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Original article

Central venous catheter related bloodstream infections in adult patients on home parenteral nutrition: Prevalence, predictive factors, therapeutic outcome

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SUMMARY

Background: The prevalence of central venous catheter (CVC)-related blood-stream infections (CRBSI), infecting agents and the effectiveness of antibiotic therapy were evaluated in 172 adult patients on Home Parenteral Nutrition (HPN) at the Clinical Nutrition Outpatient Unit of Federico II University Hospital in Naples, Italy.

Materials and methods: The study population consisted of 127 oncological (74%) and 45 (26%) non-oncological patients, for a total of 53,818 (median 104; range 14–1080) CVC days.

Results: Ninety-four CRBSIs were diagnosed on 238 CVC (infection rate 1.74/1000 CVC days). Coagulase negative (CoNs) Staphylococci were the most frequently infecting agents (52.8% as single agent) with 17.1% *Staphylococcus epidermidis* infections. Eighty-three percent *S. epidermidis* were beta-lattamase producer (BLACT), 66.6% methicillin-resistant (MR) and 55.5% had a MIC for Vancomicin $\geq$1. Gram-negative bacteria represented 18.6% infections, fungi 7.1%, finally 15% infections were polymicrobial. Previous catheterizations and the presence of an enterocutaneous stoma were significantly related with a higher infection risk ($p < 0.0001$ in both cases).

Conclusions: CRBSI and antibiotic resistance of infecting agents remain an important challenge in adult patients on HPN; an active research on strategies to counteract the phenomena is required.

1. Introduction

Parenteral nutrition (PN) is a lifesaving treatment for patients with chronic benign intestinal failure and an effective support for patients with gastrointestinal involvement by neoplastic diseases. Home PN (HPN) is now a well recognized and widely spread procedure which may be performed in the long-term, thus ameliorating patients' quality of life and reducing public health costs [1,2].

Central venous catheter (CVC)-related blood-stream infections (CRBSI) represent the most serious and common complication of long-term HPN and can contribute to patients' morbidity and mortality; they usually require hospital admission, with increasing costs for the healthcare system [3–5].

1.1. Aim of the study

The study aims: 1) to retrospectively evaluate CVC infection rate and the type of infectious agent determining CRBSI in a setting of oncological and non-oncological outpatients on HPN; 2) to evaluate possible predictive risk factors of CVC infection and effectiveness of antibiotic therapy.

2. Patient and methods

A retrospective, observational study on all consecutive patients receiving HPN from January 2010 to December 2012 at the Clinical

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Medicine and Surgery Department of Federico II University Hospital in Naples, Italy, was performed. Adult patients receiving HPN for less than 2 weeks and those receiving PN through a peripheral vein were excluded from the study.

2.1. Patients

Information about age, gender, underlying disease (oncological, non-oncological), implanted CVC type, number of CRBSI, infecting agent type, days of catheterization, infusion frequency, previous CVC infections, duration, modality of antibiotic treatment and clinical outcome were collected for each patient.

2.2. CRBSI diagnosis

CRBSI diagnosis was made according to the ESPEN and IDSA guidelines [6,7]. CRBSI is defined as isolation of the same microorganism from semi-quantitative or quantitative cultures of both blood drawn from the catheter lumen and the blood peripherally drawn of the patient with clinical symptoms of a bloodstream infection and no other apparent source of infection.

In some circumstances, in particular in terminal oncologic patients already followed by the oncologist and/or the medical practitioner, empiric antibiotic therapy was started before taking blood for culture. In these cases, when no other sources of infection were suspected, CRBSI diagnosis was performed according to hard clinical findings such as fever and shivering during catheter use, despite the negative/missing blood culture results.

Before HPN initiation, all patients and/or their caregivers received oral and written instructions by the clinical-nutrition team on CVC aseptic management and how to recognize both infectious and non-infectious complications [8,9].

2.3. Statistical analysis

The data obtained were analyzed with specific software for statistical analysis (SPSS 15.0). Results are expressed as mean, standard deviation and range. The *t*-test was used for comparison of unpaired data and χ^2 test for proportions. A logistic regression analyzed the correlation between variables. Multi-variate analysis was applied for risk factor evaluation. Differences among variables were considered statistically significant for p values <0.05.

3. Results

One hundred seventy two [91 (53%) M, 81 (47%) F] patients receiving HPN between January 2010 and December 2012 at the Clinical Nutrition Unit were evaluated.

The study population consisted of 127 (74%) oncological and 45 (26%) non-oncological adult patients, for a total of 53,818 days of catheterization and 49,254 days of HPN (Table 1). The type of disease in oncological and non-oncological patients is detailed in Table 2.

HPN frequency was 7 days per week in 151 (88%) patients, and 3–5 days per week in 21 (12%) patients.

In non-oncological patients, HPN generally began soon after CVC insertion (1 ± 2 days, min 0, max 10, median 1), whereas in oncological patients CVC generally was previously inserted for intravenous chemotherapy (CHT), even several months before beginning HPN (71 ± 108 days, 0–639, median 20.5). Twenty-four (14.5%) out of 172 patients had an enterocutaneous stoma.

A total of 238 CVC were inserted in 172 patients; the type of catheters inserted was detailed in Table 1. Forty-eight out of 172 (27.9%) patients had already undergone a previous catheterization. Globally, ninety-four CRBSIs were diagnosed on 238 inserted CVC, corresponding to an infection rate of 1.74/1000 CVC days.

In 70/94 (74.5%) cases blood cultures were positive. In 24/94 (25.5%) cases blood cultures were negative due to the starting of empiric antibiotic therapy before blood culture.

By focusing the attention only on the 70 infections with positive blood culture results (Table 3), in 55/70 (78.6%) cases the infection was due to a single infecting agent and in 15/70 (21.4%) to 2 or more germs: 4 with fungi, 9 with 2 infecting agents and 2 with 3 agents, in these last cases, fungi were always present.

Finally, 83.3% (15/18) isolated *S. epidermidis* were beta-lactamase producer, 66.6% (12/18) methicillin resistant and 66.6% (12/18) had a Minimal Inihibiting Concentration (MIC) for Vancomicine ≥1; 71.4% (5/7) *S. aureus* infections were methicillin-resistant (MRSA) with an elevated MIC for vancomicin.

3.1. Clinical outcome

In the 24/94 cases with negative cultures and hard clinical findings for CVC infection, the CVCs were promptly removed and empiric antibiotic therapy started.

As regards the 70 cases with positive blood results, 17 (24.3%) short-term CVCs were immediately removed; in 20/70 (28.6%) cases, according the current guidelines [13,14], the catheter was immediately removed for 9 fungal/polymicrobial infections, 7 S. aureus and 4 Gram negative (3 Pseudomonas, 1 Klebsiella pneumoniae) infections. As far as secondary complications, 3 S. aureus infections were complicated by septic pneumonia and 1 by septic endocarditis. Two infections by Gram negative bacteria were complicated by septic shock; 4 infections were associated with venous thrombosis.

Systemic and Local Antibiotic Therapy (Antibiotic Lock Therapy) were performed in the remaining 33/70 (41.14%) cases (Table 4), and in 22/33 (66.7%) cases the catheter salvage was successful.

Median antibiotic therapy length was 21 (range) 14–28 days according to the type of infection to treat.

A logistic regression model which considered previous catheterization, CVC use also for chemotherapy, type of catheter and the presence of a entero-cutaneous stoma as confounding variables, showed that a previous catheterization was significantly related with a higher infection risk ($p < 0.001$).

The number of infections per patient was positively related with days of catheterization ($r = 0.57$; $p < 0.0001$) and of HPN ($r = 0.61$; $p < 0.000$), whilst it was not related neither with time lasted between CVC implant and HPN initiation, nor with the weekly infusion rate.

The infection rate was higher in patients with a cutaneous stoma ($p = 0.001$), with no differences in the type of infecting agents between patients with or without stoma.

The absolute number of CVC-related bloodstream infections is significantly different ($p < 0.0001$) but, when corrected for the CVC infection rate, the difference is not statistically significant. Finally, there were no differences in the type of infecting agents between oncological and non-oncological patients, as well as, while considering different types of implanted catheters.

4. Discussion

CRBSI is a severe and frequent complication and a common cause of hospitalization for adult patients on HPN [3,9]. The infection rates reported in literature vary from 0.35 to 2.0/1000 days of catheterization, depending on age and type of patients followed, i.e oncological or non-oncological, acute or chronic basic disease, hospitalized or home patients and catheter handling frequency [3,8–15]. Our nutritional team constantly monitored the

Table 1
Characteristics of the 172 patients followed up from January 2010 to December 2012. Data are shown as mean ± DS and range.

	Patients, *n* (%)	M/F, *n* (%)	Age (years)	Days of cath (mean ± DS and range)	Days of HPN (mean ± DS and range)	CVC-IR (*n*/1000 CVC days)	Total CVC implanted, *n* (%)	Type of implanted catheter			
								Port	Long term tunneled CVC	Short term non tunneled CVC	PICC
Non onco	**45** (26%)	21/24	58.6 ± 17.3 (21–83)	**658.8 ± 395.6 (40–1080)	**579.9 ± 379.5 (40–1080)	1.75 ± 2.47	93 (39.1%)	17/93 (18.3%)	37/93 (39.8%)	24/93 (25.8%)	15/93 (16.1%)
Onco	**127** (74%)	70/57	63.5 ± 12.6 (16–88)	**164.1 ± 210.1 (14–1047)	**157.1 ± 202.8 (14–1047)	1.69 ± 4.26	145[a] (60.9%)	108/145 (74.5%)	0	25/145 (17.2%)	12/145 (8.3%)
Total	**172** (100%)	91/81 (53%)/(47%)	62.0 ± 13.5 (16–88)	190 ± 248 (14–1080)	179 ± 239 (14–1080).	1.74	238	125/238 (52.5%)	37/238 (15.5%)	49/238 (20.6%)	27/238 (11.4%)

Non onco = non-oncological patients; Onco = oncological patients; CVC = central venous catheter; PICC = peripherally inserted central venous catheter; Cath = catheterization; HPN = home parenteral nutrition. CVC-IR = CVC infection rate = /1000 CVC days.
**$p < 0.01$ Non-oncological vs oncological patients.
[a] **96** (75.5%) CVC were also used for CHT.

phenomena of CRBSI in the time, in particular in adult patients on HPN, and evaluated possible strategies to reduce the infection rate; the appropriate CVC management (adequate personnel, patient and care giver's training) seems a key factor to stem the infection rate in the time [8,10].

In the past years, uncomplicated CVC-related bloodstream infections due to coagulase-negative staphylococci were successfully treated in a high (89%) percentage of cases [16,17]. Presently, whilst the overall infection rate is progressively decreasing in the years, an increasing and alarming antibiotic resistance has been observed for all bacteria, particularly for *S. epidermidis* and CoNs, the most common infectious agents, with decreased opportunities of CVC saving [8,10,16,17].

One of the several reasons for antibiotic therapy failure could be the ability of some bacteria to produce an increased impermeable biofilm, requiring higher concentrations and prolonged administration of antibiotics to defeat the bacteria. The bacteria growing in the biofilm are in a dormant but viable state and initially may fail to grow in culture, with false-negative culture findings; it can regenerate after the interruption of antibiotic therapy, thus causing infection relapse [18–21].

For the same reasons, early CRBSI symptoms have changed over time, thus masking or delaying the diagnosis [22,23]. In the last years, in fact, the well-defined CRBSI symptoms (shivering followed by high temperature, strictly associated with parenteral nutrition infusion) have become less frequent at the onset of infection, whereas in 57.6% cases, non-specific symptoms such as prolonged mild fever in the absence of shivering, osteo-articular pain and headache (not strictly related to nutrition infusion time) have been observed. Despite a lack of observation in literature regarding the fading of CVC infection symptoms, Machado et al. reported evidence of catheter tip infection in spite of the absence of clinical symptoms in 50% of CVC used for Parenteral Nutrition and removed after therapy termination according to prescription [24]. Our study confirms a higher risk of infection in patients who have undergone a previous catheterization [25].

Our work presents a rate of isolated germs equivalent to 74.5%; a non-optimal result. The reason lies in the fact that most patients of this study are oncological and among them, some are terminal and home bedridden. In presence of fever, often an empirical antibiotic therapy was started before culture sampling, under the supervision of the oncologist or their general practitioner. In these cases, despite the negative/missing blood culture, the diagnosis of CRBSI was performed according to extremely significant clinical findings. The most frequently used antibiotics for empiric therapy were Piperacillin/Tazobactam and Ceftriaxone.

Antibiotic therapeutic efficacy, high in the first years of our clinical activity [8], gradually reduced in time, due to increasing microbial antibiotic-resistance. In fact, in our experience, the rate of successful antibiotic therapy for *S. epidermidis* CVC infections dropped from a value higher than 80% in 1995 to less than 40% in 2006 [10]. In this study, antibiotic therapy succeeded in 66.6% cases, in our opinion, also thanks to the use of Daptomicin, when appropriate. According to the literature, in case of MR bacteria with an MIC for vancomicin >2 μg/mL, Daptomicin is indicated [26,27]. This antibiotic has a potent in-vitro effect against biofilms, and numerous studies have shown its effectiveness in the treatment of CVC infections by coagulase negative staphylococci or *Enterococcus faecalis*, especially when combined with Rifampicin due to their synergistic action on the bacterial biofilm [26,28,29]. In our experience, Daptomicin proved its effectiveness by sterilizing all treated catheters.

In our study, the infection rate and the probability of CVC saving were not affected by the type of implanted CVC (totally implantable, tunneled, short term) whilst methicillin resistance or the

Table 2
Primary diseases in the 127 oncological and 145 non-oncological patients evaluated since January 2010 to December 2012.

n.	Type of disease	*n.*	Primary disease	Indication for HPN
45	Non-oncological			
29	Short bowel syndrome	9	Mesenteric infarction	Intestinal malabsorption
		7	Multiple intestinal resections (Crohn)	
		4	Radiation enteritis	
		5	Postsurgical adhesions	
		4	Intestinal volvulus	
16	Other diseases	4	Systemic sclerosis and other collagen diseases	
		4	Bariatric surgery complications	
		4	Active Crohn's disease	
		2	Eosinophilic enteropathy	
		2	Intestinal pseudo-obstruction	Intestinal dismotility
127	Oncological			
127	Peritoneal carcinomatosis	52	Gastro-esophageal cancer	Intestinal sub-obstruction/obstruction
		18	Pancreas or biliary tract cancer	
		43	Colon cancer	
		8	Ovarian or uterine cancer	
		6	Advanced cancer of other origins	

Table 3
Infecting agents of the 70 positive cultures in 172 patients followed up since January 2010 to December 2012.

	Number of checks	Single agent	Associated
Gram positive bacteria	55/70 (78.6%)	37	18
S. epidermidis	18/70 (25.7%)	12	6
CoNs Staphylococci	24/70 (34.3%)	17	8
S. aureus	7/70 (10%)	6	1
Enterococcus	3/70 (4.3%)	2	1
Streptococcus	2/70 (2.8%)	–	1
Corynebacteria	1/70 (1.4%)	–	1
Gram negative bacteria	21/70 (30%)	13	8
Klebsiella spp.	8/70 (11.4%)	4	4
Enterobacteria	6/70 (8.6%)	5	1
E. coli	3/70 (4.3%)	1	2
Pseudomonas spp.	3/70 (4.3%)	3	–
Proteus spp.	1/70 (1.43%)	–	1
Fungi	9/70 (12.8%)	5	4
C. albicans	5 (5.3%)	3	2
C. glabrata	4 (4.3%)	2	2
Polimicrobial infections	15/70 (21.42%)	–	–

CoNs = Coagulase negative Staphylococci.

Table 4
Systemic and local antibiotic therapy in the 33 treated cases.

Treated cases, *n* (%)	Lock therapy	Systemic therapy
11	Teicoplanin	Carbapenems (Meropenem, Imipenem),
6	Teicoplanin	Quinolons (Ciprofloxacin/Levofloxacin)
3	Teicoplanin	Aminoglycosides (Gentamicin/Netilmicin)
9	Daptomicin	Rifampicin
4	Meropenem	Ciprofloxacin

presence of bacteria with an MIC for Vancomicin $\geq$1 strongly increased the probability of CVC removal.

To counteract the winning and refined mechanisms of antibiotic resistance, prevention with a strict compliance to evidence-based instructions for correct CVC management seems the only real effective strategy against CRBSI, in particular in patients receiving long term HPN, with the needing of strict a clinical supervision by a well trained team and adherence to evidence-based instructions for CVC management [8,10].

Taurolidine lock has recently been shown to be beneficial as secondary prophylaxis for patients with recurrent episodes of CRBSI and as primary prophylaxis in selected patients, such as for those with very limited vascular access [30–32]. Further multicenter randomized studies are required to better define which patients could benefit from taurolidine lock.

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Conflict of interest

None.

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