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ORIGINAL ARTICLE

Risk factors for catheter-related bloodstream infections in patients with intestinal failure undergoing home parenteral nutrition: a single-center study

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Abstract

Purpose The incidence and risk factors of catheter-related bloodstream infections (CRBSI) in patients with intestinal failure (IF) have not been established, partly because catheter management methods vary from different facilities. This study aimed to identify the risk factors and incidence rate of CRBSIs in patients with IF who were given prophylactic treatment.

Methods Sixteen patients with IF who required home parenteral nutrition were enrolled in this study. Prophylactic management of CRBSI included monthly ethanol lock therapy and standardized infection prevention education. The outcomes included the incidence and risk factors of CRBSI.

Results The median incidence rate of CRBSI was 1.2 per 1000 catheter days. Univariate analysis showed that the risk of developing CRBSI was significantly associated with short bowel syndrome (< 30 cm) ($p = 0.016$). Other relevant findings included a significant negative correlation between serum albumin and CRBSI rate ($r = -0.505$, $p = 0.046$), and past history of mixed bacterial infections was significantly associated with increased CRBSI rate ($p = 0.013$).

Conclusion CRBSIs can still develop despite undergoing prophylactic management. Risk factors for CRBSI include the residual intestinal length, nutritional status, and susceptibility to certain microorganisms.

Keywords Catheter-related blood stream infection · Intestinal failure · Short bowel syndrome · Home parenteral nutrition

Introduction

Intestinal failure (IF) is defined as the inability of the intestinal tract to absorb the minimum amount of nutrients, fluids, and electrolytes necessary for life and growth owing to intestinal dysfunction; thus, requiring intravenous replacement [1]. IF includes short bowel syndrome (SBS) and motility disorder (MD), such as Hirschsprung's disease and its related disorders, as well as congenital enterocyte disorders. In most cases, mechanical or functional malabsorption from the gastrointestinal tract requires home parental nutrition (HPN) for a prolonged period [2].

Catheter-related bloodstream infection (CRBSI) is a well-known complication associated with HPN, which should be prevented because it can lead to mortality. There have been many reports on the risk factors of CRBSI in patients with IF. In 2013, a systematic review by Dreesen et al. categorized the previously noted risk factors for CRBSI into five groups: (1) device-related risk factors (catheter type, catheter caliber, and insertion site), (2) education-related risk factors (method of patients or family education), (3) follow-up-related risk factors (how to care for the central venous catheter), (4) patient-related risk factors (age, education level, social circumstance, medications, and underlying diseases), (5) and therapy-related risk factors (duration of HPN, stoma) [3]. Several other studies on the risk of CRBSI have been published which yielded similar findings [4–8].

Various preventive measures have been implemented in recent years. Previous studies have reported on the association of ethanol lock prophylaxis and a reduction in infection rates [9, 10]. In recent years, other drug lock therapies have been compared, and the ESPEN guidelines currently recommend taurolidine [11, 12]. In addition, setting up countermeasure teams and pruning infection prevention bundles

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have been reported as effective [13–15]. The effectiveness of antimicrobial-containing catheters and dressings has also been reported; however, these are mostly short-term indwelling catheters [16, 17].

Despite the development of preventive measures which have been advantageous, CRBSI has not been completely eliminated. Therefore, we aimed to examine the incidence and risk factors of CRBSI in patients with IF who were given prophylactic management at our institution.

Materials and methods

Patient population and data collection

Twenty-six patients with confirmed IF requiring HPN who were being followed-up at the outpatient clinic of the Department of Pediatric Surgery, Tohoku University Hospital, from 2015 to 2022, were enrolled in the study. We excluded four patients who were treated for CRBSIs in collaboration with other hospitals, two patients who underwent small intestinal transplantations, three patients with peripherally inserted central venous catheter, and one patient with a port device. The remaining 16 patients with tunneled central venous catheters were retrospectively reviewed for clinical data such as age, sex, presence of motility disorders, parenteral nutrition duration, length of residual small bowel, and presence of ileocecal valves. Serum biochemistry data were also determined, and the averages of data collected during regular outpatient visits were used in the analysis. The primary outcome was the CRBSI rate, which was analyzed by examining the background factors of the participants.

Definition of catheter-related bloodstream infection

A definitive diagnosis of CRBSI was made according to the Clinical Practice Guidelines by the Infectious Diseases Society of America [IDSA], which includes clinical signs of bacteremia or sepsis (fever, tremors, decreased circulating blood volume, or sudden hypotension not explained by heart failure) and no other cause of bacteremia or sepsis. The same organism grows from at least one percutaneous blood culture and from a culture of the blood flow from the catheter.

Catheter management

A single-lumen tunneled central venous catheter was used in all cases. Prophylactic ethanol lock therapy was performed for 1–2 h with 70% ethanol during regular monthly visits. All patients underwent ethanol lock therapy in the manner previously described, throughout the study period, except during unplanned hospitalizations. When CRBSIs developed, ethanol lock and systemic antibiotic therapies were performed to preserve the catheter. When the infection was uncontrolled, when reinfection with the same pathogen occurred within a short period of time, or when sepsis was suspected, after the catheter was removed when necessary according to the instructions of the infectious disease physician, it was reinserted after a negative blood culture was confirmed. Additionally, we replaced the catheters that had been inserted for approximately 3 years even though they were not infected. All patients were educated according to the Institutional Care Manual at the time of HPN induction.

Statistical analysis

For statistical comparison, the obtained data were assessed using the exact Wilcoxon rank-sum test or Pearson correlation coefficient (Pearson's r), depending on each variable within and between groups. All statistical analyses were performed using the JMP Pro 16 software (SAS Institute Japan Ltd. Roppongi, Minato-ku, Tokyo). Statistical significance was set at $p < 0.05$.

Results

Background of study population

Table 1 summarizes the diagnosis, background factors, and average serum chemistry data. All the patients diagnosed with MD had a residual intestinal length of > 30 cm. All but one patient without a diagnosis of MD had intestinal tract lengths of < 30 cm. Five patients were 15 years old

Table 1 Background factors of patients with intestinal failure

	($n = 16$)	
Age	11.9	[8.3, 17.7]
Sex (female:male)	8:8	
Motility disorder (present:absent)	7:9	
Parental nutrition duration (years)	10	[7.1, 14.1]
Residual small bowel length (cm)	25	[9, 70]
Ileocecal valve (present:absent)	8: 8	
Serum chemistry		
AST (U/L)	39.6	[33.3, 45.5]
ALT (U/L)	47.1	[25.6, 58.6]
Albumin (mg/dL)	4.0	[3.7, 4.1]
eGFRcys (mL/min/1.73 m^2)	109.7	[94, 120.5]
Citrulline (nmol/mL)	21.2	[12.1, 28]
CRBSI rate (n/1000 catheter days)	1.22	[0.78, 2.3]

Data are presented as median [interquartile range] for continuous parameters

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFRcys* estimated glomerular filtration rate by cystatin C, *CRBSI* catheter-related blood stream infection

and 11 were < 15 years of age. The serum biochemical data were generally within the reference range. The median rate of CRBSI was 1.2 per 1000 catheter days, and the median duration of catheter insertion was 2501 days.

Coagulase-negative *Staphylococcus* (43%) was the most common causative organism of the CRBSIs, followed by Gram-negative rods (18.3%), *Staphylococcus aureus* (15.1%), and *Candida* spp. (14%). Mixed infections occurred in 15 cases during the study period (20%), and approximately 1/2 of *Staphylococcus epidermidis* and *Staphylococcus aureus* were methicillin resistant (Table 2).

Table 2 Pathogens isolated from blood cultures in the patients with catheter-related bloodstream infections

	n (%)
Coagulase-negative *Staphylococcus*	40 (43)
Staphylococcus epidermidis	17
Methicillin-resistant *Staphylococcus epidermidis*	8
Miscellaneous	15
Staphylococcus aureus	14 (15.1)
Methicillin-resistant *Staphylococcus aureus*	7
Gram-negative rods	17 (18.3)
Klebsiella spp.	9
Enterococcus spp.	4
Acinetobacter spp.	2
Serratia liquefaciens	1
Clostridium butyricum	1
Candida spp.	13 (14)
Others	9 (9.7)
Polymicrobial infection	(20)

Risk factors for catheter-related bloodstream infection

Table 3 shows the risk factors for the development of CRBSI in patients with IF. On univariate analysis, the risk of developing CRBSI was significantly associated with the absence of motility disorders ($p = 0.03$) and short bowel syndrome < 30 cm ($p = 0.016$) (Fig. 1). However, the cases divided into these two categories were almost identical. No significant correlations were found between other social background factors and the CRBSI rates. With regard to serum biochemical data, there was a significant negative correlation between albumin level and CRBSI rate ($r = -0.505$, $p = 0.046$) (Fig. 2). No significant correlations were found in the other serum chemical data. Furthermore, the past history of mixed bacterial infections revealed a significant association with increased CRBSI rate ($p = 0.013$); however, previous *Candida* infections did not reveal significant findings.

Table 3 Comparison of the background factors and serum chemistry data among the intestinal failure patients with catheter-related bloodstream infection

	CRBSI rate (*n*/1000 catheter days)						*r* value	*p* value
Age (years)							– 0.197	0.47
Sex	Female	1.6	[0.9, 5.3]	Male	0.99	[0.48, 2.2]		0.34
Motility disorder	Yes	0.79	[0, 1.2]	No	2.1	[1.0, 4.8]		0.03*
Parental nutrition duration (years)							– 0.213	0.43
Residual small bowel length (cm)							– 0.336	0.22
Residual small bowel length	> 30 cm	2.3	[1.3, 5.5]	< 30 cm	0.8	[0.19, 1.2]		0.016*
Ileocecal valve (present: absent)	Yes	1.2	[0.2, 2.8]	No	1.6	[0.78, 2.3]		0.77
Serum chemistry								
AST (U/L)							– 0.247	0.36
ALT (U/L)							– 0.322	0.22
Albumin (mg/dL)							– 0.505	0.046*
eGFRcys (mL/min/1.73 m^2)							0.252	0.35
Citrulline (nmol/mL)							0.086	0.75
Infection of past history								
Polymicrobial	Yes	2.1	[1.8, 7.2]	No	0.8	[0.4, 1.2]		0.013*
Candida	Yes	1.8	[0.7, 6.8]	No	1.2	[0.6, 2.1]		0.41

Data are presented as median [interquartile range] for continuous parameters

CRBSI catheter-related blood stream infection, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFRcys* estimated glomerular filtration rate by cystatin C

*$p < 0.05$

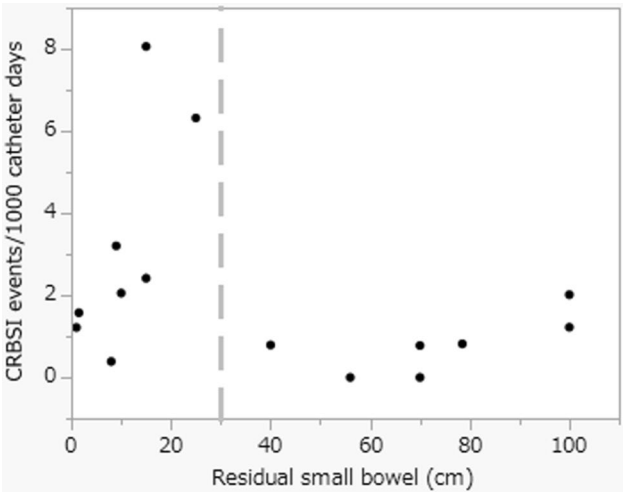

Fig. 1 Scatter plot of residual bowel length and catheter-related bloodstream infections. The dashed line represents a residual bowel length of 30 cm

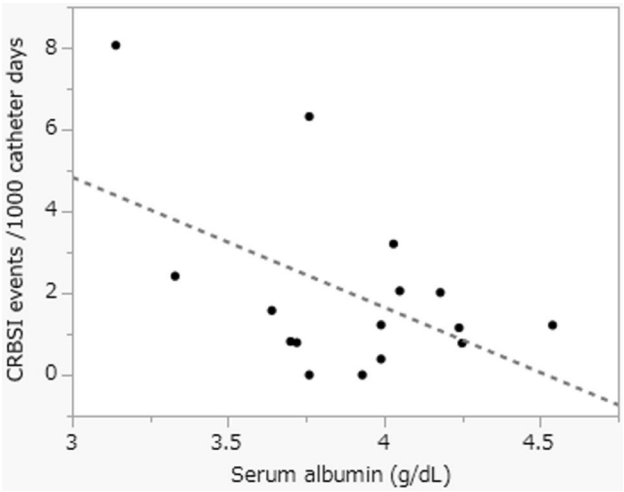

Fig. 2 Negative correlation between the albumin level and catheter-related bloodstream infections. The dashed line represents the regression line

Discussion

In the current study, the CRBSI rate was 1.2 episodes per 1000 catheter days, which is not significantly different from that in previous reports [3, 12]. Despite the fact that adequate prophylactic measures have been implemented, we were not completely able to prevent a certain number of CRBSIs. Using a single regression analysis, the present study examined the risk factors for CRBSIs, which included very short bowel syndrome with a residual bowel length of < 30 cm, low albumin serum level, and past history of mixed bacterial infections. Although several CRBSI risk factors have been reported, there are few descriptions of catheter management, including ethanol lock therapy. Therefore, this is considered a precedent study for further research in the future.

In 2013, Dreesen et al. reported that the CRBSI incidence was 0.38 and 4.58 episodes per 1000 catheter days [3]. Subsequently, in the 2021 ESPEN guideline, Cuerda et al. stated that the CRBSI rates in experienced referral centers range from 0.14 to 1.09 episodes per 1000 catheter days [12]. The decreased incidence can be attributed to the development of prophylactic procedures. Kooi et al. reported the positive effect of an intervention bundle to prevent CRBSI in a national program [15], and a multidisciplinary working group to develop an advanced care pathway for patients receiving HPN improved the rate of CRBSI [13]. Ethanol and other drug lock prophylaxis show the reduction of CRBSI rates [9–11]. Despite the implementation of preventive measures, such as prophylactic ethanol lock therapy and the development of a home parenteral nutrition care manual, CRBSIs still developed in our cases. Furthermore, the identification of infection risk factors is an important issue when these preventive measures are considered, which is one of the objectives of this study.

In this study, a residual intestine of < 30 cm significantly increased the incidence of CRBSI. Fatemizadeh et al. demonstrated that having < 30 cm of residual intestinal tract reduces the likelihood of establishing enteral autonomy [18]. Engelstad et al. found that those with < 35 cm small bowel displayed an increased relative abundance of Proteobacteria, whereas those with a longer remaining small bowel had a higher proportion of Firmicutes [19]. There has been a lot of literature on gut microbiota and the incidence of CRBSI [20–22], which is one of the reasons why residual gut length affects CRBSI. Although the presence or absence of an MD diagnosis affects CRBSIs, which was consistent in the current study, it could have been possibly confounded by residual bowel length. In our case, the plasma citrulline levels, which have been reported to reflect the functional length of the small intestine [23], were not significantly correlated with CRBSIs. The physical barrier function of the intestinal epithelium and the complex intestinal immune system of the intestinal tract protects against CRBSIs. Fragkos et al. performed a systematic review and reported that citrulline levels correlated with the disease severity of intestinal mucosal enteropathies [24]. Therefore, it is possible that the cause of CRBSIs is not simply an impairment of the mucosal barrier function caused by mucosal damage; rather, CRBSIs are mediated by the disruption of the intestinal immune system, such as intestinal dysbiosis [25]. As a result, the CRBSI rate may not have correlated with plasma citrulline levels.

Hypoalbuminemia is another risk factor for CRBSI. Serum albumin level is an indicator of nutritional status, and decreased levels may reflect a low nutritional status.

Undernourished patients are known to be more susceptible to infectious complications owing to their decreased immunocompetence [26, 27]. Our results showed that with a lower albumin level, there is a higher risk of infection; however, only two patients presented with hypoalbuminemia below the reference level, which suggests a mechanism other than hyponutrition. Gunaratnam et al. reported that *Staphylococcus aureus* adhesion to a central venous catheter was drastically reduced when the catheter surfaces were pre-incubated with human blood plasma or human serum albumin [28]. In contrast, albumin administration suppresses the production of inflammatory cytokines from leukocytes and lymphocytes and is reported to increase the frequency of infections due to its immunosuppressive effects [29]; therefore, interpretation should be done with caution.

Polymicrobial infection has different characteristics from monomicrobial infection, which includes secondary infection from the primary infection, infection of an easily infected host, characteristic biofilm composition, and worsening prognosis [30, 31]. Although a history of polymicrobial infection was a risk factor in this study, it remains unclear whether frequent CRBSIs are more likely to cause mixed infections or whether hosts with mixed infections are more likely to develop CRBSIs. Khatib et al. reported that polymicrobial infection was more common in femoral central venous catheter-associated bacteremia than in other sites and tended to be more frequent in healthcare-associated pneumonia than in community-associated cases [32]. Therefore, at least, it is highly likely that polybacteremia is related to susceptibility to infection, such as environmental or patient factors.

This study has several limitations. First, we mainly selected ethanol lock prophylaxis as a preventive treatment for CRBSIs, but we did not present data regarding its effectiveness at our institution. Second, the study had a small sample size and a wide sampling distribution, including outliers, which may have led to statistical errors and a negative impact on power. Similarly, there is the possibility of confounding bias, such as on residual bowel length and motility disorders, which cannot be ruled out. Furthermore, most of the cases had new central venous catheters replaced due to infection or obstruction, but these effects were not considered in this study. The presence or absence of fat emulsion administration, and the quantity, quality, and duration of HPN are also limiting factors that were not included in this study because of the difficulty in strictly categorizing each case.

In summary, we included IF patients with CRBSI who underwent appropriate prophylactic procedures in our institution. Furthermore, we found that the risk factors for CRBSI were residual intestinal length, low serum albumin level, and a history of multiple bacteremia. We believe that the novelty of this report is warranted because the management of CRBSI prophylaxis has changed in recent years. Thus, large-scale, prospective, randomized controlled studies are required in future studies to further verify the results.

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Author contributions TS designed the study and performed the analyses, and wrote the main manuscript text. MN, HS, TF, HK, RA, RO, MH, and KT reviewed the manuscript and provided critical feedback. MW supervised all of the study. All authors reviewed the manuscript.

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Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

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

Ethical approval This study was approved by the ethics committee of Tohoku University Hospital (Approval No. 29924) and has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki, 1964 and its later amendments.

Informed consent The institutional review board approved this retrospective study, and the requirement for informed consent was waived.

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