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Review

Candida catheter-related bloodstream infection in patients on home parenteral nutrition - Rates, risk factors, outcomes, and management

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SUMMARY

Background: Catheter-related bloodstream infections (CRBSIs) are life-threatening complications for home parenteral nutrition (HPN) patients. This review clarifies *Candida* CRBSI rates by species, risk factors, outcomes, and management to improve effectiveness of HPN programs.
Methods: A review of *Candida* CRBSIs in HPN patients was conducted around the following questions: 1. How often do adult and paediatric HPN patients contract *Candida* CRBSIs? 2. What is the proportion of different *Candida* species? 3. What are the risk factors? 4. How are outcomes in *Candida* versus other CRBSIs? 5. What are current guidelines to manage *Candida* CRBSIs? Specifically, should catheters be removed? What antimicrobial therapy is indicated? Are catheter lock techniques effective?
Results: 20 studies were included – six paediatric and 14 adult. *Candida* represented 9.8% of paediatric CRBSIs and 11.7% of adult CRBSIs. Paediatric candidal CRBSIs featured these species: *C. albicans* (46.2%), *C. parapsilosis* (34.6%), *Candida guilliermondii* (11.5%), *Candida tropicalis* (3.8%), and mixed or other types of *Candida* (3.8%). Adult candidal CRBSIs featured these species: *C. albicans* (37.3%), *C. glabrata* (33.3%), *C. parapsilosis* (22.4%), mixed or other types of *Candida* (5.7%), and *C. tropicalis* (1.3%). Risk factors for paediatric HPN CRBSIs include underlying haematological disease and previous fungaemia. *Candida* infection is associated with mortality rates around 30%. In *Candida* CRBSIs, major guidelines advocate catheter removal prior to systemic antifungal treatment (fluconazole, amphotericin B, echinocandins), ideally until 14 days after the first negative blood culture; some studies suggest the possibility of systemic therapy while catheters remain in-situ to preserve crucial line access. Various catheter lock solutions are effective as treatment and prophylaxis, but are not yet firmly established.
Conclusions: *Candida* CRBSI is a significant danger to HPN patients causing high mortality; gold standard treatment is catheter removal and antifungal treatment, although treatments with catheters in-situ and catheter locks as prophylaxis appear to be gaining traction.

1. Introduction

In patients unable to receive adequate nutrition via the oral or enteral route, parenteral nutrition via catheters is indicated to avoid malnutrition. This can be done in the hospital or at home. Catheter-related bloodstream infections (CRBSIs) are common and life-threatening complications, with parenteral nutrition being a risk factor [1]. The most common pathogens responsible for these infections are skin-derived Gram-positive bacteria, followed by Gram-negative bacteria, and fungi like *Candida* albicans [2,3]; however, long-term home parenteral nutrition (HPN) patients face higher risk of Candida infections than patients on acute hospital parenteral nutrition [1,4]. Consequently, this review focuses on *Candida* CRBSI rates and risk factors among patients on HPN, and additionally explores *Candida albicans* versus *non-albican* rates, and guidelines on managing infections, including removal versus non-removal of catheters, use of catheter lock solutions, and different types of antimicrobial treatment.

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2. Definitions

Infection is one of the most frequent complications of HPN, and is potentially fatal and associated with significant morbidity in the critically ill [5]. In this paper, candidaemia refers to a positive *Candida* blood culture, which differs from a CRBSI as defined by various organisations. The US Centers for Disease Control (CDC) defines a bloodstream infection (BSI) as at least two blood cultures from a patient with an intravascular access device featuring common skin pathogen(s) [6,7]. The Infectious Disease Society of America (IDSA) defines a CRBSI where the same organism grows from at least one percutaneous blood culture and from a catheter tip culture [8]. The European Society for Clinical Nutrition and Metabolism (ESPEN) defines a CRBSI as either a positive catheter culture when the catheter is removed, or paired cultures from both the catheter and peripheral blood [5,9,10]. Hence, IDSA and ESPEN definitions are largely similar, although ESPEN criteria can be satisfied with just a positive catheter culture. Other studies are less stringent, counting a catheter-related sepsis or infection when any positive blood culture is found. The studies shortlisted in this review used various definitions for *Candida* infection, though the majority used the IDSA/ESPEN definition for CRBSIs.

3. Materials and methods

Systematic searches associating HPN with *Candida* were performed on ScienceDirect, MEDLINE, and Web of Science. Guidelines of various HPN authorities or collaborating bodies were also consulted. The aim of this search was to determine (i) *Candida* CRBSI rates among HPN patients, (ii) the infection rate of different *Candida* species; (iii) risk factors predisposing to *Candida* CRBSIs; (iv) prognosis of *Candida* infections versus other infections; and (v) guidelines on managing and treating *Candida* CRBSIs.

Specifically to answer questions (i) and (ii), papers were included if they were English-language articles studying patients on HPN, with *Candida* species data. 221 articles from ScienceDirect, 18 articles from MEDLINE, and 28 articles from Web of Science were retrieved. After excluding duplicates, the remaining articles were screened by abstracts, and then by full-text analysis. This yielded 20 studies – six paediatric and 14 adult (see Fig. 1). The majority of studies defined a CRBSI as requiring at least one peripheral blood culture and one catheter culture identifying the same organism without other cause; others had relatively less stringent criteria, with just septicaemia i.e. positive blood culture; and one study followed CDC's definition of at least two positive blood cultures.

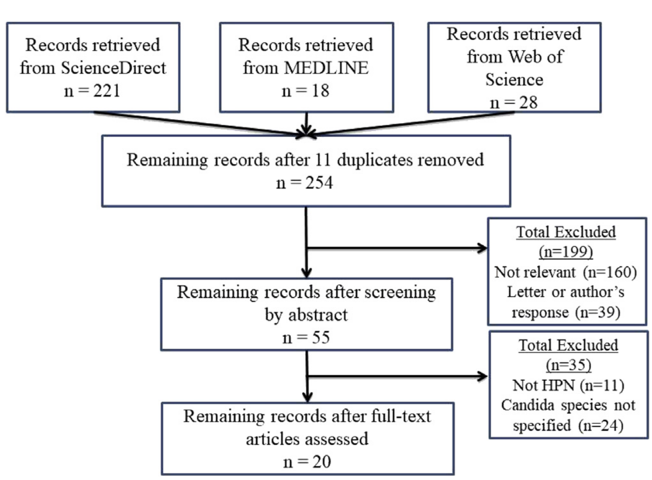

Fig. 1. Flow chart for the selection of studies included in this review.

4. Results

4.1. How often do HPN patients suffer CRBSIs? What proportion involves fungal infection with Candida?

In an epidemiological paper, Opilla found CRBSIs occurring in 1.3%–26.2% of patients on parenteral nutrition with CVCs [1]. A separate review noted that fungal infections comprise 10% of catheter-related infections, of which most are caused by *Candida* species [3].

A systematic review on catheter-related infections among adult patients receiving HPN found rates ranged between 0.38 and 4.58 episodes per 1000 catheter days (median 1.31), with Gram-positive bacteria causing the majority of infections [11]. Out of the causative pathogens, 61% were Gram-positive bacteria, 23% were Gram-negative bacteria, 8% were fungi, 4% were polymicrobial, and 4% other. Among the cases where the causative pathogens were fungi, 93% (49 out of 53) were *Candida* species.

Our own literature search yielded 20 papers which published *Candida* infection rates out of total CRBSIs (see Figs. 2,3, Appendix A & B). For paediatric patients, *Candida* infections comprised 9.8% of all CRBSIs overall, while for adult patients, they accounted for 11.9%. This appears comparable with the 10% and 8% figures given by previous reviews.

Summary – Based on an earlier systematic review, adult HPN patients suffer CRBSIs at a median rate of 1.31 episodes per 1000 catheter days (0.38–4.58). Out of these, 8–10% are due to fungi, with *Candida* species making up the majority of fungi-related

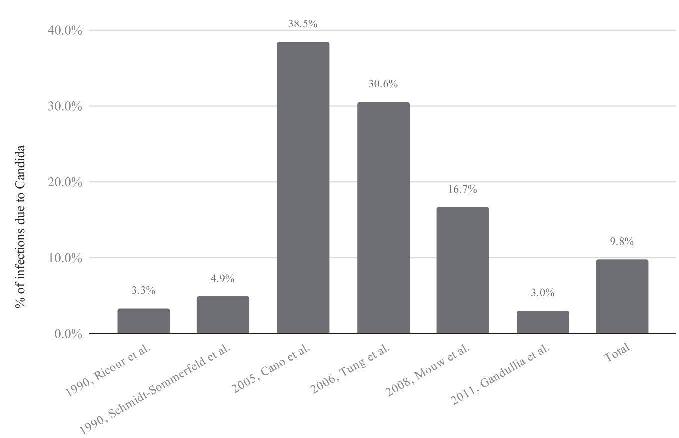

Fig. 2. Percentage of total CRBSIs caused by *Candida* species in paediatric studies.

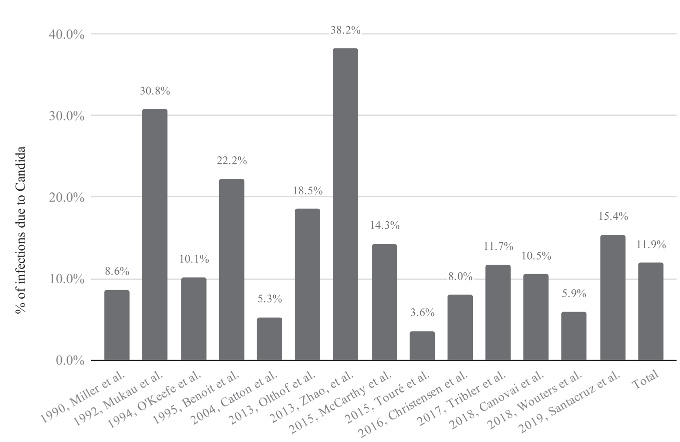

Fig. 3. Percentage of total CRBSIs caused by *Candida* species in adult studies.

CRBSIs. Our own literature search found *Candida* species responsible for 9.8% of paediatric HPN CRBSIs and 11.9% of adult HPN CRBSIs.

4.2. What is the proportion of different Candida species in CRBSIs?

While there are more than 15 *Candida* species that are responsible for human disease, but the vast majority are due to five most common pathogens: *C. albicans, C. glabrata, Candida tropicalis, C. parapsilosis*, and *Candida krusei* [12]. Different *Candida* species have unique virulence, susceptibility, and can thus influence management and patient outcomes. A 2009 paper found that most *Candida* infections were caused by *Candida* albicans or *Candida* glabrata, with mean time to final identification being 85.8 h and 154 h respectively. Hence, mean time to antifungal therapy was longer in patients with *Candida* glabrata, probably with more adverse outcomes [13]. A review of antibiotic lock therapy stated *C. albicans* binds to host fibrin proteins that coat the interior and exterior of the inserted catheter; the protein coating makes it more difficult for antimicrobials to penetrate [14]. In addition, a review article on CRBSIs noted *Candida* parapsilosis was shown to produce biofilms inferior to other *Candida* species, and is less able to develop resistance, hence may be associated with lower mortality [3,15].

Separately, a 2010 systematic review compared the relative frequency of *C. albicans* against non-*albicans* among inpatient candidaemia around the world; however, it is to be noted that these rates were in general inpatients and not isolated to patients receiving HPN. The authors found *C. albicans* the predominant species in North and Central Europe (>60%) and the USA (45–58%), while non-*albicans* species dominated in Asia [16]. In the Australian study from the review, *C. albicans* were found in 47.3%, *C. parapsilosis* in 19.9%, *C. glabrata* in 15.4%, *C. tropicalis* in 5.1%, and *C. krusei* in 4.3% of cases [17].

From our own literature search, 6 paediatric and 14 adult HPN papers detailed the different *Candida* species responsible for CRBSIs (see Appendix A & B). Within these we further investigated *Candida* species (see Appendix C & D). Most studies featured *C. albicans* as the dominant *Candida* species; *C. parapsilosis* also featured heavily. Among paediatric HPN patients, 46.2% of *Candida* CRBSIs were due to *C. albicans*, followed by *C. parapsilosis* (34.6%), *Candida guilliermondii* (11.5%), *C. tropicalis* (3.8%), and mixed or other types of *Candida* (3.8%). Among adult patients, 37.3% were due to *C. albicans*, followed by *C. glabrata* (33.3%), *C. parapsilosis* (22.4%), mixed or other types of *Candida* (5.7%), and *C. tropicalis* (1.3%). Interestingly, the paediatric cohorts did not feature any *C. glabrata* while the adult cohorts did not feature any *C. guilliermondii*. It remains to be seen if these are specific population trends or happenstance.

Summary – From our review of the literature, candidal CRBSIs among paediatric HPN patients featured *C. albicans* the most, followed by *C. parapsilosis, C. guilliermondii*, and *C. tropicalis,* while among adult HPN patients, *C. albicans* featured the most, followed by *C. glabrata, C. parapsilosis*, and *C. tropicalis*.

4.3. What risk factors predispose patients receiving HPN to Candida CRBSIs?

Previous guidelines and studies have reported risk factors for fungal line infections, such as intravenous fat emulsions (IVFE) [18], and using non-fungicidal catheter site ointments [19].

Risk factors specifically for candidaemia in patients receiving parenteral nutrition include respiratory compromise [20], malnutrition [20], long-term or broad-spectrum antibiotic therapy [20–22], diabetes mellitus [20], previous CRBSIs (especially fungal) [22–24], high-calorie infusions [22], post-surgery cases [22], chronic renal failure [23], haematologic disease [24], and solid tumours [21]. For uncommon candidaemia (species other than *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*), risk factors include outpatient settings, older age, male sex, haematological malignancy, and HIV infection [25].

Specifically from the 20 HPN studies shortlisted, risk factors often applied to CRBSIs in general rather than candidal infections. Nevertheless, one paediatric study found candidaemia associated with underlying haematological disease and past history of fungaemia [24].

Summary - Risk factors specifically for *Candida* CRBSIs among HPN patients are not widely published, but include underlying haematological disease and past history of fungaemia.

4.4. How do outcomes compare in Candida CRBSIs versus other CRBSIs?

Prognosis of *Candida* CRBSI is largely dependent on the severity of a patient's underlying illness, with early treatment benefitting some groups [21,26,27]. For example, death was more likely in patients with inflammation at insertion sites or abnormal white cell counts [22]. Nevertheless, *Candida* and S. aureus CRBSIs have been found to be associated with higher mortality as opposed to other causative agents like Gram-positive cocci or Gram-negative bacilli [28]. Candidaemia has been found to result in crude and attributable mortality rates of 32%, 34%, 30–81%, 40% and 5–71% in retrospective cohort studies [26,29–32]. *C. parapsilosis* candidaemia is associated with the lowest mortality rates while *C. krusei* is associated with the highest [4,29,33]. Authors postulated that triazole prophylaxis created resistant *Candida* species such as *C. krusei*, resulting in higher mortality.

Specifically for candidal CRBSI, only one study was found with figures of 30-day mortality of Candida CRBSI being 57.1%, significantly higher than aforementioned studies of candidaemia not necessarily catheter-related [28].

Summary – Candidal CRBSIs were found to result in 30-day mortality of 57.1% in one study; and general candidaemia is associated with mortality around 30–40%. This is a higher mortality compared with Gram-positive cocci or Gram-negative bacilli.

4.5. In managing Candida CRBSIs, should catheters be removed or left in situ?

Major governing societies' guidelines and studies were consulted for management of fungal CRBSIs – the European Society for Clinical Nutrition and Metabolism (ESPEN), the American Society for Parenteral and Enteral Nutrition (ASPEN), the Australian Society for Parenteral and Enteral Nutrition (AuSPEN), and the Infectious Diseases Society of America (IDSA).

ESPEN states that fungal infections, including *Candida,* require removal of the catheter and systemic antimicrobial treatment [34,35]. ASPEN generally recommends catheter removal and appropriate antibiotic coverage in cases of CRBSI, although their guidelines do not specifically mention management of fungaemia [18]. IDSA advocates for catheter removal in *Candida* CRBSIs, warranted by the ability of *Candida* species to form biofilms that inhibit antifungal therapy [3]. Salvaging the catheter or device is not recommended as salvage rates are in the 30% range, even with systemic fungal therapy and antibiotic lock therapy [36].

Among other sources, some allow treatment with systemic antimicrobial therapy before removal of catheters [37]. Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC) conceded that if a catheter cannot be removed for any reason, an antifungal with high activity against biofilms should be chosen, such as an echinocandin or amphotericin B [38]. A review paper on venous catheters stated that if candidaemia is of endogenous origin from the gastroenteric tract, there is no indication for catheter removal [3]; however, in *Candida* CRBSIs, removal of catheters within 72 h is an independent predictor of favourable outcomes [39].

Many studies support prompt removal of catheters on fungal infection [20,37,40]. It was found in cases that leaving catheters in situ increased treatment time and mortality rates [41]. A similar study studied early removal (within 3 days) versus late removal of CVCs (more than 3 days) following a positive *Candida* blood culture in infants. The early removal group had significantly shorter durations of candidaemia (3 versus 6 days), and significantly lower case fatality rate, supporting early catheter removal [42].

The preservation of crucial central venous access is also weighed up in the decision of catheter removal [43,44] – some centres reserved catheter removal for after treatment failure [45]. A review of intravascular catheter-related infections proposed a novel management algorithm, where *Candida* CRBSI (categorised as moderate risk due to virulence) warranted removal of catheter and antimicrobial treatment of 10–14 days in short-term and non-tunnelled catheters, versus antimicrobial flush solutions with systemic therapy of at least 14 days in tunnelled CVCs or ports, without removal of catheter [5,46,47].

Summary - A review of major guidelines and papers show that the majority support catheter removal to aid antimicrobial treatment and improve outcomes, with some novel approaches to preserve crucial line access by attempting systemic therapy prior to removal.

4.6. What type and duration of antimicrobial treatment is indicated?

In fungaemia, ESPEN recommends catheter removal and systemic antimicrobial treatment with fluconazole or amphotericin B if there is resistance to fluconazole [34,35]. IDSA recommends fluconazole (loading dose 800 mg, 400 mg daily thereafter; effective against *C. albicans* and *C. parapsilosis*) or an echinocandin (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily; effective against *C. glabrata*) or amphotericin B (if intolerant to aforementioned; 0.5–1.0 mg/kg) in non-neutropaenic patients. In neutropaenic patients, an echinocandin is indicated, with fluconazole as an alternative [3,48]. Treatment should be carried out for 14 days after the first negative blood culture and when infection signs and symptoms have subsided [8,36,49].

Other authors advised amphotericin B for *Candida* infections until the therapeutic dose of 300–500 mg is attained. Fluconazole was also suggested for susceptible strains [50,51]. Other azoles like ketoconazole and fluconazole also demonstrated effectiveness at treating candidaemia [20]. Successful treatment of candidaemia has also been reported with echinocandins including anidulafungin [52]. Anidulafungin is both antifungal and has a unique clearance profile (viable in patients with hepatic and renal dysfunction), making it a viable therapeutic option in critically ill infants and children [53]. Further, in persistent candidaemia, echinocandins were found to be more effective than fluconazole in mycological eradication [52].

Summary – Systemic antifungal treatment for candidaemia is ideally for 14 days after the first negative blood culture is returned, and includes fluconazole (loading dose 800 mg, 400 mg daily thereafter; effective against *C. albicans* and *C. parapsilosis*), amphotericin B to therapeutic levels of 300–500 mg, or echinocandins (caspofungin: loading dose of 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose of 200 mg, then 100 mg daily; effective against *C. glabrata*; viable in critically ill infants and children; more effective in persistent candidaemia).

4.7. Are antimicrobial catheter-lock solutions effective at preventing and/or treating Candida CRBSIs?

Antimicrobial lock technique (ALT) involves injecting an antimicrobial solution into the catheter hub, allowing it to dwell for a length of time and eradicate existing organisms, or prevent colonisation [14]. Its goals include prolonging catheter life and reducing infections and morbidity without removing the catheter.

Ethanol locks have been shown effective in reducing CRBSIs among HPN patients [40]; more specifically, taurolidine decreased reinfections by more than 90% when compared with low-dose heparin locks [54,55], and switching from heparin to taurolidine locks resulted in a six times decrease in catheter occlusions [56,57]. However, some studies showed candidaemia reoccurred after periods of quiescence following ALT.

In another study, 2% taurolidine inhibited *C. glabrata* growth for 30 h. The same researchers also found that adaptation to taurolidine locking solutions has yet to emerge, and the minimum inhibitory concentrations of taurolidine against *C. albicans* to be 2048 mg/l [58].

Minocycline-EDTA in 25% ethanol also prevents regrowth of complicated catheter organisms like *S. aureus* and *Candida* species [59]. Additionally, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines state the most promising antifungal lock therapy includes amphotericin B, ethanol, or echinocandins [60,61]. A study on intraluminal antibiotic therapy agrees with daily amphotericin B lock therapy, finding it effective in suppressing *Candida* CRBSIs and lengthening catheter life for months [62].

Summary - From the current evidence, it appears that 2% taurolidine (or a minimum concentration of 2048 mg/l), ethanol, amphotericin B, minocycline-EDTA in 25% ethanol, or echinocandin catheter lock solutions are effective as treatment and prophylaxis against *Candida* CRBSIs in HPN patients. Though ALT has established effectiveness in non-fungal CRBSIs, it is not yet firmly established for fungal infections.

5. Discussion

The systematic review answered several key questions about *Candida* CRBSIs in patients receiving home parenteral nutrition. Our review found *Candida* species responsible for 9.8% of paediatric HPN CRBSIs and 11.9% of adult HPN CRBSIs. Candidal CRBSIs among paediatric HPN patients featured *C. albicans* the most, followed by *C. parapsilosis, C. guilliermondii*, and *C. tropicalis,* while among adult HPN patients, *C. albicans* featured the most, followed by *C. glabrata, C. parapsilosis*, and *C. tropicalis*.

Risk factors predisposing HPN patients to *Candida* infection include underlying haematological disease and previous fungaemia. Candidal CRBSI is associated with 30-day mortality rate in one study of 57.1%, higher than Gram-positive cocci or Gram-negative bacilli. In most candidal CRBSIs, the catheter should be removed prior to systemic antifungal treatment (fluconazole, amphotericin B, echinocandins), ideally until 14 days after the first negative blood culture is returned. However, some allow for a trial of therapy before catheter removal to retain precious line access.

It also appears that 2% taurolidine (or a minimum concentration of 2048 mg/l), ethanol, amphotericin B, minocycline-EDTA in 25% ethanol, or echinocandin catheter lock solutions are effective as treatment and prophylaxis against fungaemia in HPN patients; further, there is no evidence thus far of taurolidine resistance emerging after long term use. However, although catheter locking has established effectiveness in non-fungal CRBSIs, it is not yet firmly established for fungal infections.

This review identified some best practices regarding treatment and management of *Candida* CRBSIs in HPN patients, as well as average proportion of *Candida* infections out of all infections, and proportion of *Candida* species types in such infections. These findings allow HPN units and hospitals to benchmark their own data and practices against these findings and adjust internal guidelines as required.

This review is limited by the sparseness of data in this niche field, in particular with the use of antimicrobial lock techniques with *Candida* CRBSIs. Further, the shortlisted articles had varying definitions of CRBSIs, complicating comparability. Future studies can focus on the effectiveness of different ALTs and different antimicrobial therapies on different *Candida* species, so we can identify targeted best therapies by species. Outcomes of catheter removal versus non-removal in different catheter types should also be further explored.

Conflict of interest

None.

Funding sources

None.

CRediT authorship contribution statement

Andrew Ian-Hong Phua: Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization. **Kay Yee Hon:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Andrew Holt:** Conceptualization, Resources, Writing - review & editing, Supervision. **Margie O'Callaghan:** Conceptualization, Resources, Writing - review & editing, Project administration. **Shailesh Bihari:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.03.007.

Appendix A
Paediatric HPN studies shortlisted into review

Year/First Author	Region	Population/Age	No. of Patients	Catheter Type	Infection Definition	Candidal out of total infections	Infection rate/1000 catheter days	*Candida* species	Risk factors
1990 Ricour et al. [63]	France (Paris)	Paediatric 3 months - 18 years	112	102 Broviac catheters 18 arteriovenous fistula as infusion sites 1 totally implantable catheter	Septicaemia	3/90 (3.3%)	1.68	3/3 (100%) *C. albicans*	Outbreaks associated with addition of vitamins to nutrient bags at home and lapses in asepsis
1990 Schmidt-Sommerfeld et al. [64]	USA (Illinois)	Paediatric 2 months - 23 years	35	Single-lumen Broviac catheters	Septicaemia	4/82 (4.9%)	4	4/4 (100%) *C. albicans*	Children requiring HPN from early infancy had a higher frequency of catheter-related infections than those started on HPN after the first year of life
2005 Cano et al. [24]	USA (Tennessee)	Paediatric 1–14	13	CVCs	ICD-9 Code 112.5 Disseminated candidiasis	5/13 (38.5%)	Not reported	3/5 (60%) *C. parapsilosis* 1/5 (20%) *C. albicans* 1/5 (20%) mixed *Candida*	Candidaemia was associated with underlying hematologic disease and previous history of fungaemia
2006 Tung et al. [67]	Taiwan (Taipei)	Paediatric 0.2–15.8	27	CVCs	Septicaemia	11/36 (30.6%)	3	4/11 (36.4%) *C. parapsilosis* 3/11 (27.3%) *C. guilliermondii* 3/11 (27.3%) *C. albicans* 1/11 (9.1%) *C. tropicalis*	No risk factors found in the cohort
2008 Mouw et al. [44]	USA (South Carolina)	Paediatric 1.75–8 months	10	Tunnelled silicone CVCs	CRI; IDSA	1/6 (16.7%) - without ethanol lock 1/6 (16.7%) - with ethanol lock	11.15 without ethanol lock 1.99 with ethanol lock	1/1 (100%) *C. parapsilosis* - without ethanol lock 1/1 (100%) *C. parapsilosis* - with ethanol lock	Not reported
2011 Gandullia et al. [68]	Italy (Genova)	Paediatric 0.94–15.5	36	Single-lumen Broviac catheters	Septicaemia	1/33 (3%)	1.79	1/1 (100%) *C. albicans*	No risk factors found in the cohort
Total			**233**			**26/266 (9.8%)**			

Appendix B
Adult HPN studies shortlisted into review

Year/First Author	Region	Population/Age	No. of Patients	Catheter Type	Infection Definition	Candidal out of total infections	Infection rate/1000 catheter days	*Candida* species	Risk factors
1990 Miller et al. [75]	USA (Pennsylvania)	Adult 48 ± 15	21	49 Hickman catheters 9 Port-A-Cath or Hickman port	Septicaemia with no other identifiable source	7/81 (8.6%)	Not reported	7/7 (100%) *C. parapsilosis*	Not reported
1992 Mukau et al. [65]	USA (Maryland)	Adult 18–73	44	Silicone elastomer catheters	Septicaemia	4/13 (30.8%)	1.8	2/4 (50%) *C. albicans* 2/4 (50%) *C. parapsilosis.*	Immunocompromised patients have higher risk of infection
1994 O'Keefe et al. [66]	USA (Minnesota)	Adult 16–77	41	Single-lumen Hickman catheters	Positive blood culture from the catheter or peripheral vein with indwelling catheter and clinical signs of sepsis	23/227 (10.1%)	1.08	16/23 (69.6%) *C. albicans* 7/23 (30.4%) *C. parapsilosis*	Significant distinguishing features in the frequent-infection group were younger age, Crohn's disease, jejunostomies, and central vein thrombosis.
1995 Benoit et al. [61]	USA (Chicago)	Adult Not recorded	21	Hickman catheters	Fever and the same organism from both catheter and an additional blood culture	2/9 (22.2%)	Not reported	1/2 (50%) *C. glabrata* 1/2 (50%) Mixed *C. albicans, C. glabrata,* and *enterobacter cloacae*	Not reported
2004 Catton et al. [45]	United Kingdom (Leeds)	Adult 46–61	32	Tunnelled cuffed Hickman catheters	CRBSI - either endoluminal brushing or through line quantitative blood cultures	1/19 (5.3%)	1.07	1/1 (100%) *C. albicans*	Patients recently starting HPN may be at greater risk of CRBSI than those on HPN for a longer time
2013 Olthof et al. [58]	Netherlands (Nijmegen)	Adult 17–66	158	Among patients with CRBSIs: 10 Hickman catheters 4 Port-a-Cath	CRBSI; Same organism from catheter and percutaneous blood culture	5/27 (18.5%)	Not reported	5/5 (100%) *C. albicans.*	Underlying disease and immunosuppression can result in increased susceptibility for CRBSIs
2013 Zhao et al. [6]	USA (Georgia)	Adult 28–87	101	69 PICCs 26 tunnelled Hickman/ Groshong catheters 6 subcutaneous ports	BSI; CDC	39/102 (38.2%)	11.5	16/39 (41%) *C. albicans* 13/39 (33.3%) *C. glabrata* 8/39 (20.5%) *C. parapsilosis* 2/39 (5.1%) *C. tropicalis*	Higher blood glucose during hospitalisation, an initial PICC (versus a tunnelled CVC) independently increased BSI rates
2015 McCarthy et al. [69]	UK (London)	Adult 22–76	20	Not reported	CRBSI; ESPEN	1/7 (14.3%)	1.5	1/1 (100%) *C. albicans*	Not reported
2015 Touré et al. [70]	France (Lyon)	Adult 55.6 ± 16.5	196	133 Broviac catheters 71 PICCs	CRI; same organism from catheter and peripheral blood cultures	1/67 (1.5%) - Broviac group 2/17 (11.8%) - PICC group	1.05 - Broviac group 1.87 - PICC group	1/1 (100%) *C. albicans* - Broviac group 2/2 (100%) *C. albicans* - PICC group	Catheter-associated infection rate was higher in Broviac catheters than PICCs.
2016 Christensen et al. [71]	Denmark (Aalborg)	Adult 63.6 ± 13.2 - Hickman group 65.0 ± 11.0 - PICC group	136	169 Hickman catheters 126 PICCs	CRBSI; Clinical infection with positive catheter and peripheral blood culture without obvious focus elsewhere	3/49 (6.1%) - Hickman group 3/26 (11.5%) - PICC group	0.56 - Hickman group 1.63 - PICC group	3/3 (100%) *C. albicans* - Hickman group 3/3 (100%) *C. albicans* - PICC group	There is higher risk and shorter time to first CRBSI in PICC lines compared with Hickman catheters
2017 Tribler et al. [72]	Denmark (Copenhagen)	Adult 12.2–87.6	548	1478 single-lumen silicon tunnelled cuffed CVCs 9 implanted ports	CRBSI; same organism identified from CVC tip culture and at least 1, preferably peripheral, blood culture (ESPEN)	121/1034 (11.7%)	0.92	55/121 (45.5%) *C. glabrata* 29/121 (24%) *C. albicans* 25/121 (20.7%) *C. parapsilosis* 12/121 (9.9%) other *Candida* species	Not reported

2018 Canovai et al. [73]	Belgium (Leuven)	Adult 34–85	37	30 tunnelled catheters 7 totally implantable venous access devices (ports)	CRBSI; positive blood cultures from catheter and peripheral sample, or CBC with smear	2/19 (10.5%)	1.18 - ports 0.3 - tunnelled lines	2/2 (100%) *C. glabrata*	Short-term HPN (less than 2 years) is associated with higher rates of complications including CRBSIs
2018 Wouters et al. [74]	Netherlands (Nijmegen)	Adult 52 ± 16	270	543 tunelled catheters 160 subcutaneous ports 46 non-tunnelled catheters 8 PICCs	CLABSI; CDC	12/203 (5.9%)	0.6	5/12 (41.7%) *C. albicans* 4/12 (33.3%) *C. glabrata* 2/12 (16.7%) *C. parapsilosis* 1/12 (8.3%) *C. tropicalis*.	Identified risk factors for CLABSIs include a lower age, non-tunnelled catheters, and infusion frequency.
2019 Santacruz et al. [76]	Spain (Madrid)	Adult 58 ± 13	151	116 PICCs 36 ports 18 Hickman catheters	CRBSI; same organism from blood cultures from both the catheter lumen and peripheral blood after catheter-tip removal	2/13 (15.4%)	0.15 - PICCs 2.02 - ports 0.72 - Hickman	1/2 (50%) *C. albicans* 1/2 (50%) *C. glabrata*	The only associated variable with CRBSI was multi-lumen catheters
Total			**1766**			**228/1913 (11.9%)**			

Appendix C
Catheter infection data from shortlisted paediatric HPN studies

	Total infections	*Candida* infections (% of total infections)	*C. albicans* (%)	*C. glabrata* (%)	*C. parapsilosis* (%)	*C. guilliermondii* (%)	*C. tropicalis* (%)	Mixed/other *Candida* (%)
1990, Ricour et al.	90	3	3 (100%)					
1990, Schmidt-Sommerfeld et al.	82	4	4 (100%)					
2005, Cano et al.	13	5	1 (20%)		3 (60%)			1 (20%)
2006, Tung et al.	36	11	3 (27.3%)		4 (36.4%)	3 (27.3%)	1 (9.1%)	
2008, Mouw et al.	12	2			2 (100%)			
2011, Gandullia et al.	33	1	1 (100%)					
Total	**266**	**26 (9.8%)**	**12 (46.2%)**	**0**	**9 (34.6%)**	**3 (11.5%)**	**1 (3.8%)**	**1 (3.8%)**

Appendix D
Catheter infection data from shortlisted adult HPN studies

	Total infections	*Candida* infections (% of total infections)	*C. albicans* (%)	*C. glabrata* (%)	*C. parapsilosis* (%)	*C. guilliermondii* (%)	*C. tropicalis* (%)	Mixed/other *Candida* (%)
1990, Miller et al.	81	7			7 (100%)			
1992, Mukau et al.	13	4	2 (50%)		2 (50%)			
1994, O'Keefe et al.	227	23	16 (69.6%)		7 (30.4%)			
1995, Benoit et al.	9	2		1 (50%)				1 (50%)
2004, Catton et al.	19	1	1 (100%)					
2013, Olthof et al.	27	5	5 (100%)					
2013, Zhao et al.	102	39	16 (41%)	13 (33.3%)	8 (20.5%)		2 (5.1%)	
2015, McCarthy et al.	7	1	1 (100%)					
2015, Touré et al.	84	3	3 (100%)					
2016, Christensen et al.	75	6	6 (100%)					
2017, Tribler et al.	1034	121	29 (24%)	55 (45.5%)	25 (20.7%)			12 (9.9%)
2018, Canovai et al.	19	2		2 (100%)				
2018, Wouters et al.	203	12	5 (41.7%)	4 (33.3%)	2 (16.7%)		1 (8.3%)	
2019, Santacruz et al.	13	2	1 (50%)	1 (50%)				
Total	**1913**	**228 (11.9%)**	**85 (37.3%)**	**76 (33.3%)**	**51 (22.4%)**	**0**	**3 (1.3%)**	**13 (5.7%)**

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