

# Use of Heparin-Coated Central Venous Lines to Prevent Catheter-Related Bloodstream Infection

Abderrahman Abdelkefi, MD, Wafa Achour, MD, Tarek Ben Othman, MD, Saloua Ladeb, MD, Lamia Torjman, MD, Amel Lakhal, MD, Assia Ben Hassen, MD, Mohamed Hsairi, MD, and Abdeladhim Ben Abdeladhim, MD

**C**entral venous lines (CVLs) are commonly used in patients with hemato-oncologic disease for hemodynamic monitoring, administration of medication, and parenteral nutrition.<sup>1-5</sup> Complications of catheterization include mechanical (arterial puncture, pneumothorax), thrombotic, and infectious complications.<sup>6</sup>

Approximately 80,000 central venous catheter-related bloodstream infections (CRBIs), representing 5.3 infections per 1,000 catheter days, occur annually in intensive care units in the United States.<sup>7</sup> Attributable mortality for these infections ranges from 10% to 25%; each CRBI adds as much as \$5,000–\$19,000 and 12.5 days to a hospital stay.<sup>8</sup>

Studies have shown that catheter-related infection may be due to fibrin deposition associated with catheters.<sup>9-11</sup> Interventions designed to decrease fibrin deposition and thrombus formation have the potential to reduce catheter-related infections. Recently, in a randomized, controlled study, we showed that a low-dose of unfractionated heparin (UFH; 100 U/kg/d) was a safe and effective way to prevent CRBI in patients with hemato-oncologic disease.<sup>12</sup>

**Abstract** Bloodstream infections related to the use of central venous catheters are an important cause of patient morbidity, mortality, and increased health care costs. Catheter-related infection may be due to fibrin deposition associated with catheters. Interventions designed to decrease fibrin deposition have the potential to reduce catheter-related infections. This study was a randomized, controlled trial in which 246 patients with nontunneled central venous catheters were randomly assigned to receive a heparin-coated catheter with 50 mL/d of normal saline solution as a continuous infusion (heparin-coated group) or a non-coated catheter with a continuous infusion of low-dose unfractionated heparin (control group: continuous infusion of 100 U/kg/d). Catheter-related bloodstream infection occurred in 2.5% (3/120 catheters) in the heparin-coated group (0.9 events per 1,000 days) and in 9.1% (11/120 catheters) in the control group (3.5 events per 1,000 days;  $P = 0.027$ ). No other risk factors were found for the development of catheter-related bloodstream infection. Six and seven patients experienced severe bleeding in the heparin-coated and control groups, respectively ( $P = 1.00$ ). We did not observe heparin-induced thrombocytopenia. The use of heparin-coated catheters can be a safe and effective approach to the prevention of catheter-related bloodstream infection in patients with hemato-oncologic disease.

## Methods

### STUDY DESIGN

This prospective, randomized, controlled trial was conducted between May 2005 and June 2006 at the National Center for Bone Marrow Transplantation in Tunis, Tunisia. The study protocol was approved by the local medical ethical committee. All patients or their legal representatives gave written informed consent before entering the study, which was done in accordance with the Declaration of Helsinki. This study is registered at ClinicalTrials.gov, number NCT00207779.

From the Centre National de Greffe de Moelle Osseuse, Tunis, Tunisia, and Institut National de la Santé Publique, Tunis, Tunisia.

Manuscript submitted August 1, 2006; accepted April 10, 2007.

Correspondence to: Abderrahman Abdelkefi, MD, Centre National de Greffe de Moelle Osseuse, Rue Jebel Lakhdar, 1006 Bab Saadoun, Tunis, Tunisia; telephone: 00216 98 436 516; fax: 00216 71 565 428; e-mail: aabdelkefi@yahoo.fr

J Support Oncol 2007;5:273–278

© 2007 Elsevier Inc. All rights reserved.

## PATIENTS

Patients were eligible for the study if they were between 4 and 60 years of age and had a nontunneled CVL. Exclusion criteria were the presence of a CVL at admission, catheterization for less than 7 days, a contraindication to the use of subclavian catheterization due to major blood coagulation disorders (ie, platelet count  $< 50 \times 10^9/L$ , disseminated intravascular coagulation), and an absence of catheter-tip culture at the time of catheter removal.

## RANDOMIZATION

A simple randomization sequence was generated by a centralized computer. After registration and validation of eligibility, patients were randomly assigned to receive either a heparin-coated CVL with 50 mL/day of normal saline solution as a continuous infusion (heparin-coated group) or a noncoated CVL with a continuous infusion of low-dose UFH (control group: continuous infusion of 100 U/kg/d, with a maximal dose of 10,000 U/day). The primary objective was to compare CRBI rates in the two groups. Secondary endpoints included analysis of variables that may be significant for the development of CRBI (eg, age, gender, underlying disease, therapy, side of venous puncture, duration of insertion, number of veins punctured, duration of catheterization, neutrophil count on the day of catheterization, use of a catheter for administration of parenteral nutrition, and coexisting catheter-related thrombosis).

UFH was continued until the day of hospital discharge, and all CVLs were removed before hospital discharge. UFH was discontinued for any severe bleeding episode defined as central nervous system (CNS) bleeding or that which resulted in a drop in hemoglobin of more than 2 g/dL in a 12-hour period. A platelet transfusion threshold of  $20 \times 10^9/L$  was adopted. Coagulation parameters (particularly partial thromboplastin time) were routinely performed (twice a week).

## CVL CHARACTERISTICS

CVLs were externalized, nontunneled, polyurethane, double-lumen catheters (Arrow International, Inc.; Readings, PA, USA). Catheter sizes were chosen appropriate to age (5 or 7 French diameter). All CVLs were placed in the subclavian vein by infraclavicular approach by the same physician in the operating room. Catheters were inserted percutaneously using the Seldinger technique.<sup>13</sup> The CVL tip was confirmed radiographically to lie in the superior vena cava. Study catheters were not exchanged over guidewires. The insertion sites were covered with a transparent sterile dressing. Catheter care included changing the dressing under aseptic conditions every 6 days.

## MICROBIOLOGIC METHODS

After rigorous antiseptic cleansing of the skin and the hub with povidone iodine, at least two sets of blood cultures were drawn in case of fever ( $> 38^\circ C \times 2$  over at least 1 hour) and just before ( $< 1$  hour) catheter removal. Blood samples for culture were obtained simultaneously from the catheter hub

of the CVL and from a peripheral vein. For each blood culture set, a 20-mL blood sample was drawn aseptically and inoculated into aerobic and anaerobic bottles, immediately taken to the microbiology laboratory, and placed in the automatic positive-culture detector. The differential time in positivity (DTP) technique was used for in situ diagnosis of CRBI.<sup>14</sup>

The identity of isolates from peripheral and CVL-positive blood cultures was assessed on the basis of colonial morphology, species identification, and an identical antibiogram.<sup>15</sup> Catheters were removed aseptically, at the discretion of primary care physicians, if they were no longer needed or if infection was suspected. A 5-cm segment of the removed catheter tip was aseptically cut and delivered to the microbiology laboratory for quantitative culture, according to Brun-Buisson et al.<sup>16</sup>

Combination antibiotic therapy (piperacillin/tazobactam with an aminoglycoside) was used early in the febrile neutropenia phase. Glycopeptide antibiotics were used in the absence of an adequate response to the initial antibiotics. Empiric antifungal therapy was given if fever persisted ( $\geq 72$  h) despite antibiotics.

## DEFINITIONS AND DIAGNOSIS

CRBI was defined according to Infectious Disease Society of America guidelines:<sup>17</sup> bacteremia or fungemia in a patient who has an intravascular device and at least one positive result of culture of blood samples obtained from the peripheral vein, clinical manifestations of infection (eg, fever, chills, and/or hypotension), no apparent source for bloodstream infection (with the exception of the catheter), and a positive DTP ( $> 120$  minutes). The principal investigator determined whether infections were catheter-related and had no knowledge of “the assigned arm” at the time of adjudication of the reference standard definition.

## DATA COLLECTION

Standardized data collection forms were completed for all patients. Data were collected and monitored by the investigator, and the final analysis was performed by an independent statistical office. These data included demographic characteristics; underlying disease; therapy; catheter insertion and removal date; body side of CVL location; body mass index; prior mediastinal irradiation; duration of catheter insertion (in minutes); number of attempts at catheter placement; mechanical complications; and use of catheter for administration of parenteral nutrition, asparaginase (Elspar), and/or supportive care (transfusions, antibiotics).

Additional data recorded were the presence of local signs and symptoms of infection at the catheter insertion site (eg, swelling, warmth, tenderness, or purulent discharge), the duration of fever, the neutrophil count on the day of catheter insertion, the duration of neutropenia, signs of catheter-related thrombosis (eg, arm or neck pain, localized erythema, arm swelling, or dilated superficial collateral veins), bleeding events, and the occurrence of heparin-induced thrombocytopenia (HIT). The diagnosis of HIT was accepted in

**Table 1****Baseline Characteristics for 240 Patients With a Central Venous Catheter**

	HEPARIN-COATED GROUP (n = 120)	CONTROL GROUP <sup>a</sup> (n = 120)	P VALUE
Age, median years (range)	27 (5–59)	28 (6–59)	0.8
Gender			
Male	64 (53%)	62 (52%)	0.7
Female	56 (47%)	58 (48%)	
Performance status grade, median (range)	1 (0–3)	1 (0–3)	1.0
Body mass index > 30	12 (10%)	10 (8%)	0.6
Prior mediastinal irradiation	11 (9%)	11 (9%)	1.0
Severe neutropenia <sup>b</sup> on day of catheterization			
Yes	47 (39%)	50 (42%)	0.7
No	73 (61%)	70 (58%)	
Duration of severe neutropenia <sup>b</sup> , median days (range)	15 (4–30)	14 (4–29)	0.8
Underlying malignant disease	82 (68%)	80 (67%)	0.4
Acute myeloid leukemia	14 (12%)	14 (12%)	
Acute lymphoblastic leukemia	3 (2%)	2 (1%)	
Chronic myeloid leukemia	2 (1%)	3 (2%)	
Multiple myeloma	48 (40%)	45 (38%)	
Lymphoma	15 (13%)	16 (14%)	
Underlying nonmalignant disease	38 (32%)	40 (33%)	
Aplastic anemia	32 (27%)	35 (29%)	
Hemoglobinopathy	6 (5%)	5 (4%)	

<sup>a</sup>Continuous infusion of low-dose heparin

<sup>b</sup>Absolute neutrophil count < 0.5 × 10<sup>9</sup>/L

the case of either the demonstration of heparin-dependent immunoglobulin antibodies or, when this search could not be performed, the combination of the following features: (1) the absence of any other obvious clinical explanation for thrombocytopenia, (2) the occurrence of thrombocytopenia at least 5 days after the start of heparin, and (3) either the normalization of the platelet count within 10 days after heparin discontinuation or the earlier patient's death due to an unexpected thromboembolic complication.<sup>18</sup>

## STATISTICS

In a previous study, we found that CRBI occurred in approximately 10% of patients with a low dose of UFH prophylaxis.<sup>12</sup> We estimated that only 1% of the heparin-coated catheters would present a CRBI. Randomly assigning 121 patients to each group would allow detection of this difference in CRBI rate with 80% power and a two-tailed significance level of 5%. No interim analysis was performed.

Variables between heparin-coated and control groups were compared by an uncorrected chi-squared test or, when appropriate, Fisher exact test for categorical variables and Wilcoxon test for continuous variables. The same statistical tests were performed to identify the influence of age, gender, underlying disease, therapy, body side of CVL location, duration of catheter insertion, number of attempts at catheter placement, duration of catheterization, use of a heparin-coated catheter, neutrophil count on the day of catheter-

ization, duration of severe neutropenia (absolute neutrophil count < 0.5 × 10<sup>9</sup>/L), use of catheter for administration of parenteral nutrition, and catheter-related thrombosis for the development of a CRBI.

Because randomization produced two groups of patients with comparable baseline characteristics, no indication of positive or negative confounding needed to be controlled for with multivariate analysis models. Statistical significance was established at an alpha value of 0.05. All *P* values are two-tailed.

## Results

### PATIENT POPULATION

A total of 250 consecutive patients were eligible (Figure 1) during the 14-month study period, with 246 patients randomized to study. After randomization, six patients (2.4%) were excluded (three in the heparin-coated group, three in the control group) because of catheter insertion failure. Ultimately, 240 patients were analyzed. The main characteristics of the study patients are shown in Tables 1 and 2. We have observed three mechanical complications (two pneumothorax, one arterial puncture).

### INCIDENCE OF CRBI

We have observed 14 CRBIs/240 CVLs (5.8%), representing an incidence of 2.2 episodes of CRBI per 1,000 catheter-days. The median number of days between the insertion of the

**Table 2****Central Venous Line Characteristics**

	HEPARIN-COATED GROUP (n = 120)	CONTROL GROUP <sup>a</sup> (n = 120)	P VALUE
Duration of catheterization, mean days (range)	23 (8–35)	22 (8–38)	0.8
Duration of catheterization (days)			
8–29	105 (88%)	102 (85%)	0.5
> 30	15 (12%)	18 (15%)	
Reason for catheter removal			
End of treatment	100 (83%)	95 (80%)	0.027
Symptomatic catheter-related thrombosis	6 (5%)	4 (3%)	
CRBI	3 (2.5%)	11 (9%)	
Death	11 (9.5%)	10 (8%)	
Therapy			
HSCT	95 (80%)	92 (77%)	0.6
Intensive chemotherapy	25 (20%)	28 (23%)	
Use of catheter for administration of:			
Parenteral nutrition	77 (64%)	69 (57.5%)	0.3
Antibiotics	102 (85%)	106 (88%)	
Blood products	98 (82%)	100 (83%)	
Asparaginase	3 (2.5%)	2 (2%)	

<sup>a</sup> Continuous infusion of low-dose heparin

Abbreviations: CRBI = catheter-related bloodstream infection; HSCT = hematopoietic stem cell transplantation

CVL and diagnosis of CRBI was 21 days (10–31 days): for the heparin-coated group, 22 days (11–30 days); and for the control group, 21 days (10–31 days).

CRBI occurred in 2.5% (3 CRBIs/120 CVLs) in the heparin-coated group (0.9 events per 1,000 days) and in 9.1% (11 CRBIs/120 CVLs) in the control group (3.5 events per 1,000 days;  $P = 0.027$ ). The use of heparin-coated CVLs significantly decreased CRBIs by 73% (relative risk, 0.27; 95% confidence interval, 0.08–0.95). The absence of a heparin-coated catheter was the only risk factor for the development of CRBI (Table 3).

Microorganisms involved in CRBI were coagulase-negative staphylococci (two cases in the heparin-coated group and three cases in the control group); *Staphylococcus aureus* (one case in the control group); *Candida albicans* (two cases in the control group); *Pseudomonas aeruginosa* (one case in the heparin-coated group and two cases in the control group); and *Klebsiella oxytoca*, *Enterobacter cloacae*, and *Corynebacterium* spp (one case, respectively, in the control group).

No death was attributed to CRBI. The CVL was removed in all patients with CRBI, and appropriate systemic antimicrobial therapy was administered. Choice and duration of antimicrobial therapy depended on the isolated pathogen; the resistance pattern; and the presence of complications, such as deep-seated infections.

#### INCIDENCE OF CATHETER-RELATED THROMBOSIS

Ten cases of catheter-related thrombosis were observed (10/240: 6 in the heparin-coated group and 4 in the control group;  $P = 0.7$ ). The median number of days between the insertion of the CVL and diagnosis of catheter-related thrombo-

sis was 20 days (10–30 days): for the heparin-coated group, 21 days (14–25); and for the control group, 22 days (10–30). Catheter-related thrombosis and CRBI coincided in two patients and were not significantly correlated (Table 3;  $P = 0.1$ ).

#### TOXICITY

Six and seven patients experienced severe bleeding in the heparin-coated and control groups, respectively ( $P = 1.00$ ): (CNS bleeding [ $n = 1$ ], gastrointestinal bleeding [ $n = 2$ ], hematuria [ $n = 3$ ] in the heparin-coated group; CNS bleeding [ $n = 1$ ], hematuria [ $n = 3$ ], gastrointestinal bleeding [ $n = 3$ ] in the control group). Only one patient (in the control group) died of severe bleeding (CNS bleeding). Besides bleeding, there were no other side effects, particularly no heparin-induced thrombocytopenia.

#### Discussion

Data from the National Nosocomial Infection Surveillance system (US) between January 1992 and February 1998 showed that CRBI is the third most frequent nosocomial infection and accounted for 14% of all nosocomial infections.<sup>19</sup> Several studies have identified practices that reduce the risk of CRBI. These practices include using maximal sterile barrier precautions during catheter insertion<sup>20</sup>; accessing the subclavian vein rather than the internal jugular or femoral vein<sup>21,22</sup>; exchanging CVLs only when necessary<sup>23,24</sup>; changing dressings at catheter exit sites when they become nonocclusive, soiled, or bloody<sup>25</sup>; and coating the catheters with various antimicrobial agents.<sup>26,27</sup>

Studies have shown that catheter-related infection may be due to fibrin deposition associated with catheters.<sup>9–11</sup> Interven-

tions designed to decrease fibrin deposition and thrombus formation have the potential to reduce catheter-related infections. Indeed, in a previous randomized study, we have shown that low-dose UFH (100 U/kg/d) was a safe and effective way to prevent CRBI in patients with hemato-oncologic disease.<sup>12</sup>

In the current study, we have observed 14 CRBIs/240 CVLs (5.8%), representing an incidence of 2.2 episodes of CRBI per 1,000 catheter-days. The incidence of CRBI per 1,000 catheter-days was 0.9 in the heparin-coated group and 3.5 in the control group ( $P = 0.027$ ).

Eight randomized studies<sup>12,28–34</sup> have been performed to assess the safety and efficacy of heparin (either as an infusion or bonded to CVL) on central venous CRBI. Although a meta-analysis<sup>35</sup> of four studies<sup>28–31</sup> showed a strong trend for a reduction in CRBI with the use of heparin, these studies used variable definitions of catheter-related infections. Most of these studies have been in vitro,<sup>28</sup> concerned critically ill patients,<sup>32,33</sup> or involved long-term tunneled CVLs.<sup>34</sup>

In a recent randomized study, heparin-bonded CVLs reduced catheter-related bacteremia in critically ill children.<sup>32</sup> Nevertheless, there has been some concern expressed in the literature as to the duration of the heparin bonding and the degree to which the heparin elutes from the catheter.

Another randomized trial<sup>33</sup> compared the incidence of CRBI between heparin-coated catheters and those coated with a synergistic combination of chlorhexidine and silver sulfadiazine (CSS) in critically ill children. The incidence of CRBI per 1,000 catheter-days was 3.24 in heparin-coated catheters and 2.6 in CSS-coated catheters ( $P = 0.79$ ).

Evidence-based data on anticoagulant prophylaxis in hematology patients with CVLs are limited.<sup>12</sup> Indeed, clinicians are reluctant to prescribe anticoagulant prophylaxis routinely because of a concern for bleeding complications in this vulnerable population. Although our study is the first randomized trial showing that the use of heparin-coated CVL is safe and effective in the prevention of CRBI (nontunneled percutaneous CVLs) in patients with hemato-oncologic disease, the results cannot be generalized to all patients who require a CVL, because it was based on patients who were at high risk for acquiring CRBI.

Variables that may be significant for the development of CRBI (eg, age, gender, underlying disease, therapy, side of venous puncture, duration of catheter insertion, number of veins punctured, duration of catheterization, neutrophil count on the day of catheterization, duration of severe neutropenia, use of catheter for administration of parenteral nutrition, and coexisting catheter-related thrombosis) were analyzed. The absence of a heparin-coated catheter was the only risk factor for the development of CRBI.

**Table 3**  
Risk Factors for Catheter-Related Bloodstream Infection

	# OF EVENTS/ # OF CASES (%)	P VALUE
<b>Heparin-coated catheter</b>		
Yes	3/120 (2.5%)	0.027
No	11/120 (9.1%)	
<b>Age</b>		
≤ 20 years	6/100 (6.0%)	0.9
> 20 years	8/140 (5.7%)	
<b>Gender</b>		
Male	8/126 (6.3%)	0.7
Female	6/114 (5.2%)	
<b>Underlying disease</b>		
Malignant disease	9/162 (5.5%)	0.8
Nonmalignant disease	5/78 (6.4%)	
<b>Therapy</b>		
HSCT	11/187 (5.8%)	1.0
Intensive chemotherapy	3/53 (5.6%)	
<b>Side of venous puncture</b>		
Right	12/202 (5.9%)	1.0
Left	2/38 (5.2%)	
<b>Duration of catheter insertion</b>		
≤ 4 min	11/194 (5.6%)	0.7
> 4 min	3/46 (6.5%)	
<b>Number of punctures</b>		
1	11/198 (5.5%)	0.7
> 1	3/42 (7.1%)	
<b>Duration of catheterization, days</b>		
8–29	11/207 (5.3%)	0.4
> 30	3/33 (9.0%)	
<b>Severe neutropenia<sup>b</sup> on day of catheterization</b>		
Yes	8/90 (8.8%)	0.2
No	6/150 (4.0%)	
<b>Duration of severe neutropenia<sup>b</sup>, days</b>		
≤ 15	9/169 (5.3%)	0.5
> 15	5/71 (7.0%)	
<b>Parenteral nutrition</b>		
Yes	8/146 (5.4%)	1.0
No	6/94 (6.3%)	
<b>Catheter-related thrombosis</b>		
Yes	2/10 (20.0%)	0.1
No	12/230 (5.2%)	

<sup>a</sup> Univariate, chi-squared test

<sup>b</sup> Absolute neutrophil count < 0.5 × 10<sup>9</sup>/L

Abbreviation: HSCT = hematopoietic stem cell transplantation

## References

PubMed ID in brackets

1. Male C, Chait P, Andrew M, et al. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. *Blood* 2003;101:4273–4278. [12560228]
2. Harter C, Salwender HJ, Bach A, Egerer G, Goldschmidt H, Ho AD. Catheter-related infection and thrombosis of the internal jugular vein in hematologic-oncologic patients undergoing chemotherapy: a prospective comparison of silver-coated

and uncoated catheters. *Cancer* 2002;94:245–251. [11815983]

3. Madero L, Ruano D, Villa M, et al. Non-tunneled catheters in children undergoing bone marrow transplantation. *Bone Marrow Transplant* 1996;17:87–89. [8673061]

4. Kumagai T, Sakamaki H, Tanikawa S, et al. Utility and safety of Hickman catheters for venous access after bone marrow transplantation. *Intern Med* 1998;37:286–291. [9617864]

5. Biagi E, Arrigo C, Dell'Orto MG, et al. Mechanical and infective central venous catheter-related complications: a prospective non-randomized study using Hickman and Groshong catheters in children with hematological malignancies. *Support Care Cancer* 1997;5:228–233. [9176970]

6. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med* 2003;348:1123–1133. [12646670]

7. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. *Infect Control Hosp Epidemiol* 2002;23:759–769. [12517020]

8. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282:554–560. [10450717]

9. Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. *Clin Infect Dis* 2001;33:1567–1572. [11577378]

10. Musher D, Goldsmith E, Dunbar S, et al. Association of hypercoagulable states and increased platelet adhesion and aggregation with bacterial colonization of intravenous catheters. *J Infect Dis* 2002;186:769–773. [12198610]

11. Mehall JR, Saltzman DA, Jackson RJ, Smith SD. Fibrin sheath enhances central venous catheter infection. *Crit Care Med* 2002;30:908–912. [11940768]

12. Abdelkefi A, Torjman L, Ladeb S, et al. Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *J Clin Oncol* 2005;23:7864–7870. [16258088]

13. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography: a new technique. *Acta Radiol* 1953;39:368–376. [13057644]

14. Abdelkefi A, Achour W, Ben Othman T, et al. Difference in time to positivity is useful for the diagnosis of catheter-related bloodstream infection in

hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2005;35:397–401. [15640824]

15. Mohr-O'Hara C, Weinstein MP, Michael-Miller J. Manual and automated systems for detection and identification of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Tenover FC, Tenover FC, eds. *Manual of Clinical Microbiology*. 8<sup>th</sup> ed. Washington, DC: American Society for Microbiology; 2003:185–207.

16. Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis: critical level of quantitative tip cultures. *Arch Intern Med* 1987;147:873–877. [3555377]

17. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis* 2001;32:1249–1272. [11303260]

18. Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. *Blood* 2003;101:2955–2959. [12480713]

19. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol* 2000;21:510–515. [10968716]

20. Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994;15:231–238. [8207189]

21. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;286:700–707. [11495620]

22. Goetz AM, Wagener MM, Miller JM, Muder RR. Risk of infection due to central venous catheters: effect of site of placement and catheter type. *Infect Control Hosp Epidemiol* 1998;19:842–845. [9831940]

23. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;327:1062–1068. [1522842]

24. Cook D, Randolph A, Kernerman P, et al. Central venous catheter replacement strategies: a systematic review of the literature. *Crit Care Med* 1997;25:1417–1424. [9267959]

25. Maki DG, Stolz SS, Wheeler S, Mermel LA. A prospective, randomized trial of gauze and two polyurethane dressings for site care of pulmonary artery catheters: implications for catheter management. *Crit*

*Care Med* 1994;22:1729–1737. [7956275]

26. Raad I, Darouiche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Ann Intern Med* 1997;127:267–274. [9265425]

27. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. *Ann Intern Med* 1997;127:257–266. [9265424]

28. Appelgren P, Ransjö U, Bindeslev L, Espersen F, Larm O. Surface heparinization of central venous catheters reduces microbial colonization in vitro and in vivo: results from a prospective, randomized trial. *Crit Care Med* 1996;24:1482–1489. [8797619]

29. Brismar B, Hardstedt C, Jacobson S, Kager L, Malmborg AS. Reduction of catheter-associated thrombosis in parenteral nutrition by intravenous heparin therapy. *Arch Surg* 1982;117:1196–1199. [6810843]

30. Smith S, Dawson S, Hennessey R, Andrew M. Maintenance of the patency of indwelling central venous catheters: is heparin necessary? *Am J Pediatr Hematol Oncol* 1991;13:141–143. [2069221]

31. Bailey MJ. Reduction of catheter-associated sepsis in parenteral nutrition using low-dose intravenous heparin. *Br Med J* 1979;1:1671–1673. [111759]

32. Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Med* 2000;26:967–972. [10990114]

33. Carrasco MN, Bueno A, de las Cuevas C, et al. Evaluation of a triple-lumen central venous heparin-coated catheter versus a catheter coated with chlorhexidine and silver sulfadiazine in critically ill patients. *Intensive Care Med* 2004;30:633–638. [14722639]

34. Henrickson KJ, Axtell RA, Hoover SM, et al. Prevention of central venous catheter-related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: a randomized, multicenter, double-blind trial. *J Clin Oncol* 2000;18:1269–1278. [10715297]

35. Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998;113:165–171. [9440585]