


Does Parenteral Nutrition Increase the Risk of Catheter-Related Bloodstream Infection? A Systematic Literature Review

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Nicole Clare Gavin, RN, MAP(HCR)^{1,2,3}; Elise Button, RN, MAP^{3,4}; Samantha Keogh, RN, PhD^{1,2}; David McMillan, PhD^{2,5}; and Claire Rickard, RN, PhD^{1,2}

Abstract

Background: Central venous access devices (CVADs) are used for parenteral nutrition (PN) delivery. We systematically reviewed research-based publications that reported comparative rates of catheter-related bloodstream infection (CRBSI) in patients with CVADs who received PN vs those who did not receive PN therapy. **Materials and Methods:** The literature search included the Cochrane Library, MEDLINE, CINAHL, and PubMed up to July 14, 2015, to identify studies that compared patients with a CVAD who did and did not have PN therapy. **Results:** Eleven observational studies were identified, comprising 2854 participants with 6287 CVADs. Six studies produced significant results in favor of non-PN, 4 studies showed no evidence of a difference between PN and non-PN, and 1 study produced significant results in favor of PN when analyzed per patient with multiple CVADs. Incidence ranged from 0 to 6.6 CRBSIs per 1000 CVAD days in the PN patients and 0.39 to 3.6 CRBSIs per 1000 CVAD days in the non-PN patients. The Cochrane risk of bias assessment tool for nonrandomized studies of interventions was used. Eight studies were rated as moderate risk of bias, 2 as serious, and 1 as critical. **Conclusion:** The data presented in this systematic review are not sufficient to establish whether patients receiving PN are more at risk of developing CRBSI than those who do not. Future PN studies need to adjust for baseline imbalances and improve quality and reporting. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

parenteral nutrition; central venous access device; central venous catheterization; catheter-related bloodstream infection; systematic review

Parenteral nutrition (PN) has been an accepted treatment for patients in the hospital and at home since landmark studies demonstrated that long-term PN resulted in infant growth and weight gain, as well as healing in adults with chronic complicated gastrointestinal (GI) disease.^{1,2} Patients are prescribed PN if they are unable to eat or tolerate enteral feeding due to problems with absorption through the GI tract, GI surgery, or owing to the side effects of chemotherapy and radiation treatments. PN supplies all the nutrition needs of the body intravenously, bypassing the digestive system. PN is generally infused through a central venous access device (CVAD) due to the hyperosmolarity of the solution, which can cause phlebitis and extravasation in peripheral veins.^{3–5}

Catheter-related blood stream infections (CRBSIs) are a risk factor to be considered when inserting and managing any CVAD as they can increase morbidity, mortality, length of stay, and healthcare costs.^{3,6–8} The incidence of CRBSI reported in the literature can be up to 80% dependent upon the type of CVAD, patient risk factors, and the definition used.^{9–13} PN is historically considered an additional risk factor for CRBSI.^{3,6,9,10,12,14–16} This may be due to the many patient factors and metabolic responses to receiving PN that may predispose patients to infection. Traditionally, CVADs used for PN delivery and the intravenous (IV) administration sets have had

their own unique care and management given the perceived higher infection risk related to the lipid content of PN.¹⁷ The European Society for Parenteral and Enteral Nutrition Guidelines on Parenteral Nutrition⁵ and the National Health Service epic3 Guidelines¹⁸ recommend using single-lumen CVADs for the administration of PN or lipid-based solutions, if possible. Single-lumen CVADs are generally placed in patients with uncomplicated care and therefore lead to fewer CRBSIs, which could be interpreted as less risk. The aim of this article was to systematically review research-based publications that reported comparative rates of CRBSIs in patients with CVADs who received PN vs those who did not receive PN therapy. This systematic review is the first step to understanding long-standing clinical questions about PN and CRBSIs. This review will identify the gaps in our knowledge, provide implications for practice, and inform the direction of future research.

Methods

Protocol Registration

The protocol was registered prospectively with the international prospective register of systematic reviews (PROSPERO) as CRD42015016438 at <http://www.crd.york.ac.uk/PROSPERO/>.

Search Strategy

Four electronic databases (Cochrane Library, MEDLINE, CINAHL, and PubMed), from when records were available until July 14, 2015, were screened for research studies focusing on CRBSIs in patients receiving PN through a CVAD. The following search string was used for MEDLINE and amended for each database accordingly: (MH "Parenteral Nutrition, Home+") OR (MH "Parenteral Nutrition+") OR (MH "Parenteral Nutrition, Total+") OR (MH "Parenteral Nutrition, Home Total") OR (MH "Infusions, Parenteral+") OR (MH "Parenteral Nutrition Solutions+") OR AB "parenteral nutrition" OR AB parenteral N5 feed OR AB parenteral N5 hyperalimentation AND (MH "Catheterization, Central Venous") OR (MH "Central Venous Catheters") OR (MH "Vascular Access Devices+") OR AB "Central venous catheters" OR AB "Vascular access devices" OR AB central N5 venous OR AB vascular N5 device AND (MH "Catheter-Related Infections") OR (MH "Bacteremia+") OR (MH "Fungemia+") OR (MH "Candidemia") OR (MH "Sepsis+") OR (MH "Systemic Inflammatory Response Syndrome+") OR (MH "Infection+") OR (MH "Cross Infection+") OR AB "Catheter related infections" OR AB "Bacteremia" OR AB "Fungemia" OR AB "Sepsis" OR AB "Infection" OR AB Catheter N5 infection OR AB Catheter N5 blood N5 infection OR AB Catheter N5 colonization. (N5 is an adjacency operator, which searches for terms near each other.) Search results were imported into EndNote X7 and duplicates removed. First, titles and abstracts were screened by 2 authors independently (N.G. and E.B.). Thereafter, the full-text manuscripts were read and details extracted. The reference lists of relevant publications were searched for additional studies not identified by the methods outlined. There were no limitations placed on the age of the

patients, the location (hospital or home population) where the PN was administered, the study method, or the language or year of the publication. Authors were not contacted for additional information.

Inclusion Criteria

The criteria used for selection of studies were based on participants, interventions, contexts, outcome measures, and types of study as outlined below. Adult or pediatric patients with a CVAD for infusion therapy in any healthcare setting (hospital or community) were included. This review considered studies that compared patients with a CVAD who did and did not have PN therapy (eg, patients who had enteral nutrition but also had a CVAD). CRBSI was the primary outcome. The secondary outcomes were CVAD microbial colonization and identification of clinical isolates (as reported on the blood culture reports). Data needed to be extracted for the primary outcome (CRBSI) and by patient (preferably) or by CVAD as the denominator. This review initially considered any meta-analysis or randomized controlled trials (RCTs). In the absence of a significant number of meta-analyses and RCTs, other research designs of a quantitative nature, such as non-RCTs, before and after studies, and prospective or retrospective cohort studies, were included.

Exclusion Criteria

Studies with patients with PN infusing through a peripheral venous catheter were excluded. It is not standard practice to infuse PN through a peripheral vein due to the risk of extravasation and phlebitis,³⁻⁵ and the risk of CRBSI is different in peripheral venous catheters compared with CVADs.¹⁹

From the ¹National Health and Medical Research Council Centre of Research Excellence in Nursing, Menzies Health Institute Queensland, Nathan Campus, Griffith University, Nathan, QC, Australia; ²Alliance for Vascular Access Teaching and Research Group, Menzies Health Institute Queensland, Nathan Campus, Griffith University, Nathan, QC, Australia; ³Cancer Care Services, Royal Brisbane and Women's Hospital, Herston, QC, Australia; ⁴School of Nursing, Queensland University of Technology, Kelvin Grove Campus, Kelvin Grove, QC, Australia; and the ⁵Inflammation and Healing Research Cluster, University of the Sunshine Coast, Sippy Downs, QC, Australia.

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Corresponding Author:

Nicole Clare Gavin, RN, MAP(HCR), National Health and Medical Research Council Centre of Research Excellence in Nursing, Menzies Health Institute Queensland, Nathan Campus, Griffith University, 170 Kessels Road, Nathan, QC 4111, Australia.
Email: n.gavin@griffith.edu.au

Methodological Risk of Bias

Two authors independently assessed risk of bias (N.G. and E.B.). The Cochrane risk of bias assessment tool for nonrandomized studies of interventions (ACROBAT-NRSI)²⁰ was used to assess the following domains as low, moderate, serious, critical, and no information:

1. Bias due to confounding
2. Bias in selection of participation
3. Bias in measurement of interventions
4. Bias due to departures from intended interventions
5. Bias due to missing data
6. Bias in measurements of outcomes
7. Bias in selection of the reported result

Data Extraction

Two authors independently extracted data using a template (N.G. and E.B.). The following data were extracted from each of the included publications:

1. Baseline characteristics of PN and non-PN group participants, including the number of participants, age, sex, disease, treatment, reason for insertion, profession of inserter (physician, radiographer, or nurse), anatomical location of insertion, type of CVAD, insertion care, maintenance care (dedicated CVAD or PN team, ward staff, or patient), dwell time of the CVAD, infective status, or current positive blood cultures
2. Criteria for patient inclusion and exclusion
3. Description of the intervention(s), if relevant, and the number of patients allocated to each intervention (type of PN and non-PN solutions, number of lumens on the CVAD, configuration of IV administration sets and infusions, frequency of IV administration set replacement)
4. Healthcare settings
5. Duration of follow-up and numbers lost to follow-up
6. Outcomes (CRBSI, CVAD colonization, and clinical isolates reported on blood culture reports)

Definition and Terminology

Primary outcome

- *Gold-standard definition of CRBSI*: one of the following:
 - (1) Primary bacteremia/fungemia with ≥ 1 positive blood culture from a peripheral vein with no other identifiable source for the bloodstream infection (BSI) other than the CVAD, plus one of the following: a positive semi-quantitative (>15 colony-forming units) or quantitative ($>10^3$ colony-forming units) CVAD culture, with the same organism (species and antibiogram) isolated from the CVAD and blood,^{19,21} or
 - (2) Two blood cultures (1 from a CVAD hub and 1 from a peripheral vein) that both meet the CRBSI criteria for

quantitative blood cultures (3-fold greater colony count of growth for the same organism as from the peripheral blood) or differential time to positivity (growth of the same organism from the hub drawn blood at least 2 hours before growth from the peripheral blood), or

- (3) Two quantitative blood cultures of samples obtained through 2 CVAD lumens in which the colony count for the blood sample drawn through 1 lumen is at least 3-fold greater than the colony count for the blood sample from the second lumen²²

Note. Category (1) is generally used for diagnosis in short-term catheters where the device is commonly removed and cultured when infection is suspected. Categories (2) and (3) are generally used for diagnosis in long-term CVADs where the CVAD is often left in situ when infection is suspected and may be treated with the CVAD in situ, even when infection is diagnosed.

Secondary outcomes

- CVAD colonization (CVAD tip or positive blood culture drawn through the CVAD): as defined by the trial investigators
- Clinical isolates (pathogen reported on the blood culture reports): as described by the trial investigators

Data Analysis

Meta-analysis. It was planned to use data from RCTs in a meta-analysis if the study population and the interventions studied were sufficiently similar. A qualitative summary was produced for data from nonrandomized studies.

Analysis of CRBSI. Per patient analysis was planned as preferable, with per CVAD to be accepted as an alternate.

Analysis of the incidence of CRBSI. CRBSI expressed as the number of episodes per 1000 CVAD days. The most precise measure of incidence is the incidence density, or incidence rate, which is the number of (first) infections that occur over the number of days that the CVAD is in place.

Analysis of the incidence of CVAD colonization. Calculated as incidence of CRBSIs.

Analysis of clinical isolates (blood) causing CRBSI. The pathogens that cause CRBSIs were described according to their morphology as Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci, Gram-negative bacilli, fungi/yeast, and polymicrobial.

Results

Results of the Search Strategy

The search was conducted on July 14, 2015. A total of 2112 citations were found and imported into EndNote X7. In total,

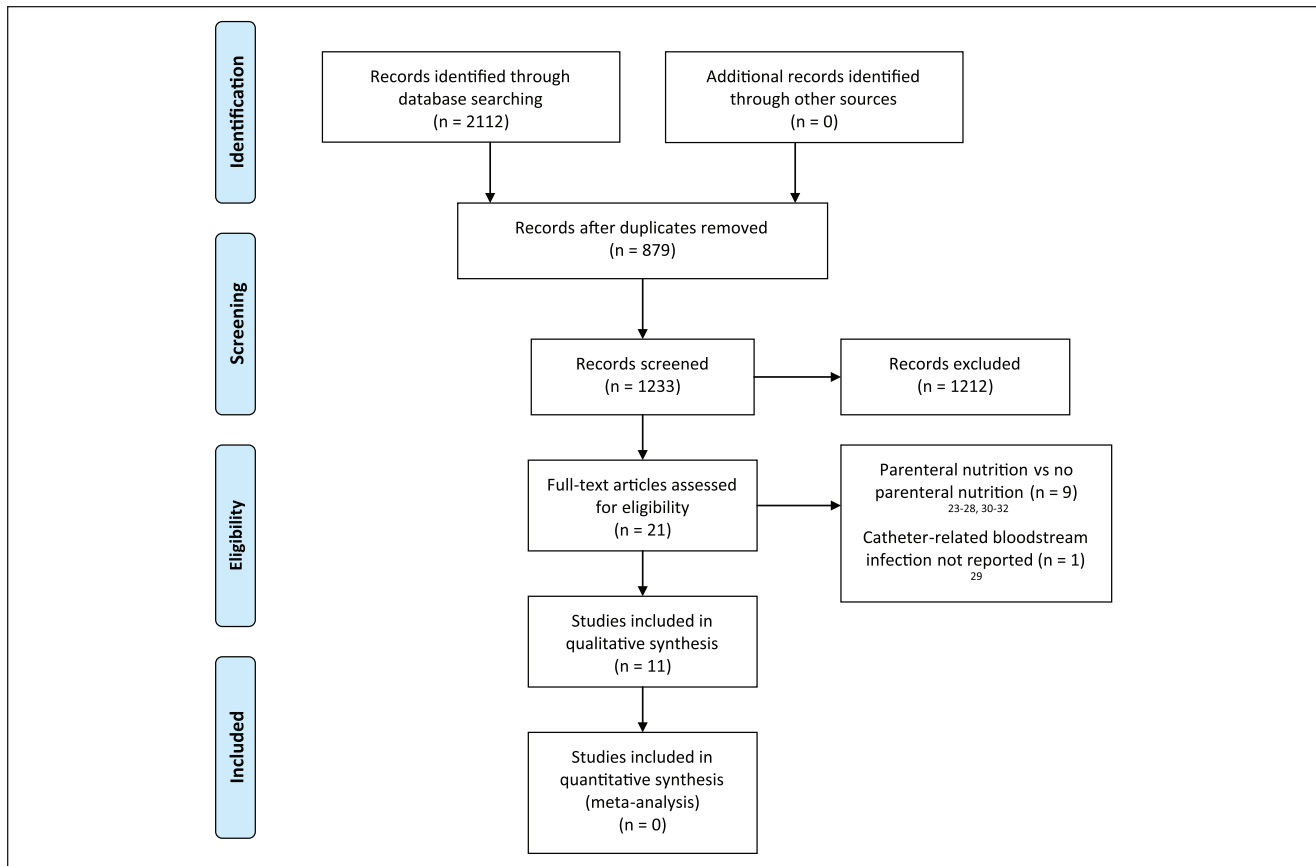


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. PRISMA diagram template source: Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. For more information, visit www.prisma-statement.org.

1233 titles were screened once 879 duplicates were removed, and 1212 were excluded. Twenty-one full-text articles were retrieved. Ten²³⁻³² were excluded as they did not meet the inclusion criteria (see Figure 1). Eleven studies were included in the analysis.

Characteristics of Included Studies

Characteristics of studies. The studies were published between 1986 and 2014. The studies were carried out in 3 countries: United States (n = 6),³³⁻³⁸ Brazil (n = 1),³⁹ and France (n = 4).⁴⁰⁻⁴³ Six studies reported both the number of patients and CVADs enrolled.^{34-36,39,40,43} Three studies reported only the number of patients enrolled.^{33,41,42} There were 2854 patients enrolled in the 9 studies^{33-36,39-43} that provided this information; these numbers ranged from 74 to 831. There were 6287 CVADs described in 8 studies.^{34-40,43} Two studies^{37,38} only reported number of CVADs and therefore may have included participants with multiple CVADs. Characteristics of the 11 included studies are summarized in Table 1.

Characteristics of patients and CVADs. Patients were hospitalized in the general medical, surgical, adult trauma, acute

care, intensive care, coronary care, oncology departments, pediatric oncology, and home infusion therapy service. Only 4 studies reported sex.^{35,40,42,43} In those studies, there were 747 males and 668 females, with a mean age of 45.5 years. Regarding CVAD type, most patients had central venous catheters,^{33,35,36,38,39,41} followed by peripherally inserted central catheters,^{34,37} tunneled cuffed catheters,^{34,40,43} and totally implantable vascular access devices,^{34,40,42,43} with 1-4 lumens. Only 1 study collected data on CVADs with 4 lumens.³⁵ The average CVAD dwell time in the 7 studies that reported it was 137 days.^{34-37,40,41,43} The average duration of PN was 26 days as reported in 3 studies.^{36,39,43} Patients were followed up until their CVAD was removed due to infection or end of treatment,^{36,38,39,42,43} until 1 year of CVAD dwell time,⁴² or 1 month post-CVAD insertion.⁴⁰ The other 5 studies did not describe any follow-up duration.^{33-35,37,41}

Characteristics of CVAD insertion and maintenance care. The care for CVAD insertion and maintenance was described in 8 studies.^{33,35-40,43} These studies described CVAD insertion under maximal sterile procedures. The products used to decontaminate the skin for insertion and maintenance varied according to the age of the study. The older studies used acetone and 10%

Table 2. Constituents of Parenteral Nutrition Solutions.

Study	All-in-One	2:1	Lipids
Beghetto et al ³⁹	NA	10% amino acid 50% glucose	Not described
Christensen et al ⁴³	NA	Amino acids Dextrose Electrolytes Vitamins Mineral	Not described
Tueux et al ⁴¹	Not described	NA	NA

NA, not applicable.

povidone-iodine in 70% alcohol, and more recent studies used 2% chlorhexidine in 70% alcohol. CVAD dressings included gauze and tape, semi-permeable transparent dressings, and chlorhexidine-impregnated sponges or discs, with the dressings replaced from daily to weekly. Christensen and colleagues⁴³ described twice-daily flushing of tunneled CVADs and fortnightly flushing of totally implantable venous access devices with heparinized saline. Danzig and colleagues³³ described a change in practice from a protected needle IV access device to a needleless access device.

Characteristics of IV administration set and PN care and maintenance. The care and maintenance of the IV administration sets and PN was described in 6 studies.^{35,36,38,39,41,43} PN was administered on a dedicated lumen in 3 studies.^{35,36,38} Only 1 study described a dedicated PN team who inserted the single-lumen CVADs solely for PN administration and then provided the maintenance care of the PN and CVAD.³⁵ PN was infused continuously in 1 study.³⁶ PN and IV administration sets were replaced every 24 hours in 3 studies^{39,41,43} or after every bag of lipids in 1 study.³⁸ A 0.22-micron filter was added to the administration set.⁴³ PN comprised 2:1 solution and/or lipid-only solution^{39,43} and all-in-one solution⁴¹ (Table 2). The other studies did not describe the component parts of the PN solution.

Characteristics of IV administration set and non-PN care and maintenance. The care and maintenance of IV administration sets was described in 3 studies.^{38,39,41} The administration sets were changed every 24 hours,³⁸ every 48 hours,⁴¹ or every 72 hours.³⁹ Routine blood sampling from CVAD lumens was not described in any of the studies. The IV medications administered through the CVAD were described in 8 studies.^{35-37,39-43} Chemotherapy was administered in 5 studies.^{36,37,40,42,43} Blood products were administered in 3 studies.^{36,40,43} Antibiotics were administered in 3 studies^{36,37,39} (see Table 3).

Risk of Bias and Quality of Included Studies

There were 8 prospective studies^{35,36,38-43} and 3 retrospective studies.^{33,34,37} Table 4 summarizes the risk of bias in the 11 studies. Eight studies were rated as moderate risk of bias, 2 as

Table 3. Other Intravenous Medications Administered Through the Central Venous Access Device.

Intravenous Medication Administered	Reference
Chemotherapy	36, 37, 40, 42, 43
Blood products	36, 40, 43
Antibiotics	36, 37, 39
Anticoagulants	36
Vasoactive medications	36
Crystalloids	35, 36, 41
Insulin	39
Other medications	35-37, 41, 43

serious, and 1 as critical. Three studies were rated as serious bias in the confounding domain.^{34,36,37} Differences between the intervention and the control group characteristics were not accounted for in the study design. Despite these reasons not being articulated, they had to exist. Two studies were rated as serious³⁷ and critical³⁵ bias due to departures from intended interventions. This arises when there are systematic differences between intervention and comparator groups in the care provided, which represents a departure from the intended interventions.²⁰ A serious or critical risk of bias rating alerts the reader to a limitation in the study design, and the results should therefore be interpreted with caution.

Five studies reported ethical approval.^{35,39,40,42,43} Inclusion and exclusion criteria were stated in 6 studies.^{9,35,36,38,39,42} Nine studies outlined their aims and objectives.^{33,35,36,38-43} No studies reported sample size calculations. Statistical tests were described by 6 study authors.^{33,35,36,39,42,43}

Primary Outcome

Only 1 study analyzed CRBSI per patient.⁴⁰ All studies were observational studies and 10 studies included patients with multiple CVADs. Therefore, a decision was made to analyze CRBSI per CVAD or per patient (with multiple CVADs) dependent upon the data presented by the study authors.

CRBSI per CVAD

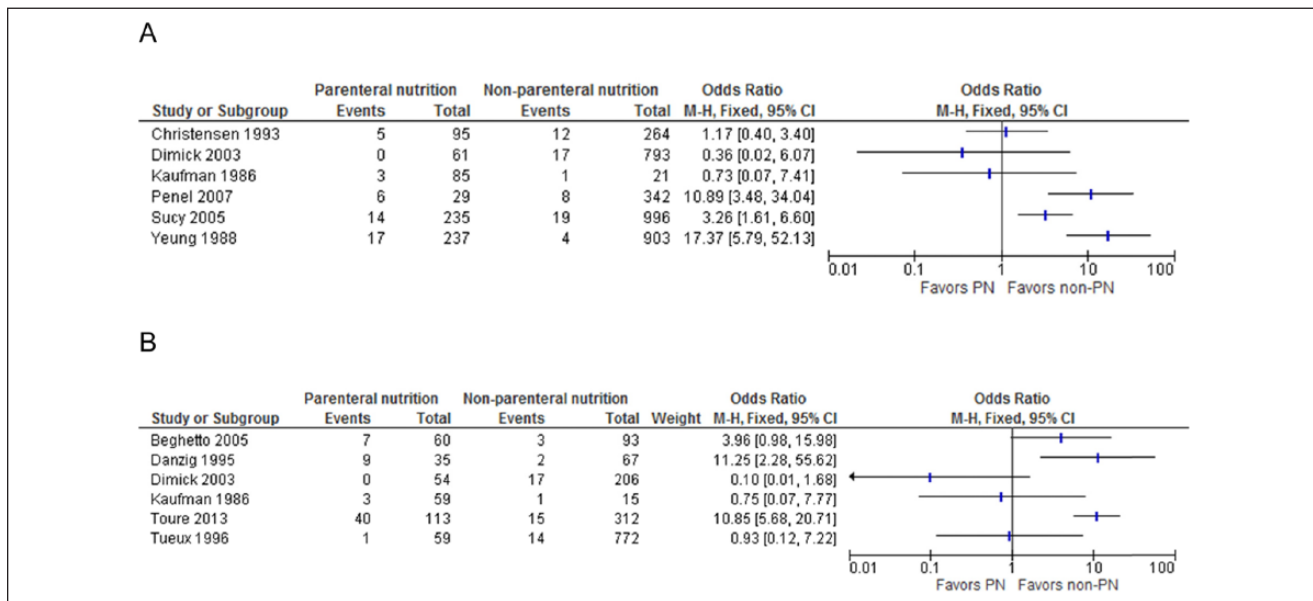
Three studies had results in favor of non-PN^{37,38,40} (Figure 2A). Additional analyses (Fisher's exact test) indicated that these results significantly favored non-PN ($P = .002$, $P < .001$, and $P < .001$, respectively). The 3 remaining studies showed no evidence of a difference between PN and non-PN^{35,36,43} (Figure 2A), but confidence intervals were wide, indicating a lack of precision in these estimates.

CRBSI per Patient With Multiple CVADs

Three studies produced significant results in favor of non-PN.^{33,39,42} Additional analyses (Fisher's exact test) indicated these results favoring were statistically significant ($P = .001$,

Table 4. Risk of Bias Ratings for Catheter-Related Bloodstream Infection Outcome in Each Study.

Study	Bias Due to Confounding	Bias in Selection of Participation	Bias in Measurement of Interventions	Bias Due to Departures From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall
Beghetto et al ³⁹	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Christensen et al ⁴³	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Danzig et al ³³	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Dimick et al ³⁵	Moderate	Low	Low	Critical	Low	Low	Low	Serious
Kaufman et al ³⁶	Serious	Low	Low	Low	Low	Low	Low	Moderate
Leone ³⁴	Serious	Low	Low	Moderate	Low	Moderate	Moderate	Serious
Penel et al ⁴⁰	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sucy et al ³⁷	Serious	Moderate	Serious	Serious	Low	Low	Low	Critical
Toure et al ⁴²	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Tueux et al ⁴¹	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Yeung et al ³⁸	Moderate	Low	Low	Low	Low	Low	Low	Moderate

**Figure 2.** Odds ratio for CRBSI. (A) Events, number of CRBSIs; Total, number of CVADs included in the study. (B) Events, number of CRBSIs; Total, number of patients with multiple CVADs included in the study. CRBSI, catheter-related bloodstream infection; CVAD, central venous access device; M-H, Mantel-Haenszel; PN, parenteral nutrition.

$P = .049$, and $P < .001$, respectively). Two studies found no evidence of a difference between PN and non-PN^{36,41} (Figure 2B), but confidence intervals were wide, indicating a lack of precision in these estimates. Dimick and colleagues³⁵ found a significant result favoring PN ($P = .028$).

Incidence of CRBSI per 1000 CVAD Days

Only 4 studies reported CRBSI per 1000 CVAD days in PN and non-PN patients^{34,35,39,41} (see Table 1). It was not possible to calculate incidence manually from the other studies as number of CVAD days was not reported. Incidence ranged from 0 to 6.6

CRBSIs per 1000 CVAD days in the PN patients and 0.39 to 3.6 CRBSIs per 1000 CVAD days in the non-PN patients.

Secondary Outcomes

Three studies detailed the microbiological techniques for testing blood cultures and CVAD colonization.^{38–40}

CVAD Colonization

Only 1 study³⁵ reported CVAD colonization. The odds ratio of colonization with PN was 0.09 with a 95% confidence interval

Table 5. Clinical Isolates Colonizing CVADs.

Clinical Isolates From CVAD	Colonized PN CVADs (n = 27), No. (%)	Colonized Non-PN CVADs (n = 103), No. (%)
Gram-positive cocci	12 (44)	78 (76)
Gram-negative cocci	0	0
Gram-positive bacilli	1 (4)	0
Gram-negative bacilli	4 (15)	14 (14)
Fungi and yeasts	6 (22)	9 (9)
Polymicrobial	4 (15)	1 (1)

CVAD, central venous access device; PN, parenteral nutrition.

of 0.01–0.65. This point estimate had a wide confidence interval, which indicates low precision in the results. In this study, patients receiving PN were statistically less likely to develop colonization compared with those who did not receive PN.

Clinical Isolates (Blood)

Only 2 studies reported the pathogens isolated from patients' blood cultures receiving PN and non-PN solutions.^{35,38} Table 5 shows the combined data for these studies for clinical isolates colonizing the blood of patients receiving PN and non-PN solutions. Gram-positive cocci were responsible for most positive blood cultures in both patient groups. Gram-positive cocci represent bacteria that commonly colonize the skin. Fungi and yeasts were reported to colonize the blood of patients receiving PN more frequently than patients receiving non-PN infusions.

Discussion

The combined results from the studies suggest that there is a higher risk of developing CRBSIs in patients receiving PN. Six studies produced significant results in favor of non-PN, 2 studies nonsignificant results with the point estimate in favor of non-PN, and 2 studies nonsignificant results with the point estimate in favor of PN. It was possible to analyze 1 study per CVAD and per patient with multiple CVADs. When analyzed per patient with multiple CVADs, a significant result in favor of PN was produced. There was no obvious difference in the studies to explain these findings. This difference in outcomes is likely to be due to the higher risk at baseline in patients and inadequate sample sizes. PN is reserved for the critically ill in the hospital, but often these patients are malnourished in the presence of inflammatory processes before PN is prescribed due to concerns about developing CRBSI. None of the studies in this review controlled for these patient factors at baseline. Therefore, there is a high risk of selection bias, and pooling of CRBSI is not possible.

Many of the variations observed in the analysis are likely due to differences in research designs, CVAD insertion, and maintenance practices. None of the studies included in the analysis were RCTs but rather cohort studies. Due to ethical and clinical issues, an RCT would pose significant challenges. Patients are prescribed PN when they are unable to eat or tolerate enteral

feeding. Future cohort studies should endeavor to control for confounding variables, such as differences in insertion and maintenance practices and glycemic control; ensure blinding of investigators diagnosing CRBSI; state a priori research aims and statistical methods on a clinical trials registry; calculate sample size; and ensure good quality and transparent reporting in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.⁴⁴

Future studies also need to clearly describe CVAD insertion and IV administration sets and PN maintenance procedures that will enable meta-synthesis of homogeneous samples. Ideally, insertion and maintenance practices should be guided by evidence-based guidelines. The included studies were published between 1986 and 2014 from 3 countries. This may account for the variations observed in the odds ratio of CRBSI associated with PN administration (0.36–17.36) since insertion and maintenance practices have changed over time. Solutions to decontaminate the skin and dressings have evolved in the past 30 years and will have an impact on bacterial burden. The care and maintenance of PN and non-PN IV administration sets were poorly reported in the included studies. This potential heterogeneity of clinical practice made it difficult to compare results.

Skin commensals were the most common clinical isolates found to be colonizing patients' CVADs. Gram-positive cocci were the predominant group in both, followed by Gram-negative bacilli in the non-PN group. Fungi and yeasts were more frequently found in the PN group. This may be an indication of the immunocompromised status of these patients. Patients receiving PN may be more likely to be prescribed antibiotics due to their primary diagnosis and therefore are more at risk of being colonized with fungi and yeasts. This supports the theory that the administration of PN alone may not inherently hold additional risk for the development of CRBSIs. Alonso-Echanove et al⁴⁵ and Rodriguez-Pardo et al³² found that the distribution of pathogens was influenced by PN. Fungi and yeasts were isolated more frequently when PN was prescribed (16% vs 6%; $P = .01$). This finding is consistent with the results presented in Table 5.

Reducing rates of CRBSI is complex and multifactorial. While Dimick and colleagues³⁵ reported no CRBSIs in their PN cohort, their sample size was not large enough to detect a statistical difference in CRBSIs. In this study, the PN cohort was cared for by a dedicated PN team, and single-lumen CVADs were inserted solely for PN administration. These practices may have prevented CRBSI but may not be practical in an acute hospital setting where patients require multiple-lumen CVADs for complex IV therapies.

The epic3 National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in National Health System Hospitals in England¹⁸ recommend using a designated single-lumen CVAD to administer lipid-containing PN or lipid-based solutions, which reflects current thinking that PN increases CRBSI risk. This recommendation is based upon nonanalytical studies and expert opinion with Class D rating and is therefore recognized as being based on lower level evidence. The European Society for Parenteral and Enteral Nutrition Guidelines

on Parenteral Nutrition: Central Venous Catheters (access, care, diagnosis, and therapy of complications)⁵ also recommend the use of a single-lumen CVAD for PN, unless multiple lumens are required for patient management with a Grade B rating. If multiple-lumen CVADs are required, 1 lumen should be reserved exclusively for PN with a Grade C rating. The classification taxonomy used in their guidelines is not described.⁵ The authors of these guidelines have classified the strength of their recommendations differently based upon the same systematic reviews that focused on single- vs multiple-lumen CVADs rather than explicitly on CVADs for PN administration.^{46,47} Both guidelines have drawn similar conclusions from the systematic reviews but have phrased their recommendations slightly differently and given varied classifications. This difference may exist due to guideline emphasis. One concentrates on healthcare-associated infections, and the other focuses on PN administration.

To our knowledge, this is the first systematic review comparing CRBSI, CVAD colonization, and the pathogens causing CRBSI in patients receiving PN and those who do not. This review has used a rigorous approach to study selection, data extraction, and quality assessment. Patients included in the 11 nonrandomized studies were predominantly adults being treated as inpatients in general medical, surgical, oncology, acute, coronary, and intensive care units. Only 2 studies included children.^{40,43} Patients included in the study were generally receiving short-term PN treatment. However, patients receiving long-term home PN were represented in 2 studies.^{33,34} There were unit-of-analysis issues in undertaking this systematic review. Most studies analyzed CRBSI per CVAD rather than per patient. This meant that each patient may have had >1 CVAD. Using the CVAD as the unit of analysis is a potential weakness as each patient may be exposed to the intervention more than once. Estimates of the true values were imprecise, so the actual estimate remains unclear. Due to the serious risk of bias in some of the included studies, it was not possible to pool the data for meta-analysis; the studies were therefore reported descriptively. From the available data, no conclusions can be made about the effect of PN on CRBSI. However, this review provides a strong platform for further research to lead to definitive results.

The Joint Commission published a monograph titled *Preventing Central Line–Associated Bloodstream Infections: A Global Challenge, a Global Perspective*⁴⁸ in 2012. CLABSIs are described as largely preventable and describe a zero tolerance where organizations aim to eliminate by employing evidence-based practices. Targeting zero CRBSIs is a reality for patients receiving PN when managed by a comprehensive team approach using evidence-based guidelines as demonstrated by Dimick and colleagues.³⁵ All patients with a CVAD have an increased risk of BSI and death. Therefore, it is counterintuitive to segregate only the PN group as high risk. Alonso-Echanove et al⁴⁵ found that intensive care patients cared for by a “float nurse” >60% of the time were 2.6 times more likely to develop a CRBSI (3.04 vs 7.92 BSIs per 1000 CVAD days). Floating is the process of reassigning nurses from their usual units to

short-staffed areas.⁴⁹ Emphasis on quality CVAD insertion and maintenance practices needs to be highlighted to all healthcare professionals, including hand washing and aseptic nontouch technique, through ongoing education and surveillance. The prevention and management of CRBSI is complex. “Bundle” approaches are used to optimize insertion and maintenance practices.⁵⁰ They comprise practices such as maximal barrier insertion techniques, chlorhexidine skin preparation, avoidance of the femoral vein for insertion, prompt removal of CVADs no longer required, hand washing before and after accessing the CVAD, daily inspection of the site, and effective dressings.^{5,18}

Future research needs to move on from the question of PN being an independent risk factor for CRBSI as this may be inherent in the patient group. We need to focus on clinical questions and interventions that will improve outcomes of all patients with a CVAD. These infection control questions should be answered with high-quality studies so as to provide strong evidence for clinicians and policy makers.

The data presented in this systematic review are not sufficient to establish whether patients receiving PN are more at risk of developing CRBSIs than those who do not. Gold-standard insertion and maintenance practices can work in this vulnerable population and are achievable. Single-lumen CVADs are rarely practical in high-acuity patients. Future PN studies need to adjust for baseline imbalances and improve quality and reporting. Future research needs to focus on improving safety for this complex group of patients and all patients with a CVAD.

Statement of Authorship

N. C. Gavin, S. Keogh, D. McMillan, and C. Rickard contributed to the conception/design of the research; N. C. Gavin, E. Button, and C. Rickard contributed to the acquisition, analysis, or interpretation of the data; N. C. Gavin drafted the manuscript; and E. Button, S. Keogh, D. McMillan, and C. Rickard critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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