surveillance cultures is currently unknown, and this clearly needs prospective evaluation before being routinely implemented. Whether such intervention is based on a single or multiple subsequent positive lock cultures is uncertain. However, as in CVC-related infection, the accuracy indices of surveillance cultures to predict clinically manifest thrombosis improved with more subsequent cultures (two or more) that were positive for identical types and strains of micro-organisms. Serially positive cultures are likely to reflect a more significant colonization of the CVC, or less frequently, contamination as compared with a single positive surveillance culture.

In conclusion, we have shown a close association of CVC-related infection with thrombosis. The risk of developing clinically manifest thrombosis increases substantially after an episode of CVC-related infection (RR, 17.6) and is enhanced by the severity of the infection. Routine culturing of CVC lock fluid is clinically useful to monitor the risk of clinically manifest thrombosis, which might allow early intervention. However, the outcome of such a strategy is currently unknown and clearly needs to be explored prospectively.

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### Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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