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# Risk factors for catheter-related bloodstream infections associated with home parental nutrition in children with intestinal failure: A prospective cohort study

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SUMMARY

*Background & aims:* Catheter-related bloodstream infection (CRBSI) is the most common, potentially life-threatening complication of long-term parenteral nutrition (PN). We prospectively assessed the incidence and risk factors for CRBSI in children receiving long-term home PN (HPN) for intestinal failure (IF) in a single IF rehabilitation center.

*Methods:* Data regarding episodes and potential risk factors for CRBSI in children on HPN were prospectively recorded.

*Results:* Forty-one of 75 children were diagnosed with CRBSI. The overall CRBSI rate was 1.61 per 1000 catheter days. The indications for HPN were gastrointestinal motility disorders in 35%, short bowel syndrome (SBS) in 28% graft versus host disease (GvHD) post bone marrow transplant in 17%, congenital enteropathy in 15%, and severe neurodevelopmental impairment in 5%. Gastrointestinal motility disorders had significantly higher CRBSI rate compared to other groups ($p < 0.0005$; 2.74 in motility group vs 1.54 in GvHD group vs 0.52 in congenital enteropathies vs 0.36 in SBS group vs 0.67 in severe neurodevelopmental delay).

Multivariate analysis revealed that enterocutaneous distal stoma (ileostomy or colostomy) (HR 3.35 [95% CI, 1.63–6.86]; $p < 0.001$), age <2 years (HR 0.28 [95% CI, 0.15–0.53]; $p < 0.0001$), male sex (HR 2.28 [95% CI, 1.51–3.43]; $p < 0.0001$), non-use of taurolidine citrate lock (HR 2.70 [95% CI, 1.72–4.11]; $p < 0.0001$) and gastrointestinal motility disorder (HR 3.02 [95% CI, 1.81–4.91]; $p < 0.001$) were independent risk factors for developing CRBSI.

*Conclusions:* Extra care in managing PN connections and disconnections should be taken in children with an underlying gastrointestinal motility disorder, distal enterocutaneous stoma, male sex and those aged <2 years since they are at a significantly higher risk of CRBSI. Early introduction of taurolidine lock should be considered.



## 1. Introduction

Intestinal failure (IF) is defined as the reduction in functional gut mass below the minimum necessary for adequate digestion and absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and growth [1]. In children the main etiology of IF is short bowel syndrome (SBS), when there is a reduction in the absorptive surface of the intestine. The major SBS aetiologies are necrotising enterocolitis (NEC), intestinal malformations and volvulus. Other etiologies of

*Abbreviations:* CRBSI, Catheter Related Blood Stream Infection; CVC, Central Venous Catheter; DLHL, Double-Lumen Hickman Line; HPN, Home Parental Nutrition; IF, Intestinal Failure; PICC, Peripherally Inserted Central Catheter; PN, Parental Nutrition; SBS, Short Bowel Syndrome; SLHL, Single-Lumen Hickman Line.

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primary IF are gastrointestinal motility disorders and congenital enteropathy [2]. Secondary causes of IF in childhood include malignancy, immunodeficiency, graft versus host disease (GvHD), metabolic disease, and severe neurodevelopmental impairment (SDI).

In children with long-term chronic IF, Type 3 IF develops when there is persistence of the condition with subsequent need for parenteral nutrition (PN) for several months or years [3]. In the latter PN at home (HPN) with care by parents is the best alternative to prolonged hospitalisation and best option for improving quality of life in children dependent on long-term PN [4,5]. Quality of life scores in children on HPN have not differed significantly from healthy children of the same age [5]. The parents/carers are formally trained to administer PN overnight leaving the child free during the day to attend school and participate in other childhood activities [6].

Although PN is a life-saving treatment, it is associated with complications that can become life-threatening.

Catheter-related blood stream infection (CRBSI) is the most common, serious complication in children receiving PN, that can lead to significant morbidity and mortality [7]. Its mortality rate has been identified to be about 2.3% in a mixed population of children and adults on HPN [8–13].

Particularly in younger children with IF and dependence on PN preserving venous access is paramount for survival as replacing central venous catheters (CVC) can damage blood vessels and reduce the limited immature venous access [11].

Over the last few years, the introduction of antimicrobial lock procedure has decreased dramatically the rate of CRBSI. Ethanol lock has been shown to reduce CRBSI rate by 81% in children [14].

Prophylactic taurolidine lock has been shown to reduce CRBSI from a rate ranging from 1.04 to 14.9 episodes per 1000 catheter days on PN, to between 0.61 and 3.1 episodes per 1000 catheter days after implementation [15–19].

To date only a few studies have prospectively assessed outcome and risk factors of CRBSIs in children on HPN and most of them only in a small cohort of children [20–24]. Risk factors that have been associated with an increased rate of CRBSI include prematurity, malignancy, previous abdominal surgery, small bowel length, presence of enterocutaneous stoma, lack of enteral nutrition, use of CVC for PN, duration of PN and use of antacids [20–24]. In the Unites States Medicard insurance and age <1 year were also associated with increased risk for CRBSI in children on HPN [25].

The aim of our study was to prospectively identify the incidence and risk factors associated with CRBSI in children receiving HPN for IF managed by our specialist multidisciplinary IF rehabilitation service.

## 2. Material and methods

### 2.1. Inclusion criteria

This study was performed in a single multidisciplinary specialist paediatric IF rehabilitation service. Eligible patients included those 1) <18 years of age; and 2) treated with HPN at any time during the study. All variables including demographics, risk factors, HPN details and episodes of CRBSIs in eligible patients were recorded prospectively in a longitudinal maintained database from January 2015–April 2019.

### 2.2. Home parental nutrition care pathway

Patients were discharged home on PN after rigorous investigation of their underlying disease that had predisposed to IF, and when repeated attempts to reduce and stop PN had failed. Once it was clear that they were likely to need PN for at least the next 2–3 months parent/s or carer/s underwent a formal training programme over about 30 h in a two week-period to learn how to connect and disconnect the PN infusion and what to do if any complications arose. They were taught a single person 'aseptic non-touch technique'ANTT [26]. Tuition included hand hygiene procedures and antiseptic techniques for the skin when handling the catheter, use of a sterile gauze with tape and transparent semi-permeable polyurethane dressing to cover the catheter insertion site and a dressing method that kept the catheter exit-site visible and dry [35].

### 2.3. Central venous catheter locks

Heparin locks were used routinely when the CVC was clamped off during the day. In children who had 2 CRBSIs in a 12-month period taurolidine locks were substituted [27].

Taurolidine citrate lock (taurolidine 1.35%, citrate 4%; *Taurolock* catheter lock solution; TauroPharmGmbh, Germany), was introduced after completing treatment of a CRBSI when there had been no positive blood cultures for at least 10 days. Parents/carers were trained to use the lock by our specialist intestinal rehabilitation nurses. After disconnecting the PN infusion the CVC was flushed with 10 mL of sodium chloride 0.9% solution for injection followed by slow instillation (in around 5 s) to the positive pressure valve of sufficient taurolock to fill the CVC lumen; ranging from 0.4 mL for 4.2Fr to 1 mL for 6.6Fr. The lock was left 'in situ' until the next PN connection with a minimum indwelling time of >2 h. Prior to the subsequent PN connection the taurolidine citrate was withdrawn from the CVC using a 1-mL syringe, the CVC was flushed with 10 mL, 0.9% sodium chloride solution and PN was connected.

At the time of discharge home on PN a meeting was held with the child's parents/carers along with the child if age appropriate, our specialist multidisciplinary team and an assigned paediatrician working in the acute paediatric service most local to the child's home to set up direct access to the local service and a management plan should the child present with symptoms consistent with CRBSI. The parents/cares were given a copy of the plan.

The plan was for when the child was assessed to have clinical symptoms consistent with a CRBSI, to have a blood sample taken for culture and at least two antibiotics administered via the CVC to give broad spectrum cover on arrival at the local hospital. The symptoms included fever >38 °C, with/without rigors, and/or respiratory distress, and in certain children, symptoms previously associated with CRBSI in absence of fever.

Once admitted to hospital the child was to remain on antibiotic treatment until the culture result was available. If the blood culture was positive, treatment was adjusted according to antibiotic sensitivities. Once the blood culture was negative if the child was well s/he was usually discharged home to continue the course of antibiotics. The first line antibiotics were usually Piperacillin/Tazobactam and Aminoglycoside, based on regional prevalence and pathogen resistance. Teicoplanin was added for methicillin-resistant Staphylococcus Aureus (MRSA). Antibiotic therapy was continued for at least 10 days after the first negative blood culture. Anti-fungal treatment was considered if lack of response to antibiotic therapy or blood culture was positive for fungi. PN administration was continued throughout with a 'Y' connector for antibiotic administration via the CVC if a dose was required during the hours that PN was infused.

### 2.4. Diagnosis of CRBSIs

The diagnosis of CRBSI was defined in accordance with European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines as positive blood culture obtained from paired CVC and peripheral vein samples when possible, clinical manifestations of infection such as fever >38c, rigors and/or

hypotension, and no apparent source for other potential bloodstream infection [7].

All positive cultures were classified according to microscopy and staining as gram-positive, gram-negative, polymicrobial flora and fungal infection. Details of antimicrobial therapy such as systemic antibiotics or line-lock therapy, where appropriate, were recorded. The CVC was removed if septic shock developed or when a patient was not responding to antibiotic treatment with persistent fever or other symptoms and/or persistently positive blood culture despite appropriate antibiotic administration.

### 2.5. Data collection

A longitudinal database including all eligible patients was set up at the beginning of the study including child's age at enrollment, sex, primary indication for HPN, number of infusions/week, number of lipid containing infusions/week, use of taurolidine lock and duration of HPN as total number of days from starting to stopping PN during the study period. Additional data recorded for each CRBSI episode included microorganism(s) isolated, antibiotic therapy administered and use of lock therapy. Data on enteral intake, presence of gastrostomy, gastro-jejunostomy or proximal jejunostomy used for drainage or feeding, presence of distal enterocutaneous stoma (ileostomy or colostomy), absence of ileocecal valve, use of prophylactic taurolidine lock and details regarding type and number of CVC lumens, additional caregivers connecting/disconnecting the CVC as well as the one or two assigned parents/carers and evidence of vulnerable family circumstances were also collected to assess risk factors for CRBSI. Vulnerable families were defined as those that were unusually disorganized and/or with a parent with significant mental health issues.

### 2.6. Statistical analysis

Statistical analysis was performed by using the R studio software package (Version 1.2.1335 © 2009–2019 RStudio, Inc.).

Continuous data were summarized as mean ± SD with normal distribution or as median (range) with skewed distribution; categorical data were summarized as number of patients (percentage of sample).

Student *t* test and one-way analysis of variance (ANOVA) with Bonferroni comparisons were used for parametric data and the Mann Whitney *U* test was used for non-parametric data. For categorical data, $\chi^2$ was used with Fisher's exact test.

The unit of measurement of CRBSI was the *Number of episodes per 1000 catheter days* i.e. ratio between the number of CRBSI and total number of catheter days during the study period multiplied by 1000.

Log-rank survival analysis and Cox regressions were performed to compare the incidence rate of CRBSIs between different groups of patients based on different diagnoses, demographics and clinical characteristics.

Statistical significance was taken as $P < 0.05$.

### 2.7. Ethics

The project was registered as a clinical audit with the hospital Clinical Audit Department and did not require approval by our research ethics committee.

## 3. Results

### 3.1. Demographics

A total of 75 home PN patients were included in the database from January 2015–April 2019. Median age at enrollment was 5.7 years (range 0.1–17.6 years). Patients were followed for a total of 52 months (range 2.5–52 months), accounting for a total of 70490 catheter days. The median duration of HPN was 964 days (range 75–1565).

The indication for PN was IF in all patients. The etiologies of IF were motility disorders in 26/75 (35%), SBS in 21/75 (28%), graft versus host disease (GvHD) post bone marrow transplant in 13/75 (BMT) (17%), congenital enteropathy 11/75 (15%), and patient with severe neurodevelopmental impairment 4/75 (5%). Median follow up for each group was as follows: motility group 37.6 months (range 2.5–52), SBS group 27.3 months (range 4.2–52), GvHD 13.3 months (range 3–52), congenital enteropathy group 46.6 months (range 4.2–52) and severe neurodevelopmental impairment group 42.6 months (range 30.1–49). Clinical details are summarized in Table 1 and Table 2.

Forty-one children were already receiving PN when enrolled, 34 started PN during the study period, 32 weaned off PN during the study and 43 were still receiving PN when data collection was stopped. Five patients in GvHD group died during the study period for causes unrelated to CRBSIs.

### 3.2. CRBSI prophylaxis

During the study period prophylactic taurolidine citrate lock was used in 23, 30.1% patients. Ethanol lock was used only in 1 patient. Ten children were on taurolidine citrate lock from the start of the study, 13 were commenced on it after the initiation of the study (Table 1) and Fifty-two, 69.3% patients did not receive taurolidine treatment. The indwelling time between 2 PN cycles was at least 6 h (median 12 h, range 6–12).

### 3.3. Episode of CRBSIs

During the study period, a total of 124 CRBSIs developed in 41 (55%) patients with an overall CRBSI rate of 1.61 per 1000 catheter days. Thirty-four patients (45%) remained free of infection throughout the study period. The median number of CVC infections per patient was 1 (range 0–14).

**Table 1**
Clinical characteristics of all children on HPN included in the study.

| Clinical characteristics | Total |
|---|---|
| Patients, number | 75 |
| Patients with CRBSI, number (%) | 41 (55) |
| Age at enrollment, median (range) | 5.7 (0.1–17.6) |
| Sex, number (%) | |
| Male | 36 (48) |
| Female | 39 (52) |
| PN details | |
| Number of CVC days, median (range) | 964 (75–1575) |
| Days/week PN infused, median (range) | 7 (1–7) |
| Days/week lipid infused, median (range) | 3 (0–5) |
| Catheter-related bloodstream infection details | |
| CRBSI, number | 122 |
| CRBSI per patient, median (range) | 1 (0–14) |
| Microorganism, number (%) | |
| Gram positive | 50 (40) |
| Gram negative | 40 (32) |
| Polymicrobial | 27 (22) |
| Fungal | 7 (6) |
| Patients on prophylactic lock, number (%) | |
| Taurolidine | 23 (30) |
| From the beginning of the study | 10 (13) |
| Started during the study | 13 (17) |
| Ethanol | 1 |

HPN: home parental nutrition; CRBSI: catheter-related blood stream infection; CVC central venous catheter.

**Table 2**
PN indications in patients with CRBSI included in the study.

| | Numbers |
|---|---|
| *Gastrointestinal motility disorders* | 26 |
| Intestinal dysmotility | 19 |
| Paediatric intestinal pseudo-obstruction | 4 |
| Megacystis microcolon hypoperistaltic syndrome | 1 |
| Intestinal atresia | 1 |
| Eosinophilic myenteric ganglionitis | 1 |
| *Short bowel syndrome* | 21 |
| Necrotizing enterocolitis | 7 |
| Volvulus | 5 |
| Gastroschisis | 4 |
| Intestinal aganglionosis | 2 |
| Intestinal ischaemia due to artery thrombosis | 1 |
| Jejunal atresia | 1 |
| Small bowel lymphangioma | 1 |
| *Mucosal diseases* | 11 |
| Tufting enteropathy | 4 |
| Microvillus inclusion disease | 2 |
| Hennekam Beemer syndrome | 2 |
| Crohn's disease (unresponsive to medical treatment) | 1 |
| Eosinophilic enterocolitis | 1 |
| Lymphocytic colitis | 1 |
| *GvHD post bone marrow transplant* | 13 |
| Perforin deficiency | 1 |
| Neuroblastoma | 1 |
| Burkitt's lymphoma | 1 |
| Acute lymphoblastic leukemia | 3 |
| Juvenile myelomonocytic leukaemia | 2 |
| X-linked inhibitor of apoptosis protein deficiency | 1 |
| Severe combined immunodeficiency | 2 |
| TTC7A deficiency | 1 |
| Di George syndrome | 1 |
| *Severe Neurodevelopmental impairment* | 4 |

PN: parental nutrition; CRBSI: catheter-related blood stream infection; GvHD: graft versus host disease.

Thirteen of 23 (56%) children on prophylaxis with taurolidine citrate lock developed CRBSIs. Ten of the 13 had an underlying gastrointestinal motility disorder. Median number of infections in children whilst on taurolidine prophylaxis was 2 (range 1–8).

The median weekly PN infusion frequency was 7 days (range 1–7) and the median weekly infusion incorporating lipid was 3 days (range 0–5).

The total number of CVCs used during the study was 108. The venous access devices were single-lumen Hickman line (SLHL) (80/108, 74%), double-lumen Hickman line (DLHL) (24/108, 22%), and single lumen peripherally inserted central catheters (PICC) (4/108, 4%). CVC replacement was required in 33/122, 27% of CRBSIs.

The number of children with CRBSI according to IF diagnosis was 16/26 (62%) with a motility disorder (73 CRBSIs), 11/21 (52%) with SBS (22 CRBSIs), 8/13 (46%) with GvHD (11 CRBSIs), 5/11 (45%) with congenital enteropathy median (13 CRBSIs), and 1/4 (25%) children with severe neurodevelopmental impairment (3 CRBSIs).

The CRBSI rate was 2.74/1000 catheter days for motility disorders, 1.54/1000 catheter days for GvHD group, 0.67/1000 catheter days for severe neurodevelopmental impairment, 0.52/1000 catheter days for congenital enteropathy and 0.36/1000 catheter days for SBS. There was a significantly higher infection rate in motility disorder group when compared to others ($p < 0.0005$) (Fig. 1).

### 3.4. Microbiology of CRBSIs

Of the 124 CRBSIs, 97 (78%) were monomicrobial and 27 (22%) were polymicrobial infections. In the latter the numbers of organisms isolated from blood cultures was 2 ($n = 19$), 3 ($n = 7$) and 4 ($n = 1$).

Gram positive bacteria were the most common (48/124, 39%) followed by gram negative bacteria (40/124, 32%), polymicrobial infection (27/124, 22%) and fungal infections (7/124, 7%). Five of the polymicrobial infection grew Candida species and all fungal CRBSI were due to Candida species.

In total 160 microorganisms were identified from all blood cultures. Staphylococcus Aureus ($n = 26$) and Klebsiella sp ($n = 24$) were the most common pathogens isolated (Table 3).

### 3.5. Antimicrobial treatment of CRBSIs

All episodes of CRBSI were treated with a course of antibiotics for at least 10 days. The most commonly used antibiotics were Gentamicin ($n = 72$) and Teicoplanin ($n = 71$). Amphotericin was the most used antifungal ($n = 7$).

### 3.6. Potential risk factors for CRBSIs

Presence of risk factors for CRBSIs were considered for each CRBSI. At the time of the CRBSI episodes 51/124, 41% cases (had an enteral artificial feeding device (gastrostomy, gastro-jejunostomy or jejunostomy) 'in situ', 64/124, 52% where on partial PN and tolerating an oral/enteral intake of at least 25% of daily calorie requirements, 75/124, 60% had a distal intestinal stoma (ileostomy or colostomy) in situ and 47/124, 38% cases had had ileocecal valve resection.

Eleven families were considered vulnerable and additional professionals were accessing the CVC in 4 children during the study duration.

Statistical analysis demonstrated that motility disorders had the highest risk of infection. Compared to the group with motility disorders, the hazard risk of CVC-sepsis was significantly lower for children with SBS (HR 0.54, 95% CI 0.33–0.84), GvHD (0.41, 95% CI 0.19–0.89), congenital intestinal mucosal disease (HR0.36, 95% CI 0.19–0.65) and severe neurodevelopmental disorder (HR 0.27, 95% CI 0.08–0.87) ($p < 0.0005$) (Fig. 1).

Log-rank survival analysis showed that age <2 years, male sex, double-lumen CVC, distal intestinal stoma, PN infusion >4 nights/week, total PN with lack of oral nutrition, presence of gastrostomy or jejunostomy, previous resection of ileocecal valve, non-use of taurolidine citrate lock, vulnerable families and >2 caregivers handling the CVC were all risk factors significantly associated with higher CRBSI rate.

COX multivariate analysis showed that only age <2 years, male sex, underlying diagnosis of gastrointestinal motility disorder, distal intestinal stoma and non-use of taurolidine citrate lock were independently associated with a higher risk of CRBSI (Table 4).

## 4. Discussion

Our prospective observational study revealed that the CRBSI rate of our cohort was 1.61 per 1000 catheter days over a 52-month period. Our study also demonstrated that age <2 years, male sex, distal intestinal stoma, underlying gastrointestinal motility disorder and non-use of taurolidine citrate prophylactic lock - were all significantly and independently associated with higher CRBSI rate. This data is consistent with available literature [15–19,28–32].

The significantly greater risk of CRBSI with gastrointestinal motility disorders (2.74/1000 catheter days) raised the overall CRBSI rate of our cohort to 1.61/1000 catheter days. In contrast to the motility cases, the CRBSI rates for our patients with SBS, congenital enteropathy, neurodevelopmental delay and GvHD were in line with the CRBSI rate reported after implementation of taurolidine lock prophylaxis [15–19]. Since motility disorders were the commonest diagnosis in our patients the incidence of CRBSI would have been expected to be higher than that reported by other

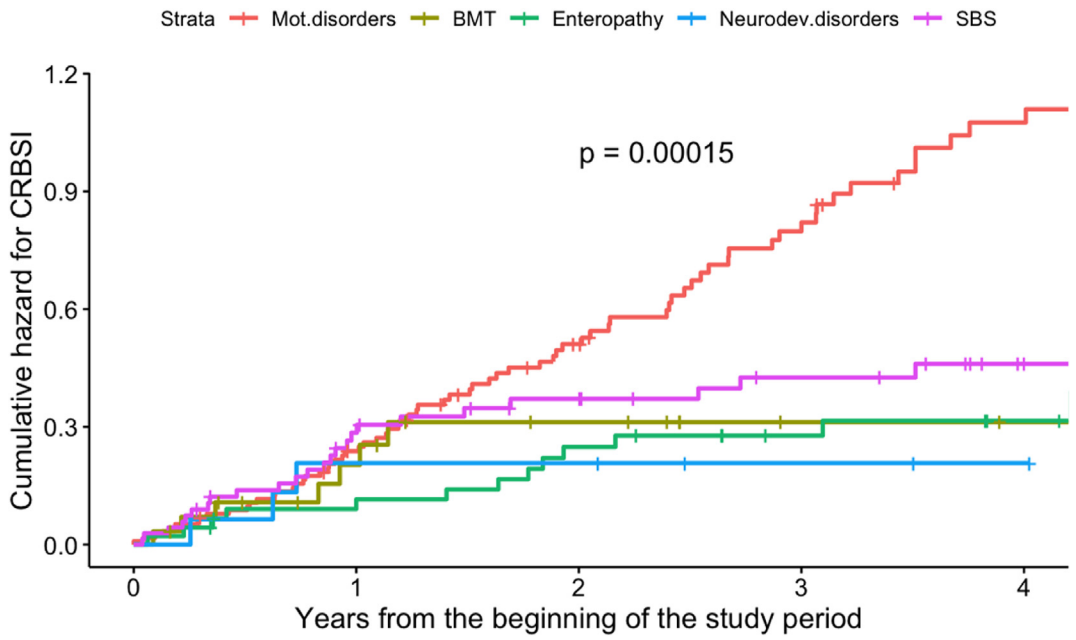


**Fig. 1.** CRBSI rates in the study groups according to diagnosis of intestinal failure.

**Table 3**
Characteristics of the 160 pathogens isolated in 124 CRBSIs.

| Pathogens | No |
|---|---|
| Gram positive organisms | |
| *Staphylococcus aureus* | 26 |
| *Streptococcus* sp | 11 |
| *Staphylococcus epidermidis* | 10 |
| *Enterococcus faecalis* | 7 |
| *Streptococcus oralis* | 5 |
| *Corynebacterium* | 5 |
| *Streptococcus mitis* | 4 |
| *Coagulase-negative staphylococci* | 4 |
| *Streptococcus salivarius* | 3 |
| *Gordonia* sp | 1 |
| *Bacillus* sp | 1 |
| *Lactobacillus* | 1 |
| *Granulicatella adiacens* | 1 |
| Gram negative organisms | |
| *Klebsiella* sp | 24 |
| *Enterobacter* sp | 11 |
| *Pseudomonas* sp | 11 |
| *Escherichia Coli* | 10 |
| *Proteus* sp | 5 |
| *Acinetobacter* sp | 2 |
| *Stenotrophomonas* sp | 2 |
| *Citrobacter* sp | 1 |
| *Aeromonas* sp | 1 |
| *Hafnia Alvei* | 1 |
| *Coliforms* | 1 |
| Fungi | |
| *Candida albicans* | 6 |
| *Candida parapsilosis* | 4 |
| *Candida glabrata* | 2 |

CRBSI: catheter-related blood stream infection.

paediatric IF centres with SBS (the commonest aetiology of paediatric IF) as the most frequent diagnosis.

The significantly higher incidence of CRBSIs in children with gastrointestinal motility disorders could be related to several factors. Firstly, children with motility disorders often have a more severe irreversible condition and are less likely to gain enteral tolerance with long-term total PN dependance when compared to SBS or some congenital enteropathies that develop partial and, in some cases, total enteral autonomy over time [33]. Also, patients with motility disorders often need gastrostomy or jejunostomy formation for feeding or gastric drainage when gastric emptying is impaired or require a distal enterocutaneous stoma such as ileostomy or colostomy to allow decompression of the gastrointestinal tract - which were found to be significant risk factors for CRBSI in our study.

The higher infection rate in children with an enterocutaneous stoma (ileostomy, colostomy, distal jejunostomy) may be related to leakage of intestinal fluid from a stoma onto the skin that then contaminates the CVC when disconnecting/connecting the PN infusion. In addition, leakage of stomal fluid onto the CVC dressing may penetrate the dressing and contaminate the CVC tip. Parents/carers were advised on how to minimise CVC contamination when trained to manage HPN. Firstly, they were shown how to secure the external part of the CVC on the child's back with the catheter looped to help prevent it from becoming dislodged if it were pulled. They were instructed to loop the CVC tip away from the patient's nappy area/stoma/enteral feeding device to reduce the chance of contamination. They were also shown how to apply a dressing that was routinely changed once a week (or sooner if wet, dirty, or peeling). They were advised to use *Statlocks* (Foley stabilization device) to clip the CVC tip in place to reduce the impact of a sudden pull and dislodgement of the CVC. They were taught to cover the tip of the CVC with a *curos cap* (3M Curos disinfecting port protector with 70% isopropyl alcohol) or a self sealing, waterproof, flexible, mouldable film, *parafilm* (Bemis Company,Inc), to minimise the possibility of contamination with vomit, stool, saliva/other potentially infectious biological fluid.

Families were also informed of the option to purchase a specially designed vest with a pocket for the CVC to be tucked into to prevent the tip from dangling into the nappy or stoma area. If the patient was mobile, e.g. if infusing PN during daytime hours, there was the option to carry the PN bag and pump in a backpack if the child was capable of doing so. The backpack would keep the CVC and the administration line more secure than if the patient were using a drip stand. Finally, parents were taught to clean the CVC before

**Table 4**
Risk factors for CRBSIs analyzed in multivariate cox proportional-hazards model.

| Risk factors | HR | 95% CI | P value Cox-model |
|---|---|---|---|
| Diagnosis of gastrointestinal motility disorder | 3.02 | 1.81–4.91 | <0.001* |
| Patients with GvHD | 0.41 | 0.19–0.89 | 0.50 |
| Diagnosis of congenital enteropathy | 0.36 | 0.20–0.65 | 0.25 |
| Patients with neurodevelopmental disorders | 0.27 | 0.08–0.87 | 0.50 |
| Diagnosis of short bowel syndrome | 0.54 | 0.33–0.84 | 0.82 |
| Age <2 years | 0.28 | 0.15–0.53 | <0.0001* |
| Male sex | 2.28 | 1.51–3.43 | <0.0001* |
| Total HPN with lack of oral intake | 0.75 | 0.47–1.20 | 0.23 |
| Presence of gastric or jejunal tube | 1.23 | 0.80–1.88 | 0.36 |
| Absence of ileocecal valve | 2.34 | 1.10–4.98 | 0.06 |
| Presence of distal intestinal stoma | 3.35 | 1.63–6.86 | <0.001* |
| HPN infusions frequency >4 times/week | 2.52 | 0.97–6.53 | 0.06 |
| Double lumen CVC | 0.41 | 0.11–0.92 | 0.12 |
| Non-use of prophylactic taurolidine citrate lock | 2.70 | 1.72–4.11 | <0.0001* |
| Professional handling CVC in addition to relatives | 0.93 | 041–2.12 | 0.871 |
| Social issues | 1.71 | 0.81–3.61 | 0.155 |

CRBSI: catheter-related blood stream infection; GvHD: graft versus host disease; HPN; home parenteral nutrition; CVC: central venous catheter.
*p value statistically significant as <0.05.

connecting each infusion in order to avoid contamination. They were instructed to wipe the catheter tip with 2% chlorhexidine gluconate in 70% isopropyl alcohol solution using a firm twisting action with the whole surface of the cloth/tissue for at least 30 s and allowing the end/tip to air dry for 30 s. A single person aseptic non touch technique (ANTT) was used to connect/disconnect the infusions. It is a well-established method that focuses on avoiding touching key parts when connecting/disconnecting the CVC from an infusion [26]. Despite all these preventive measurements there was still a risk that the tip of the catheter might be contaminated, particularly in children with high stoma losses that could leak onto the catheter end at night, or if parents did not adhere to the recommendations.

Younger age (<2 years) may be associated with higher risk of CRBSI for several reasons: firstly because children have not developed urinary and faecal continence yet and pass stool into a nappy/diaper that may leak onto the skin. Secondly the small size of the infant's body means that the CVC is inevitably closer to any enterocutaneous stoma and the nappy area. If the clamped off end of the CVC were allowed to dangle it is more likely to hang down near the stoma due to the child's small size. Thirdly, a young child is more likely to unpredictably move during a catheter dis/connection. Younger children also have lower systemic immunity which may predispose them to CRBSI. Finally, the higher incidence of CRBSI in the young population may reflect the learning curve process of parents/caregivers which would be expected to improve over time with experience. The use of preventative measures described above to minimize contamination risk are of particular importance in the young child.

Regarding gender difference, we speculate that discrepancies in genitalia anatomy may be responsible for higher risk. Younger males may contaminate the CVC by hand contact with genitalia skin and subsequently the catheter. Also, there may be a sex divergence in adherence to best practices in older male children. A gender gap in other medical conditions has been previously reported in adults [34].

Our finding that the CRBSI rate was significantly higher when prophylactic taurolidine catheter lock was not used was in keeping with the recent literature that has reported up to a 5-fold reduction in average incidence of CRBSI after implementation of taurolidine prophylactic lock [15–19]. This reduced CRBSI rate raises the question of implementing taurolidine lock as a primary prophylaxis, particularly in the population we have identified at increased CRBSI risk, i.e. aged <2 years, with underlying motility disorders or with a distal enterocutaneous stoma. We noted that most patients who continued to have episodes of CRBSIs even on prophylactic taurolidine had underlying gastrointestinal motility. This association needs further investigation and should be explored in future studies.

Our study identified some significant associations with CVC related sepsis. There is existing evidence for limiting infections by formally training caregivers to perform good hand hygiene prior to handling a CVC and using an aseptic technique when /dis/connecting the catheter, use of tunnelled single-lumen CVC catheter, infusing the PN from a single bag (as opposed to separate lipid and aqueous/glucose with amino acid bags) when possible, and using CVC-lock therapy with e.g taurolidine or ethanol [35–37].

In addition when patients have the risk factors identified in our study all possible measures should be taken to minimize CRBSI risk. Most importantly all professionals/parents/caregivers who have been accessing the CVC should have a formal training update to ensure they are able to handle the CVC in the best possible manner. Retraining points would include hand hygiene procedures and antiseptic techniques for the skin when handling the catheter. A sterile gauze with tape and transparent semi-permeable polyurethane dressing can be used to cover the catheter insertion site. The dressing method must be selected in order to keep the catheter exit-site visible and dry [35].

In addition to all the points already mentioned the family's psychosocial situation is an important factor to assess before discharge on HPN [6]. In our study we did not find a significant association with what we assessed to be a vulnerable high risk family situation and increased CRBSI incidence. It is possible that the lack of association was related to our team being aware of which families were at risk prior to the child's discharge and ensuring that greater support was given to families who required it.

The strengths of our study were the prospective assessment, the long time-frame and the large sample size. This study is one of the largest analyses of CRBSIs in children receiving HPN.

As the data were prospectively recorded all cases of CRBSIs were captured and truly reflected the CRBSI rate. Also, the prospective analysis allowed us to consider all changes of risk factors over the time as patients have changed their characteristics during the study period: age, intestinal anatomy, PN volume and enteral intake. In this respect our statistical model enabled us to analyze risk factors for each episode of CRBSI.

One of the limitations of our study is that the CRBSI were not usually managed in our centre, although the families all had

handheld/electronic guidelines that were accessed and followed by the treating hospital. Also it needs to be taken into account that parents/care givers were responsible for the daily management of HPN and then their approach could impact the CRBSI rate. Every effort was made to update HPN training in order to minimize the risk of infection. A further limitation was difficulty in obtaining peripheral blood samples, particularly in younger children, although central blood cultures were obtained in all cases.

## 5. Conclusion

Our study has identified that age <2 years, male sex, presence of ileostomy or colostomy and gastrointestinal motility disorder are all independent risk factors associated with significantly greater risk of CRBSIs and Taurolidine lock significantly reduced the risk. Children with any of the above risk factors should be prioritized for early introduction of taurolidine lock and regular review of catheter management to minimize the health risk and disruption to family life with the need for urgent admission to hospital when a CRBSI is suspected. Further studies assessing effectiveness of CRBSI prevention measures are required.

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Nothing to declare.

## Author contribution

MGP, CD and SH designed research; CD and EK collected the data; MGP, CD and SH conducted research; MGP and CD analyzed data and performed statistical analysis; MGP, CD and SH wrote the paper; SH and JK had primary responsibility for final content. All authors read and approved the final manuscript.

## Conflict of interest

No Conflict of interest declared.

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