Impact of prompt catheter withdrawal and adequate antimicrobial therapy on the prognosis of hospital-acquired parenteral nutrition catheter-related bacteraemia

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Abstract

Catheter-related bacteraemia (CRB) is a cause of death in hospitalized patients, and parenteral nutrition (PN) is a risk factor. We aim to describe the prognosis of PN-CRB and the impact of catheter extraction within 48 h from bacteraemia. All consecutive hospitalized adult patients with CRB (2007–2012) were prospectively enrolled. Factors associated with 30-day mortality were determined by logistic regression analysis. Among 847 episodes of CRB identified, 291 (34%) episodes were associated with short-term catheter use for PN. Cure was achieved in 236 (81%) episodes, 42 (14.5%) patients died within the first 30 days, 7 (2.5%) relapsed, and 6 (2%) had re-infection. On multivariate analysis, previous immunosuppressive therapy (OR 5.62; 95% CI 1.69–18.68; p 0.0048) and patient age (OR 1.05; 95% CI 1.02–1.07; p 0.0009) were predictors of 30-day mortality, whereas catheter removal within 48 h of bacteraemia onset (OR 0.26; 95% CI 0.12–0.58; p 0.0010) and adequate empirical antibiotic treatment (OR 0.36; 95% CI 0.17–0.77; p 0.0081) were protective factors. Incidence of PN-CRB decreased from 5.36 episodes/1000 days of PN in 2007 to 2.9 in 2012, yielding a 46.1% rate reduction (95% CI 15.7–65.5%), which may be attributable to implementation of a multifaceted prevention strategy. In conclusion, short-term PN-CRB accounted for one-third of all episodes of CRB in our setting, and 14.5% of patients died within 30 days following bacteraemia. Our findings suggest that prompt catheter removal and adequate empirical antibiotic treatment could be protective factors for 30-day mortality. Concomitantly with implementation of a multifaceted prevention strategy, PN-CRB incidence was reduced by half.

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Introduction

Catheter-related bacteraemia (CRB) is a common hospital-acquired infection that remains a daily concern for many clinicians. Administration of parenteral nutrition (PN) is a known risk factor, but there is little information on infections caused by catheters used for PN in hospitalized patients [1,2]. In Catalonia, parenteral nutrition catheter-related bacteraemia (PN-CRB) accounts for 25% of all cases of CRB, with a median rate of 1.57 episodes/1000 catheter-days [3].

Catheter-related bacteraemia is considered potentially preventable by implementation of educational campaigns for staff focused on improving catheter care. Central-line care bundles have proven effective for reducing CRB in intensive care units (ICUs) [4–6], but few interventions have focused on non-ICU areas [7]. Starting in 2008 and still ongoing, a multifaceted strategy for CRB prevention was applied in our hospital including various actions focusing on PN central venous catheters (CVCs) to reduce PN-CRB (see Supporting information, Table S1). There are no reported data in the

literature on the impact of such measures for reducing PN-CRB. Nor is there available information regarding the effect of catheter removal within 48 h of bacteraemia onset on the prognosis of PN-CRB. Hence, we aim to describe the incidence, epidemiology and prognosis of PN-CRB in our hospital and to evaluate the impact of catheter extraction within 48 h from bacteraemia onset on 30-day mortality due to this cause.

Patients and Methods

Study design, setting and study population

A prospective, observational, follow-up cohort study performed from 2007 to 2012, including all adult patients (≥18 years) diagnosed with PN-CRB admitted to Hospital Universitari Vall d'Hebron (Barcelona, Spain), a 1200-bed teaching hospital providing a complete range of medical and surgical services.

In our setting, data from all adult patients hospitalized for >48 h and with CRB are entered onto a database as part of a continuous, laboratory-based, prospective surveillance programme of nosocomial infections in Catalonia, named VINCat (available at: http://vincat.gencat.cat Accessed 10 January 2014). Within the VINCat programme, all cases of bacteraemia are reported daily and prospectively evaluated, treated and followed by an infectious disease specialist. Empirical and pathogen-specific antibiotic treatments are prescribed according to Infectious Diseases Society of America guidelines [8] and attending to local microbial prevalence patterns. The focus of the present study was PN-CRB episodes occurring in our hospital. The infection rate was calculated using the total number of PN-CRB episodes per 1000 days of catheter use for PN (data from the hospital pharmacy registry). As the VINCat programme only evaluates nosocomial infections, outpatients with home PN-CRB, patients with catheters inserted before hospitalization, and patients hospitalized for <48 h before bacteraemia onset were not included. Institutional review board approval was not required because patients were treated according to local standards of care; no clinical interventions were made based on the data collected.

Definitions

A PN catheter was any catheter used for PN administration during the week before the onset of bloodstream infection. In all cases, the PN catheter had been placed during the current hospital admission. The methods used to diagnose CRB have been described elsewhere [3].

Multidrug-resistant organisms included methicillin-resistant *Staphylococcus aureus* and Gram-negative bacteria with acquired resistance to at least one agent in three or more antimicrobial categories [9].

When it was indicated, empirical antibiotic treatment was considered for suspected CRB. Empirical treatment was deemed adequate if it showed *in vitro* effectiveness against the microorganism isolated in blood cultures and had been started within the first 48 h after the drawing of blood samples to investigate clinical signs and symptoms of the bloodstream infection, referred to here as bacteraemia onset. In patients with coagulase-negative *Staphylococcus* bacteraemia, antibiotic management was considered adequate when patients with uncomplicated CRB and no orthopaedic or intravascular devices were managed by observation without antibiotics once the catheter was removed, as is stated in the Infectious Diseases Society of America catheter guidelines [8].

Cure was defined as resolution of clinical signs 30 days after CRB onset. Relapse was defined as a new episode of CRB caused by the same microorganism and diagnosed within 30 days following completion of treatment, and re-infection was defined as a new episode of CRB caused by a different microorganism in a patient carrying the same catheter used during the first episode. Overall mortality included all deaths occurring within 30 days after CRB onset.

Statistical analysis

Infection rates were calculated using the total number per year of episodes of PN-CRB per 1000 days of PN catheter use. The Mantel–Haenszel test was used to evaluate reductions in the incidence of PN-CRB over the total study period.

Categorical data are expressed as the count and percentage, and numerical data as the median and interquartile range (IQR). The chi-square test or Fisher exact test was used to compare categorical variables and the Mann–Whitney *U*-test was used for continuous variables. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

Logistic regression analysis was applied to identify predictive factors of 30-day mortality. To preserve the assumption of independence of observations in the multivariate analysis, only the first episode of PN-CRB recorded for each patient was included. Candidate variables were those with $p < 0.1$ on univariate analysis. In addition, variables with p values >0.1 and considered clinically relevant based on experience and reported data were forced into the multivariate model to investigate their effect. Removal of the catheter within 48 h from bacteraemia was maintained in the final model as a fixed variable. A selection method was used based on improved likelihood and the Akaike information criterion. Variables that improved likelihood were gradually entered into the model until inclusion did not improve the previous model. Potential confounders of treatment strategies were tested. Significant

interactions between variables were ruled out. Results are given as the odds ratio (OR) and 95% confidence interval. Statistical analyses were performed with SPSS, version 15.0 (SPSS; Chicago, IL, USA).

Results

During the 6-year study period, 847 consecutive CRB episodes were identified; 291 (34%) of them were PN-CRB affecting 263 patients (median age, 64 years, IQR 49–73), 148 (56%) of whom were men. Median Charlson comorbidity index value was 2 (IQR 0–3), with the most common comorbidity being malignancy in 94 (36%) patients.

Median inpatient days before CVC insertion was 9.5 (IQR 1–28) days and median duration of catheterization before CRB onset was 13 days (IQR 8–21). Most episodes were detected in non-ICU patients (241, 83%), mainly patients in surgical areas (157, 54%). There were no differences in the length of PN catheterization between non-ICU and ICU patients (13 days; IQR 8.75–21 versus 12 days; IQR 8–21, p 0.56).

Central venous catheters were affected in 223 (77%) episodes, peripherally inserted CVCs in 62 (21%) episodes, and peripheral venous catheters in 6 (2%) episodes. In patients with CVCs, the venous access was subclavian in 159 (55%) cases, femoral in 43 (15%), and jugular in 21 (7%).

Microorganisms causing PN-CRB and those causing bacteraemia related to catheters used for other purposes are shown in Table 1. *Staphylococcus* spp. were the most common causative agents in both PN-CRB and non-PN-CRB, with coagulase-negative *Staphylococcus* being more frequent in PN-CRB and *S. aureus* in non-PN-CRB. *Candida* spp. were more commonly found on catheters used for PN than on those used for other purposes: 60 (21%) versus 23 (4%) (p <0.001). Non-*albicans Candida* species were identified in 24 (40%) cases of PN catheter-related candidaemia, with 17 of them caused by *Candida parapsilosis*.

Data regarding PN catheter management, empirical antibiotic treatments and outcome, sorted by aetiology, are shown in Table 2. Focusing on PN catheter management, catheters were removed in 274 (94%) episodes, retained in 13 (5%), and in four episodes catheter management was not recorded. The reason for not removing the catheter was patient death in nine cases and use of antibiotic-lock plus systemic antibiotics in four. Median time from bacteraemia to catheter removal was 1 day (IQR 0–2 days); in 226 (79%) episodes the catheter was removed within 48 h after bacteraemia onset.

Appropriate empirical antimicrobial therapy was administered in 157/284 (55%) cases (in seven cases, these data were missing). Stratifying by microbiological aetiology, empirical antibiotic treatment was adequate in most PN-CRB episodes caused by Gram-positive microorganisms (131/171, 77%), but in only 12 of 30 cases (40%) caused by multidrug-resistant organisms.

TABLE 1. Microorganisms causing parenteral nutrition catheter-related bacteraemia (PN-CRB) (*n* = 291) and those causing bacteraemia related to catheters used for other purposes (*n* = 556)

	PN-CRB *n* = 291 (100%)	Non-PN-CRB *n* = 556 (100%)	p
Gram-positive cocci	175 (60)	399 (72)	0.001
Coagulase-negative staphylococci	149 (51)	222 (40)	0.002
Methicillin-sensitive *Staphylococcus aureus*	13 (4)	99 (18)	<0.001
Methicillin-resistant *Staphylococcus aureus*	9 (3)	48 (8.5)	0.002
Enterococcus spp.	4 (1)	28 (5)	0.008
Streptococcus spp.	0 (0)	2 (0.5)	0.306
Candida spp.	60 (21)	23 (4)	<0.001
Candida albicans	36 (13)	10 (1.7)	<0.001
Non-*albicans* Candida	24 (8)	13 (2.3)	<0.001
Gram-negative bacilli	42 (14)	107 (19)	0.081
Klebsiella spp.	14 (5)	21 (3.7)	0.473
Pseudomonas aeruginosa	13 (4)	31 (5.5)	0.490
Enterobacter spp.	8 (3)	26 (4.5)	0.175
Escherichia coli	2 (0.5)	13 (2.3)	0.084
Acinetobacter baumannii	2 (0.5)	2 (0.5)	0.509
Serratia marcescens	–	11 (2)	–
Miscellaneous[a]	3 (1)	3 (0.5)	–
Polymicrobial bloodstream infections[b]	15 (5)	27 (5)	0.849

[a]Miscellaneous infection includes one *Proteus mirabilis*, one *Citrobacter* spp. and one *Serratia* spp. for PN-CRB and two *Morganella morganii* and one *Proteus mirabilis* for non-PN-CRB.
[b]Polymicrobial bloodstream infections in PN-CRB include a mixed infection due to *Candida* spp. and Gram-positive cocci (GPC) in six cases, two different Gram-negative bacilli (GNB) in five cases, two different GPC in three, and *Candida* spp. and GNB in one. Non-PN-CRB mixed infections include a GNB and GPC in 12 cases, two different GNB in nine cases, two different GPC in four cases and *Candida* spp. and GPC in two cases.

Cure was achieved in 236 (81%) episodes, 42 (14.5%) patients died within 30 days after onset of infection (24 (8%) within the first 7 days), 7 (2.5%) relapsed, and 6 (2%) had a re-infection.

Over the 6-year study period, there was a sustained decrease in the incidence of PN-CRB from 5.36 episodes/1000 days of PN catheter use in 2007 to 2.9 episodes/1000 days in 2012; that is, a rate reduction of 46.1% (95% CI 15.7–65.54%) (Fig. 1). The trend of the median rate reduction for the overall period was statistically significant (p 0.00082).

Multivariate logistic regression analysis was performed to explore predictive factors of 30-day mortality (Table 3). Previous immunosuppressive therapy (OR 5.62; 95% CI 1.69–18.68; p 0.0048) and patient age (OR 1.05; 95% CI 1.02–1.07; p 0.0009) were independent predictors of 30-day mortality, whereas catheter removal within 48 h after bacteraemia onset (OR 0.269; 95% CI 0.12–0.58; p 0.0010) and adequate empirical antibiotic treatment (OR 0.36; 95% CI 0.17–0.77; p 0.0081) were protective factors.

TABLE 2. Treatment and outcome of 291 episodes of parenteral nutrition catheter-related bacteraemia (PN-CRB), sorted by aetiology

	Gram-positive cocci *n* = 174	*Candida* spp. *n* = 60	Gram-negative bacilli *n* = 42	Polymicrobial CRB *n* = 15	Total *n* = 291
Adequate empirical antibiotic therapy[a]	131/171 (77)[a]	3/59 (5)[a]	19/40 (48)[a]	4/14 (29)[a]	157/284 (55)[a]
PN-catheter withdrawal within first 48 hours from bacteraemia[b]	130/170(76)[b]	49/60 (82)	36/42 (86)	11/15 (73)	226/287 (79)[b]
Cured	147 (84)	47 (79)	31 (74)	11 (73)	236 (81)
Death					
Early death (0–7 days)	10 (6)	7 (12)	4 (9.5)	3 (20)	24 (8.3)
Late death (8–30 days)	10 (6)	3 (4)	4 (9.5)	1 (7)	18 (6.2)
Relapsed	3 (2)	2 (3)	2 (5)	–	7 (2.4)
Re-infection	4 (2)	1 (2)	1 (2)	–	6 (2.1)

[a]Data on empirical antibiotic therapy was missing in seven cases (three Gram-positive cocci CRB, two Gram-negative CRB, one catheter-related candidaemia, and one polymicrobial CRB).
[b]Data on catheter management were missing in four cases of PN-CRB cause by Gram-positive cocci.

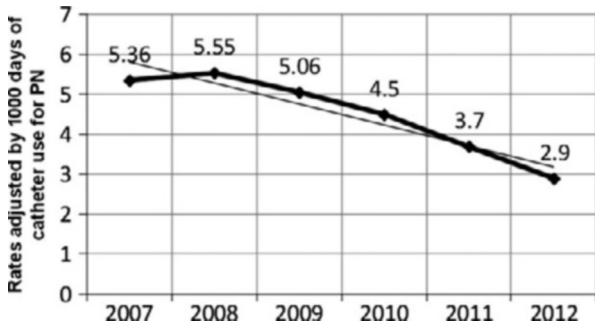

FIG. 1. Incidence of parenteral nutrition catheter-related bacteraemia (PN-CRB) (episodes/1000 days of catheter use for parenteral nutrition).

Discussion

To our knowledge, this is the largest study investigating CRB in patients with temporary catheters for PN, accounting for one-third of all CRB cases occurring in our hospital. Our study identifies the risk factors associated with 30-day mortality, and suggests the effectiveness of a multifaceted strategy for PN-CRB prevention.

Parenteral nutrition is a recognized risk factor for CRB, an infection occurring in 1.3–26.2% of patients receiving PN [3,10–14]. Nonetheless, published information is scarce regarding PN-CRB in patients with temporary catheters [1,2]. In our study, 83% of PN-CRB episodes were detected outside the ICU, mainly in surgical wards, probably because nutritional requirement after surgery is the most common reason for PN prescription.

Femoral venous catheterization has been considered a major risk factor for CRB [15] because the groin area is subject to considerable movement and potential contamination from urine and faecal matter. Hence, current educational campaigns are attempting to reduce femoral access in favour of subclavian placement. In our series, femoral CVCs had been used in 15% of PN-CRB episodes and we consider this result a target for improvement.

Regarding the microbiological data, Gram-positive cocci were the most common microorganisms isolated in blood cultures, coagulase-negative *Staphylococcus*, responsible for 51% of all PN-CRBs, were the most frequent microorganisms identified, in accordance with the results of other studies, which have reported incidences up to 69% of cases [2,16–18]. *Candida* spp. were the second most isolated microorganisms in frequency, accounting for 21% of cases. Parenteral nutrition has traditionally been associated with CRB due to *Candida* spp., particularly *C. albicans*, although the related literature is limited [2,10,18,19]. Marra *et al.* [18] reported that fungi accounted for 22% of CRBs in long-term PN-CRB, a percentage similar to our 21%. *Candida*-caused bloodstream infections are common in immunocompromised and ICU patients, but they are also common in patients who have undergone recent abdominal surgery and in those receiving broad-spectrum antibiotics [20]. Overall 157 (54%) of our PN-CRB episodes were diagnosed in patients in surgical areas; therefore we believe that this could explain, at least in part, the high incidence of candidaemia in our series.

We found that 14.5% of our patients died within 30 days of PN-CRB onset. In critically ill patients, the attributable mortality of CRB and fungaemia in the USA ranges from 2% to 35% [21,22], rates in accordance with our results. Braun *et al.* [23] described an increase in CRB-associated mortality concomitantly with a shift towards Gram-negative bacteria in their institution; however, we have not observed this shift in our hospital. To our knowledge, there are no recent data on CRB-associated mortality focusing in non-critically ill patients and no data on PN-CRB-associated mortality.

Catheter removal within the first 48 h following CRB onset and adequate empirical antibiotic treatment were protective factors. Catheter removal in septic patients is considered the standard of care [8], and this practice agrees with the

TABLE 3. Univariate and multivariate analysis of predictors of 30-day mortality (*n* = 263 first episodes of parenteral nutrition catheter-related bacteraemia (PN-CRB)

Variable	Died *n* = 41 (16%)	Alive *n* = 222 (84%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p	OR (95% CI)	p
Age, years	73 (62.5–80)	61.5 (47–71)	1.04 (1.02–1.07)	0.001	1.05 (1.02–1.07)	0.0009
Male sex	25 (61)	124 (56)	1.23 (0.62–2.44)	0.543	–	–
Charlson Comorbidity Index score	2 (1–3)	2 (0–3)	1.16 (0.97–1.39)	0.098	–	–
Malignancy	17/39 (44)	77/215 (36)	1.38 (0.69–2.76)	0.355	–	–
Diabetes mellitus	8/39 (20)	38/215 (18)	1.20 (0.51–2.82)	0.672	–	–
Immunosuppressive treatment	6/39 (15)	11/215 (5)	3.37 (1.17–9.74)	0.018	5.62 (1.69–18.68)	0.0048
Femoral catheter location	8 (19)	30 (13)	1.55 (0.65–3.68)	0.316	–	–
PN-CRB due to Gram-positive cocci	20 (50)	134 (60)	0.62 (0.32–1.22)	0.167	–	–
PN-CRB due to *Candida* spp.	9 (22)	48 (22)	1.02 (0.46–2.28)	0.962	–	–
PN-CRB due to Gram-negative bacilli	8 (19)	33 (15)	1.39 (0.59–3.27)	0.451	–	–
PN-CRB due to polymicrobial infection	3 (7)	11 (5)	1.51 (0.40–5.68)	0.536	–	–
CRB caused by multidrug-resitant organisms	7 (17)	23 (10)	1.78 (0.71–4.47)	0.214	–	–
Catheter removal within 48 h after PN-CRB	26 (63)	178/219 (81)	0.40 (0.19–0.82)	0.011	0.26 (0.12–0.58)	0.001
Adequate empirical antibiotic treatment	15 (37)	125/218 (57)	0.43 (0.21–0.86)	0.014	0.36 (0.17–0.77)	0.0081

Categorical data are expressed in absolute number (percentage); continuous variables are expressed in median (interquartile range).

observations in our series, where most PN catheters were removed within the first 48 h of bacteraemia. Permanent catheters, such as tunnelled catheters, are not included in our study. Withdrawal of PN catheters is not as much of a problem as removal of permanent CVCs, because patients usually have an alternative venous access and PN can be discontinued, at least temporarily, when bacteraemia is diagnosed. These factors may explain the high percentage of early catheter removal in our series. Prompt initiation of appropriate antibiotic treatment is also a prognostic determinant. Knowledge of local epidemiology and the particular characteristics and risk factors of each patient are the keys to choosing an appropriate antibiotic.

During the period studied, the aggregate median incidence of PN-CRB dropped by 46% following implementation of a global prevention strategy, suggesting its effectiveness. Incidence of PN-CRB has not been extensively described; available studies report values ranging from 13.1 per 1000 PN-days in patients outside the ICU [14,17] to 25 per 1000 PN-days in studies including all hospitalized patients [16]. In our case, establishment of a surveillance programme highlighted the true burden of this infection and the need for an intervention. Collins *et al.* [2] reported an overall reduction in PN-CRBs from 33.6 cases/1000 catheter-days in 1997 to 6.8 cases/1000 catheter-days in 2008. The authors attributed these favourable results to creation of a PN support team to promote high standards in CVC insertion and care, and to regular infection audit meetings to monitor trends in CRB [24]. Current guidelines for the prevention of intravascular CRB recommend educational programmes [25], and the effectiveness of central-line care bundles has been well demonstrated [4–7]. As an example of the efficacy of these measures, Seisdedos *et al.* [17] reported that there were no cases of PN-CRB in critically ill patients after the Zero Bacteremia project was implemented in their ICU. In our institution, a global strategy for CRB prevention achieved a significant reduction in overall PN-CRB rates.

The observations presented are subject to limitations. First, this was not a randomized study, with the resulting risk of bias due to various confounding factors, such as the fact that all preventive measures are more carefully applied when one is being observed. Second, the components of PN solutions can support microbial growth, but the composition of PN solutions used in our patients was not investigated, so we were unable to assess the impact of this factor on PN-CRB. Third, although malnutrition is considered a relevant risk factor for PN-CRB [10], there were no available data on the nutritional status of our patients, so the role of this factor could not be evaluated. Nonetheless, the prospective design of a multimodal intervention programme for CRB prevention and the uniform patient management by a specialized multidisciplinary team are both strengths of the study.

In conclusion, PN-CRB accounts for one-third of all CRB episodes in our setting and 14.5% of patients with PN-CRB die within 30 days. Immunosuppression and patient age are risk factors for 30-day mortality, whereas catheter removal within 48 h after PN-CRB and adequate empirical antibiotic treatment may lead to a reduction in the PN-CRB rate. Concomitant with implementation of a multifaceted prevention strategy, PN-CRB incidence dropped by half.

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Transparency Declaration

All authors report that they have no conflicts of interest relevant to this article.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Multimodal intervention strategy for catheter-related bacteraemia prevention put into practice in our hospital.

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