Ann Hematol (2013) 92:1405–1412
DOI 10.1007/s00277-013-1794-1

ORIGINAL ARTICLE

Guidelines for the use of long-term central venous catheter in children with hemato-oncological disorders. On behalf of supportive therapy working group of Italian Association of Pediatric Hematology and Oncology (AIEOP)

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Received: 26 February 2013 / Accepted: 13 May 2013 / Published online: 16 June 2013
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Abstract In the last 30 years, the use of long-term central venous catheters (CVC) is increased especially for children with hemato-oncological disorders. However, the use of CVC is associated to complications, as mechanical accidents, thrombosis, and infections that can determine a prolongation of hospital stay, an increase of costs, and sometimes life-threatening conditions that require urgent systemic treatment or CVC removal. CVC removal may be troublesome especially in neonates, infants, or any other "highly needed CVC patients"; in these selected cases, the prevention and treatment of CVC-related complications play a pivotal role and specific surveillance programs are crucial. While extensive literature is focused on CVC management in adults, no guidelines are available for children. To this aim, the first recommendations for the management of CVC infectious complication in pediatric age have been written after pediatric and adult literature review and collegial discussion among members of Supportive Therapy working group of Italian Association of Pediatric Hematology and Oncology. Compared to the adult age, the necessity of peripheral vein cultures for the diagnosis of CVC-related infection remains controversial in children because of the poorer venous asset and a conservative, pharmacologically focused management through CVC remains mandatory, with CVC removal to be performed only in selected cases.

Keywords Central venous catheter · Infections · Cancer · Pediatric age

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Introduction

Long-term central venous catheter (CVC) has been increasingly used in the last 30 years for the management of pediatric oncology patients. The CVC is fundamental to deliver safely multidrug chemotherapy and intensive support therapy such as antimicrobial agents, analgesics, blood products, hyperhydration, and hyperosmolar parenteral nutrition. CVC can be either tunneled (single lumen or multilumen) with a subcutaneous cuff adjacent to the catheter exit

site, i.e., Broviac Hickman or Groshong CVC, or totally implanted port system with subcutaneous reservoir [1, 2].

The use of CVC is associated to some adverse events, such as mechanical accidents, infections, and thrombosis that can determine a prolongation of hospital stay and an increase of costs. Moreover, in case of life-threatening situation, urgent removal of the CVC may be required. Catheter-related infections (CRI) cause considerable morbidity in patients with CVC; Gram+ bacteria, coagulase-negative staphylococci (CONS), and *Staphylococcus* aureus are the pathogens most frequently cultured, followed by *Candida* species [1].

The CRI incidence rates reported in literature are 1.7–11.3 cases per 1,000 CVC days [3–5]. In pediatric hemato-oncology patients with long-term CVC, the reported rates were 1.4 per 1,000 CVC days for implantable port (Port-a-Cath) and 1–4.6 per 1,000 CVC days for partially implanted CVC [4–6]. From 27 to 46 % of infected CVC are removed because of persistent bacteremia, despite an adequate systemic antibiotic treatment [4, 5]. Once infected, CVC removal may be difficult, especially in neonates, infant children, or any other patients who have a limited reserve of venous vessels for different reasons (so-called "highly needed CVC patients"). The prevention and treatment of CVC-related complications thus play a pivotal role, and specific surveillance programs are crucial both to monitor the risk factors for CVC complications and to improve their management [1, 4, 6].

While an extensive body of literature is focused on CVC in adults, no guidelines are available for the pediatric patients. To this aim, we reviewed the pediatric and adult literature to propose specific guidelines for the pediatric onco-hematological patients.

Methods

The Working Group (WG) of Supportive Therapy of Italian Association of Pediatric Hematology Oncology (AIEOP) promoted the definition of the guidelines for the management of long-term catheter (CVC) in pediatric onco-hematological patients in collaboration with the WGs of Infection, Coagulation, Surgery and Nursing. In a first meeting in 2011, each WG indicated members skilled in the arguments of CVC and infection. This expert panel defined the topics to discuss and performed a literature search. The key words used for the selection of the studies were "central venous catheter, bloodstream infections, catheter-related infections, oncologic patients and pediatric malignancy." The search was limited to English language papers and the period analyzed was from January 2000 to January 2012. Reference list of papers selected by literature was also used as a source for recommendations. The results of the search were discussed and scored by the members of the panel using the scoring system proposed by Infectious Diseases Society of America (Table 1). The recommendations were proposed and discussed in a second meeting among all members of WGs and the results of this debate were the basis for the final document. The definite document was approved by all members in a third meeting during 2012.

Results

Diagnosis The definitions of CRI according to the international guidelines [1] are summarized in Table 2. Surveillance blood cultures are not indicated in onco-hematological patients and in children who undergo hematopoietic stem cell transplantation [1, 7].

In febrile cancer patients with CVC, the signs and symptoms of infection can be shaded by neutropenia and, in leukemic patients, by concomitant steroid treatment [8]. Therefore, a febrile cancer patient requires an early diagnostic investigation including at least two sets of blood cultures, blood sampling being performed by aseptic technique [9]. In patients with CVC, most of experts recommend to obtain a blood culture set from peripheral vein simultaneously with blood culture set from each lumen of the CVC, before the initiation of an empirical antibiotic therapy (AII) [1, 2]. The amount of blood taken from CVC and from peripheral vein must be equal [1] (AII). Moreover, the use of blood cultures sets for aerobic and anaerobic bacteria is recommended in immunocompromised patients [1] (BII).

In pediatric patients, the compliance to this indication may be difficult in the routine practice, especially in neonates and infants or in children with poor venous asset or with hypotension and shock. On the other hand, CVC is largely used to sample the patients for routine blood tests to avoid the use of peripheral vein that may cause continuous distress and painful experience for patients and parents.

The major advantage of obtaining a set of blood culture from peripheral vein is the possibility to differentiate bacteremia from CRI, according to the points 1, 2 and 3 listed in Table 2. It has been demonstrated that the differential time to positivity (dTTP) is a sensitive and specific method to distinguish bacteremia from CRI. Using a dTTP cutoff of 120 min (or 150 min in pediatric patients) between blood culture from CVC and blood culture from peripheral, the sensitivity resulted in 91 % and the specificity in 94 % [2–4, 8, 10]. Therefore, this method is highly recommended to diagnose a CRI (AI). Moreover, in a patients with double-lumen CVC, a dTTP of 180 min between the blood cultures taken from different lumens allows to distinguish the infected lumen responsible of CRI [3, 11, 12] (AII). In centers that do not routinely adopt microbiological quantitative culture techniques or differential time to positivity method, this expert panel considers reasonable the choice to withdraw the blood culture only from CVC of a febrile pediatric patients (CII). Moreover, in a patient with single-lumen CVC, it is recommended to perform at least two

Table 1 IDSA-United States Public Health Service grading system for ranking recommendations

Quality of evidence		Strength of recommendation	
I	Evidence from ≥1 properly randomized, controlled trial	A	Good evidence to support a recommendation for use
II	Evidence from ≥1well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments	B	Moderate evidence to support a recommendation for use
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	C	Poor evidence to support a recommendation

blood cultures in a short span of time (15–30 min) before the start of antibiotic treatment to distinguish a real bacteremia/CRI from a false-positivity due to contamination of health personnel [1, 4, 10] (BIII). In fact, in case of isolation of common skin bacteria (CONS, *Corynebacteria* apart from *Campylobacter jejuni*, *Propionibacteria*), there is a general agreement that two blood cultures are needed to attribute a causative role to these opportunistic germs [1, 3, 8] (AI). The execution of at least two blood cultures at a short span of time increases the sensitivity of the test: 65 % with one blood culture, 88 % with two blood cultures [13].

In the presence of signs of CVC exit site or CVC tunnel infection, a skin swab must be performed [1–3, 8] (AI). In Table 3, the main risk factors for CRI on the basis of published reports are summarized.

Empirical therapy for catheter-related bloodstream infection Febrile cancer patients with CVC need a prompt antibiotic treatment after obtaining blood cultures [1]. At the beginning, when catheter-related bloodstream infection (CRBSI) is suspected but not yet documented, the choice of antibiotic treatment is empirical, based on the principles of febrile neutropenia, i.e., the use of broad-spectrum antibiotic/s targeting Gram+ and Gram−, administered through the CVC [1, 2] (BII). The epidemiology of the center, together with the clinical condition of the patient and his/her

Table 2 Definition of catheter-related infection (CRI)

Exit site infections	Clinical signs of inflammation (redness, swelling, pain, bleeding) at the site of leakage of the CVC
Infections of the subcutaneous tunnel	Signs of inflammation along the subcutaneous way of CVC at a distance >2 cm from the point of discharge of the CVC
Infection of the port-à-cath pocket	Signs of inflammation in the pocket of the port +/− exudation or necrosis of the overlying skin
CVC-related bloodstream infections (CRSBI)	Bacteremia or fungemia in a patient with a CVC with clinical symptoms (fever, chills +/− hypotension) and detection of at least one positive blood culture from peripheral vein in the absence of other infectious sources The diagnosis is supported by: 1. Positive semiquantitative (> 15 cfu) or quantitative (>10^2 cfu) culture of the tip of the CVC removed and concomitant blood culture from peripheral vein (AII); 2. Concomitant positivity of quantitative blood cultures from CVC and peripheral vein with a 3:1 ratio (AII); 3. Different positivization time (dTTP) between blood cultures from CVC and peripheral vein (positivization of blood cultures from CVC at least 2 h before the peripheral one) [1–4, 8, 40] (AII) 4. Infection at the exit site or in the subcutaneous tunnel with positive blood cultures from CVC
Probable CVC-related infection	Resolution of the fever within 48 h after the CVC removal in a patient with positive blood cultures with fever resistant to therapy
Possible CVC-related infection	Bacteremia by pathogens typically causative of CVC infection (*S. epidermidis*, *S. aureus*, *Candida* spp.); bacteremia without detection of other infectious foci
Polymicrobial CRBSI	Sepsis with isolation of >1 pathogen from single blood culture or from two different blood cultures in 24 h [1] (AI)

Table 3 Main risk factors for catheter-related infection

Risk factor	Notes	Type of study	Recommendation
Immunosuppression and level of neutropenia [2]	The type and severity of immunosuppression are associated with increased incidence of CRI; the duration of neutropenia correlates with risk of septic complications and with mortality	Adult population Guidelines Onco-hematological population	BII
Underline disease [6, 39]	Hematological disease correlates with increased incidence of infectious complications due to more frequent catheter manipulation	Pediatric population Prospective, observational study Onco-hematological population	BII
The time of CVC in situ permanence [2, 41]	It is straight correlated to the risk of infectious complication	Adult population Guidelines, review	BII
Frequency of manipulation [2, 9]	The frequency of manipulation is straight correlated to the risk of infectious complication	Adult population Guidelines, review	BII
Children age [6, 39]	Children age <4–6 years correlates with risk of septic complications	Pediatric population Prospective study Onco-hematological population	BII
Number of CVC lumen [6]	Double lumen CVC is associated with increased incidence of CRI	Pediatric population Prospective study Onco-hematological population	BII
Use of the subclavian vein [42, 43]	The use of the subclavian vein correlates with a reduced risk of infectious complications	Adult population Review, observational study	BII
Microbial colonization of the skin [2, 41, 42, 44]	Microbial colonization of the skin at the point of connection or the junction of the CVC is associated with increased incidence of CRI	Adult/pediatric population Guidelines, review, observational study	BII
Parenteral nutrition (TPN) or blood components administration [2, 41, 42, 44]	Administration of TPN or blood components through the CVC is associated with increased risk of septic complication	Adult/pediatric population Guidelines, review, observational study	BII
Prolonged hospitalization [2, 41, 42, 44]	A prolonged hospitalization before the implantation of the CVC correlates with increased risk of infectious complication	Adult/pediatric population Guidelines, review, observational study	BII

recent medical history, is to take into account in the choice of the type of antibiotic and of its use alone or in combination with other antibiotics [1, 2] (BII). The empirical treatment generally involves the use of a third/fourth generation cephalosporin (ceftazidime, cefepime) or of a β-lactam β-lactamases antibiotic (piperacillin/tazobactam). The addition of an aminoglycoside (amikacin) is not mandatory but it is recommended in case of suspicion of infection by multidrug-resistant *Pseudomonas aeruginosa* or *Escherichia coli* [1–3, 14–18] (BII). The carbapenems (imipenem, meropenem) have a broad spectrum of action and are active against the extended-spectrum β-lactamases (ESBL) strain producers but their use is not indicated as first choice in all CRSBI for the risk to select carbapenemases producer strains. Glycopeptides (teicoplanin, vancomycin) are not indicated as first-line treatment, as its early use is not associated with improvement of survival [1, 2]. Its use as first-line treatment may be justified in case of high incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections or in patients with a medical history positive for MRSA or in case of clinical picture of severe sepsis or infection of the subcutaneous tunnel [1–3, 14, 15] (BII).

The antibiotic treatment has to be reassessed in case of persistence of fever after 72–96 h from the initiation of empiric therapy (BII) and modified according to the results of blood cultures and/or on the basis of clinical conditions of the patients. The duration of antimicrobial treatment in case of CRBSI is of 10–14 days [1–3, 19] (BII). In case of bacteremia complicated with thrombosis, endocarditis, and osteomyelitis, treatment should be continued for at least 6 weeks [1, 8].

The empirical use of an antifungal is not generally indicated as first choice in the treatment of CRBSI but may be suggested in cases of septic shock [1, 2, 20]. In patients with one or more risk factors for sepsis by *Candida*, such as total parenteral nutrition, previous prolonged broad-spectrum antibiotic treatment, previous or current colonization in multiple sites by *Candida*, or recent hematopoietic stem cells or solid organ transplant, it is recommended to associate to initial antibiotic treatment an antifungal treatment for *Candida* [1, 2] (BII). Echinocandins are the first choice antifungal treatment both in neutropenic and non-neutropenic patients for infections caused both by *Candida albicans* and *Candida* non-*albicans*. Second choice drugs are liposomal amphotericin B (LAMB) and voriconazole. Fluconazole is indicated for patients colonized by *Candida* fluconazole-sensitive strains or patients with a proven candidemia by *C. albicans* and no hemodynamic instability [1, 2] (BIII).

Exit site and tunnel infection An uncomplicated exit site infection in non-neutropenic patient, characterized by hyperemia and redness, is treated with topical antimicrobials chosen according to antibiotic susceptibility test [1] (BIII). In the neutropenic patient, or in presence of fever, purulent drainage or no response to topical treatment alone, an intravenous antimicrobial therapy together with topical treatment is indicated [1] (BII).

The infection of the tunnel of partially implantable CVC or of the Port-a-cath reservoir, requires the CVC removal and systemic antimicrobial treatment for at least 7–10 days [1] (BIII). Most of these infections are caused by Gram− (CONS). Therefore, it is indicated to include a glycopeptide in the initial antibiotic treatment until the causative germ is identified [1, 21] (BIII).

Targeted therapy Several studies, even in non-oncologic setting, showed the success of systemic treatment in the resolution of CRBSI without CVC removal [1, 4]. Several authors agree that in children with CRBSI it is generally worthy to start empirical treatment and to postpone the CVC removal, performing it only in case of non-response [1, 4] (BIII). Once the germ is identified, the empiric antibiotic therapy has to comply with the susceptibility test. The indications for targeted therapy are summarized in Table 4. Antibiotics are generally administered intravenously by slow infusion. An alternative method of administration is the intravenous continuous infusion. Antibiotics that exhibit a time-dependent bactericidal activity and 12–24 h stability in solution at room temperature, such as beta-lactams and glycopeptides, can be used by continuous 24-h administration. The rationale is to ensure high (>MIC) and continuous antibiotic concentrations systemically through the CVC, to avoid frequent CVC manipulation and rapid infusion that can generate septic emboli [22–25]. The use of β-lactams or glycopeptides in a 24-h continuous infusion through the CVC is indicated in case of bacteremia by Gram+ and Gram− drug-resistant or difficult to eradicate germs, where it is important to preserve the CVC. The ideal concentrations are <5 mg/ml vancomycin and <6 mg/ml ceftazidime [23–25] (BIII). This modality of infusion may also be used in case of CVC subcutaneous tunnel infections [21] (BIII).

Lock therapy Lock therapy is indicated in case of CVC colonization by CONS or other germs in patients with highly needed CVC. Lock therapy is indicated for 10–14 days in order to prevent the removal of CVC [26] (BII). In CRBSI, it can be used in association with systemic antibiotic for 7–14 days because it has been associated to a reduction of CRBSI recurrence. The renewal of the lock is suggested every 24–48 h, without serial monitoring with blood cultures [1, 5, 27–30] (BIII).

CVC removal The removal of CVC is indicated in cases of CRI by *S. aureus*, *P. aeruginosa*, mycobacteria or fungi, or in case of suppurative thrombophlebitis, endocarditis, and bacteremia unresponsive to 72–96 h of adequate targeted antibiotic therapy [1–3, 5, 9] (BII). In case of *Candida* infection, there are no studies that demonstrate the real benefit of early CVC removal, but all experts agree that success of therapy is associated with early CVC removal [31–33] (BIII). There are no studies to assess what is the optimal time for a CVC re-implantation. The CVC re-implantation requires at least two negative blood cultures, performed after appropriate antibiotic therapy (at least 5–7 days), to confirm the eradication of the pathogen [1, 3] (BIII).

In case of fungal infection, antifungal treatment should be continued for at least 14 days after the finding of the first negative blood culture, except for documented fungal localization in other sites [1].

Prophylaxis It is known that compliance with the rules of asepsis and proper handling of the CVC is the basis for the prevention of CVC-related infections [1, 2, 9, 19] (AI). No evidence is supported in the literature about the success of the systemic antibacterial prophylaxis in the reduction of the incidence of CRBSI in adult patients [9, 34]. In oncologic neutropenic adults and children, the administration of vancomycin/teicoplanin before the placement of a tunneled CVC does not significantly reduce the number of Gram + CRI [34]. The use of systemic antimicrobials is not routinely indicated before CVC insertion or during its use [34] (BI). In pediatric patients with severe neutropenia or fever, the use of short-term, prophylactic, systemic, preoperative therapy with intravenous glycopeptide may be considered (CIII). A wide variety of solutions containing antibiotics or antiseptics have been used for CVC irrigation (flushing) or

Table 4 Targeted therapy [1, 2, 8]

Pathogen	1st choice treatment	Alternative treatments	Notes
Gram + cocci			
Staphylococcus aureus			Recommended CVC removal and targeted antibiotic treatment for at least 4–6 weeks. Stop treatment at 14th day if infection is not complicated or in non-neutropenic patient, not transplanted and without comorbidities or risk factors such as diabetes and steroidal or immunosuppressive therapy. Lock therapy is indicated; CVC removal in case of no response or complicated infection
Methicillin-sensitive	Penicillin penicillinase-resistant	Cephalosporins, glycopeptide	
Methicillin-resistant	Vancomycin	Teicoplanin, daptomycin, linezolid, rifampicin + vancomycin, vancomycin + gentamicin	
Coagulase-negative staphylococci (CONS)			Generally benign clinical course, intravenous antibiotic treatment for 7–14 days and in persistently neutropenic patients for at least 7 days after the resolution of the fever
Methicillin-sensitive	Penicillin penicillinase-resistant	Cephalosporins, glycopeptide	
Methicillin-resistant	Vancomycin	Teicoplanin, daptomycin, linezolid	
Enterococci			Intravenous antibiotic treatment for 7–14 days, and in persistently neutropenic patients for at least 7 days after the resolution of the fever
Ampicillin-sensitive	Ampicillin sulbactam + aminoglycoside	Aminoglycoside + glycopeptide	
Ampicillin-resistant vancomycin-sensitive	Vancomycin or teicoplanin + aminoglycoside	Linezolid/daptomycin + aminoglycoside	
Ampicillin-resistant vancomycin-resistant	Linezolid/daptomycin		
Gram− bacilli			
Escherichia coli and *Klebsiella* spp.			In case of resistance to carbapenems, targeted treatment with colistin or aminoglycoside. In case of persistent fever and/or positive cultures, CVC removal indicated
ESBL neg	3rd-generation cephalosporins	Quinolone	
ESBL pos	Carbapenem	Quinolone	
Enterobacter species, *Serratia marcescens*	Carbapenem	Ciprofloxacin/cefepime	In case of persistent fever and/or positive cultures, CVC removal indicated
Acinetobacter species	Ampicillin sulbactam, carbapenem		In case of persistent fever and/or positive cultures, CVC removal indicated
Pseudomonas aeruginosa	3rd- to 4th-generation cephalosporins, carbapenem, piperacillin–tazobactam+/– aminoglycoside		In case of persistent fever and/or positive cultures, CVC removal indicated
Stenotrophomonas maltophilia	Cotrimoxazole	Colistin/tigecycline/ticarcillin–clavulanic acid	In case of persistent fever and/or positive cultures, CVC removal indicated
Candida spp.			CVC should be removed and antifungal therapy should be performed for 14 days from the first negative blood culture. The use of systemic antifungal therapy associated with lock therapy is still under investigation
C. albicans	Fluconazole/echinocandins in neutropenic patients	Echinocandins/LAMB	
C. non-*albicans*	Echinocandins	LAMB	

CONS coagulase-negative staphylococci

lock therapy for a period ranging from several hours to 24–48 h [34–38]. A recent meta-analysis on adult patients has showed that CVC flushing with vancomycin and low-dose heparin, compared to heparin alone, reduces the risk of CVC early infection (within 30 days) in high-risk patients [34]. In a randomized study, lock therapy with vancomycin has been shown to be more effective than flushing with normal saline or heparin [37] (AIII). As a low CRI rate has been documented in several pediatric studies using normal saline flushing, this expert panel recommends the use of vancomycin flushing solution for the centers that have a higher incidence of CRI by CONS or MRSA. [6, 17, 26, 39] (BII).

Conclusions

This is the first review about the management of CVC infectious complications that proposes specific indications about pediatric onco-hematological patients. Considering the small

number of well done study in pediatric age, many considerations in this paper are similar to the onco-hematological adult population. However, if compared to the adult age, in children a major indication is the importance of conservative, pharmacological therapy through CVC and the CVC remotion postponement due to the exiguity of venous access. The necessity to perform periferal vein cultures remains controversial in children, due to the younger age and the poor venous asset.

Other prospective randomized pediatric studies are necessary to obtain specific indications about the diagnosis of CVC infection and the time for remotion and replacement of the device.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: update by the Infectious Diseases Society of America. Clin Infect Dis 49(1):1–45
2. Wolf HH, Leithäuser M, Maschmeyer G, Salwender H, Klein U, Chaberny I, Weissinger F, Buchheidt D, Ruhnke M, Egerer G, Cornely O, Fätkenheuer G, Mousset S (2008) Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Central venous catheter-related infections in hematology and oncology: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 87(11):863–76
3. Simon A, Bode U, Beutel K (2006) Diagnosis and treatment of catheter-related infections in paediatric oncology: an update. Clin Microbiol Infect 12(7):606–20
4. Flynn PM (2009) Diagnosis and management of central venous catheter-related bloodstream infections in pediatric patients. Pediatr Infect Dis J 28:1016–7
5. Megged O, Shalit I, Yaniv I, Fisher S, Livni G, Levy I (2010) Outcome of antibiotic lock technique for persistent central venous catheter-associated coagulase-negative *Staphylococcus* bacteremia in children. Eur J Clin Microbiol Infect Dis 29(2):157–61
6. Pinon M, Bezzio S, Tovo PA, Fagioli F, Farinasso L, Calabrese R, Marengo M, Giacchino M (2009) A prospective 7-year survey on central venous catheter-related complications at a single pediatric hospital. Eur J Pediatr 168(12):1505–12, Dec
7. Chizuka A, Kami M, Kanda Y, Murashige N, Kishi Y, Hamaki T, Kim SW, Hori A, Kojima R, Mori SI, Tanosaki R, Gomi H, Takaue Y (2005) Value of surveillance blood culture for early diagnosis of occult bacteremia in patients on corticosteroid therapy following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 35(6):577–582
8. Tomlinson D, Mermel LA, Ethier M-C, Matlow A, Gillmeister B, Sung L (2011) Defining bloodstream infections related to central venous catheters in patients with cancer: a systematic review. Clin Infect Dis 53(7):697–710
9. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, Lipsett PA, Masur H, Mermel LA, Pearson ML, Raad II, Randolph AG, Rupp KE, Saint S, Healthcare Infection Control Practices Advisory Committee (HICPAC) (2011) Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 52(9):162–193
10. Scheinemann K, Ethier MC, Dupuis LL, Richardson SE, Doyle J, Allen U, Sung L (2010) Utility of peripheral blood cultures in bacteremic pediatric cancer patients with a central line. Support Care Cancer 18(8):913–9
11. Guembe M, Rodríguez-Créixems M, Sánchez-Carrillo C, Pérez-Parra A, Martín-Rabadán P, Bouza E (2010) How many lumens should be cultured in the conservative diagnosis of catheter-related bloodstream infections? Clin Infect Dis 50(12):1575–1579
12. Gaur AH, Flynn PM, Heine DJ, Giannini MA, Shenep JL, Hayden RT (2005) Diagnosis of catheter-related bloodstream infections among pediatric oncology patients lacking a peripheral culture, using differential time to detection. Pediatr Infect Dis J 24(5):445–9
13. Cockerill FR III, Wilson JW, Vetter EA (2004) Optimal testing parameters for blood cultures. Clin Infect Dis 38:1724–1730
14. Adler A, Yaniv I, Solter E, Freud E, Samra Z, Stein J, Fisher S, Levy I (2006) Catheter-associated bloodstream infections in pediatric hematology–oncology patients: factors associated with catheter removal and recurrence. J Pediatr Hematol Oncol 28(1):23–28
15. Adler A, Yaniv I, Steiberg R, Solter E, Samra Z, Stein J, Levy I (2006) Infectious complications of implantable ports and Hickman catheters in paediatric haematology–oncology patients. J Hosp Infect 62:358–365
16. Averbuch D, Makhoul R, Rotshild V, Weintraub M, Engelhard D (2008) Empiric treatment with once-daily cefonicid and gentamicin for febrile non-neutropenic pediatric cancer patients with indwelling central venous catheters. J Pediatr Hematol Oncol 30(7):527–532
17. Cesaro S, Corrò R, Pelosin A, Gamba P, Zadra N, Fusaro F, Pillon M, Cusinato R, Zampieri C, Magagna L, Cavaliere M, Tridello G, Zanon G, Zanesco L (2004) A prospective survey on incidence and outcome of Broviac/Hickman catheter-related complications in pediatric patients affected by hematological and oncological diseases. Ann Hematol 83(3):183–188
18. Vescia S, Baumgärtner AK, Jacobs VR, Kiechle-Bahat M, Rody A, Loibl S, Harbeck N (2008) Management of venous port systems in oncology: a review of current evidence. Ann Oncol 19(1):9–15
19. Raad I, Hanna HA, Maki D (2007) Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis 7:645–657
20. Giacchino M, Milano GM, Carraro F, Bezzio S, Pegoraro A, Aversa F, Cesaro S (2011) Current evidence of antifungal prophylaxis and therapy in pediatric patients. Pediatr Rep 24;3(1):e6
21. Giacchino M, Bezzio S, Chiapello N, Saracco P, Fagioli F, Caviglia I, Moroni C, Castagnola E (2007) Continuous antibiotic infusion for salvage therapy of partially implanted central venous catheter tunnel infections due to staphylococci. Pediatr Blood Cancer 49(7):1010–1012
22. Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME (2005) Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. Lancet Infect Dis 5:581–589
23. Chua K, Howden PB (2009) Treating Gram-positive infections: vancomycin update and whys, wherefores and evidence base for continuous infusion anti-Gram-positive antibiotics. Curr Opin Infect Dis 22:525–534
24. Pea F, Viale P, Damiani D, Pavan F, Cristini F, Fanin R, Furlanut M (2005) Ceftazidime in acute myeloid leukemia patients with febrile neutropenia: helpfulness of continuous intravenous infusion in maximizing pharmacodynamic exposure. Antimicrob Agents and Chemoth 49(8):3550–3553
25. Courter JD, Kuti JL, Girotto JE, Nicolau DP (2009) Optimizing bactericidal exposure for β-lactams using prolonged and continuous infusions in pediatric population. Pediatr Blood Cancer 53:379–385

26. Cesaro S, Cavaliere M, Spiller M, Rossi L, Magagna L, Gavin P, Sonetto M, Carli M (2007) A simplified method of antibiotic lock therapy for Broviac–Hickman catheters using a CLC 2000 connector device. Support Care Cancer 15:95–99
27. De Sio L, Jenkner A, Milano GM, Ilari I, Fidani P, Castellano A, Gareri R, Donfrancesco A (2004) Antibiotic lock with vancomycin and urokinase can successfully treat colonized central venous catheters in pediatric cancer patients. Pediatr Infect Dis J 23(10):963–965
28. Fernandez-Hidalgo N, Almirante B, Calleja R, Ruiz I, Planes AM, Rodriguez D, Pigrau C, Pahissa A (2006) Antibiotic-lock therapy for long-term intravascular catheter-related bacteraemia: results of an open, non-comparative study. J Antimicrob Chemother 57:1172–1180
29. Rijnders BJ, Van Wijngaerden E, Vandecasteele SJ, Stas M, Peetermans WE (2005) Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. J Antimicrob Chemother 55:90–94
30. Fortún J, Grill F, Martín-Dávila P, Blázquez J, Tato M, Sánchez-Corral J, García-San Miguel L, Moreno S (2006) Treatment of long-term intravascular catheter-related bacteraemia with antibiotic-lock therapy. J Antimicrob Chemother 58:816–821
31. Nucci M, Colombo AL, Silveira F, Richtmann R, Salomão R, Branchini ML, Spector N (1998) Risk factors for death in patients with candidemia. Infect Control Hosp Epidemiol 19:846–850
32. Raad I, Hanna H, Boktour M, Girgawy E, Danawi H, Mardani M, Kontoyiannis D, Darouiche R, Hachem R, Bodey GP (2004) Management of central venous catheters in patients with cancer and candidemia. Clin Infect Dis 38:1119–1127
33. Velasco E, Doyle Portugal R (2011) Factors prompting early central venous catheter removal from cancer patients with candidaemia. Scand J Infect Dis 43:27–31
34. van de Wetering MD, van Woensel JB (2007). Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients. Cochrane Database Syst Rev. (1):CD003295.
35. Carratala J, Niubo J, Fernandez-Sevilla A, Juvé E, Castellsagué X, Berlanga J, Liñares J, Gudiol F (1999) Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. Antimicrob Agents Chemother 43:2200–2204
36. Henrickson KJ, Axtell RA, Hoover SM, Kuhn SM, Pritchett J, Kehl SC, Klein JP (2000) 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 18:1269–1278
37. Safdar N, Maki DG (2006) Use of vancomycin-containing lock or flush solutions for prevention of bloodstream infection associated with central venous access devices: a meta-analysis of prospective, randomized trials. Clin Infect Dis 43:474–484
38. Sanders J, Pithie A, Ganly P, Surgenor L, Wilson R, Merriman E, Loudon G, Judkins R, Chambers S (2008) A prospective double-blind randomized trial comparing intraluminal ethanol with heparinized saline for the prevention of catheter-associated bloodstream infection in immunosuppressed haematology patients. J Antimicrob Chemother 62:809–815
39. Fratino G, Molinari AC, Parodi S, Longo S, Saracco P, Castagnola E, Haupt R (2005) Central venous catheter-related complications in children with oncological/hematological diseases: an observational study of 418 devices. Ann Oncol 16(4):648–654, Apr
40. Guembe M, Rodríguez-Créixems M, Sánchez-Carrillo C, Martín-Rabadán P, Bouza E (2012) Differential time to positivity (DTTP) for the diagnosis of catheter-related bloodstream infection: do we need to obtain one or more peripheral vein blood cultures? Eur J Clin Microbiol Infect Dis 31(7):1367–72
41. Rosado V, Romanelli RM, Camargos PA (2011) Risk factors and preventive measures for catheter-related bloodstream infections. J Pediatr 87(6):469–477
42. Weber DJ, Rutala WA (2011) Central line-associated bloodstream infections: prevention and management. Infect Dis Clin N Am 25:77–102
43. Hamilton HC, Foxcroft D (2007) Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long term intravenous therapy. Cochrane Database Syst Rev 18(3), CD004084
44. Almuneef MA, Memish ZA, Balkhy HH (2006) Rate, risk factors and outcomes of catheter-related bloodstream infections in a paediatric intensive care unit in Saudi Arabia. J Hosp Infect 62:207–213