

# Comparing success rates in central venous catheter salvage for catheter-related bloodstream infections in adult patients on home parenteral nutrition: a systematic review and meta-analysis

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## ABSTRACT

**Background:** Catheter-related bloodstream infection (CRBSI) is a life-threatening complication of parenteral nutrition. Therefore, optimal management, ideally with catheter salvage, is required to maintain long-term venous access.

**Objectives:** We aimed to evaluate successful catheter salvage rates in patients on home parenteral nutrition (HPN).

**Methods:** Studies were retrieved from medical databases, conference proceedings, and article reference lists. Data were collected relating to clinical outcomes of 3 treatments: systemic antibiotics, antimicrobial lock therapy (ALT), and catheter exchange. ORs and 95% CIs were calculated from a mixed logistic effects model.

**Results:** From 10,036 identified publications, 28 met the inclusion criteria (22 cohort studies, 5 case-control studies, and 1 randomized clinical trial), resulting in a total of 4911 CRBSIs. To achieve successful catheter salvage, the addition of an antimicrobial lock solution was superior to systemic antibiotics alone (OR: 1.75; 95% CI: 1.21, 2.53;  $P = 0.003$ ). Recurrence of infection was less common in studies that used ALT than in those that used systemic antibiotics alone (OR: 0.26; 95% CI: 0.11, 0.61;  $P = 0.002$ ). The catheter exchange group was excluded from multilevel regression analysis because only 1 included study applied this treatment. Successful salvage rates were highest for coagulase-negative staphylococci, followed by Gram-negative rods and *Staphylococcus aureus*.

**Conclusions:** The addition of an antimicrobial lock solution seems beneficial for successful catheter salvage in HPN-dependent patients with a CRBSI. Future prospective randomized studies should identify the most effective and pathogen-specific strategy. This review was registered at [www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO) as CRD42018102959. *Am J Clin Nutr* 2021;114:1173–1188.

**Keywords:** home parenteral nutrition, catheter-related bloodstream infection, antimicrobial lock solution, catheter salvage, catheter exchange, antimicrobial therapy

## Introduction

Catheter-related bloodstream infection (CRBSI) is a frequent and life-threatening complication in patients receiving home parenteral nutrition (HPN). HPN is a life-sustaining therapy in patients who suffer from intestinal failure (IF) and hence cannot meet their nutritional and/or fluid requirements by enteral intake owing to underlying conditions that limit gastrointestinal absorption (1). HPN is administered systemically via a central venous access device, mostly in the form of a central venous catheter (CVC) or an implantable port. Although HPN is generally lifesaving in these patients, its use is also associated with the risk of infectious and noninfectious catheter-related complications (2). Of these, CRBSI is the most common and is a potentially life-threatening complication. CRBSIs can lead

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Supplemental Tables 1–9 and Supplemental Figures 1–3 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

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Abbreviations used: ALT, antimicrobial lock therapy; CLABSI, central line-associated bloodstream infection; CNS, coagulase-negative staphylococci; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; GNR, Gram-negative rods; HPN, home parenteral nutrition; IDSA, Infectious Diseases Society of America; IF, intestinal failure; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; NOS, Newcastle-Ottawa Scale; PICC, peripherally inserted central catheter; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized clinical trial.

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to CVC removal. Multiple CVC removals are associated with venous stenosis and thrombosis which, in turn, can lead to the permanent loss of vascular access. When this occurs, the patient may eventually require a small bowel transplantation (3, 4).

The impact that recurrent CVC removal can have on future venous access implies that catheter salvage should be attempted wherever possible in HPN-dependent patients with CRBSI. Whereas guidelines recommend CVC removal in most cases of CRBSI, catheter salvage aims to retain the CVC with the use of appropriate catheter lock therapy and systemic antibiotics, usually for  $\geq 10$ –14 d (5, 6). Catheter salvage is attractive because it obviates the inconveniences and risks of CVC replacement, especially in those patients who have limited remaining venous access or who cannot tolerate prolonged periods without HPN (7). Catheter removal, on the other hand, reduces the risk of infection recurrence, persistent bacteremia, and metastatic infection (8–11). However, the appropriateness of catheter salvage in specific situations remains contentious (5, 6, 12, 13). Current European HPN guidelines recommend attempting CVC salvage solely in patients with uncomplicated infections arising from *Staphylococcus aureus*, coagulase-negative staphylococci (CNS), and Gram-negative bacilli (12). The Infectious Diseases Society of America (IDSA) guidelines advocate catheter removal or replacement as a first-line approach to CRBSI (5). All guidelines agree on removing the CVC in patients who are hemodynamically unstable, for CRBSIs caused by yeasts, or in cases of complicated infections such as endocarditis, septic thrombosis, and other metastatic infections (5, 12, 14). However, the recommended treatment for certain high-virulence bacteria (e.g., *S. aureus* and *Pseudomonas aeruginosa*) remains controversial. For instance, whereas the IDSA recommends CVC removal in case of *S. aureus* and Gram-negative infections (5), some IF expert centers report high rates of successful catheter salvage with these bacteria (15–17).

In addition to the indications for CVC salvage, several other uncertainties exist around CRBSI management. One of these is the added value of an antimicrobial lock solution next to conventional systemic antibiotic treatment and another is the option of guidewire exchange instead of catheter removal; antimicrobial lock solution consists of high concentrations of an antimicrobial agent (often combined with an anticoagulant) instilled into the catheter lumen. Guidewire exchange is a technique that has previously been reported in studies mainly concerning hemodialysis patients (18). This technique involves the insertion of a guidewire through the infected CVC into the vein, followed by removal of the infected catheter and placement of a new catheter over the guidewire. However, the optimal strategy to salvage a catheter remains unclear owing to the lack of well-designed randomized clinical trials (RCTs).

Because current guidelines (5, 6, 12, 14, 19) vary in their recommendations, we conducted, to our knowledge, the first systematic review to appraise the available evidence on CRBSI management specifically in adult patients on HPN support, focusing on the safety and efficacy of available CRBSI management approaches with successful catheter salvage as the outcome. These data should lead to more consistent recommendations for CRBSI management between the different international societies.

## Methods

The systematic review and meta-analysis were performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (20). For the report format, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Before conducting this systematic review, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42018102959).

### Search strategy

Our research question was: “What is the most efficacious and safest management approach (intervention) to accomplish high catheter salvage rates (outcome) in adult patients on home parenteral nutrition with catheter-related bloodstream infection (population)?” The following databases were searched from inception through March 2021: PubMed, Excerpta medica database (Embase), Cochrane library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. The search strategy was composed by experts in the field and included the following terms: “parenteral nutrition,” “home infusion,” “catheter,” and “infection.” Because of the large variety and interchangeability of terms used for the outcomes of CRBSI management, we did not incorporate terms related to the outcome in our search strategy. **Supplemental Table 1** displays the search strategy. We hand-searched conference proceedings (period: 2000–2020) of European Society for Clinical Nutrition and Metabolism (ESPEN) meetings and clinical trial registries [clinicaltrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN) register, and Australian New Zealand Clinical Trials Registry (ANZCTR)] for unpublished studies, which were considered as gray literature. The reference lists of all relevant guidelines and reviews were manually searched to identify additional relevant studies. When needed, we contacted the authors of the included publications by e-mail to further clarify their data. We also included studies in languages other than English and translated these articles into English.

### Study selection

Articles retrieved from the literature search were first deduplicated using filters and export formats, as described by Bramer et al. (21). The remaining articles were imported into an online software program (Covidence 2018) to screen the abstracts for eligibility. Two independent reviewers (MG and CP) screened the titles and abstracts of the retrieved citations. The full texts of potentially eligible articles were reviewed to identify relevant studies for inclusion. Studies were included when they focused on managing bloodstream infections from central venous access devices in adult patients receiving HPN.

### Inclusion criteria

- 1) Adult patients (>17 y old) receiving HPN with a bacterial CRBSI;

- 2) use of either systemic antibiotics, antimicrobial lock therapy (ALT), and/or catheter exchange as the CRBSI management approach;
- 3) evaluation of treatment efficacy (i.e., successful catheter salvage, recurrence rates, and/or infectious complications).

### Main exclusion criteria

- 1) Use of ALT for prevention only;
- 2) use of catheter removal as the sole management approach.

In addition, studies that only involved patients with previous CRBSI treatment failure or infectious complications were excluded. Studies incorporating different patient populations were only included if the text outlined that patients on parenteral nutrition were included. Studies only containing children were excluded in order to limit the heterogeneity of the patient population and because of expected differences in CRBSI etiology, diagnosis, and management (22, 23). When distinct publications had partly overlapping data due to the same patients' inclusion, the results were either combined or collected from the most extensive study to avoid duplicate data. Selected studies included interventional clinical trials and case-control and observational cohort studies.

### Outcome measures

The major outcome of interest was successful catheter salvage rates, with a distinction between:

- 1) Overall catheter salvage rate = ratio of successfully salvaged catheters to total CRBSIs.
- 2) Successful catheter attempt rate = ratio of successful salvage attempts according to the protocol to total salvage attempts.

The secondary outcomes comprised recurrence, infectious complications, mortality, and catheter salvage rates per pathogen type. The infecting pathogens were divided into 4 microbiological categories: CNS, *S. aureus*, Gram-negative rods (GNR), and polymicrobial.

### Data extraction and risk of bias

Two reviewers (MG and CP) independently extracted data from each included study relating to patient and venous access characteristics, CRBSI management approach, microbiological results, reported outcomes, and follow-up duration. All included studies were appraised for methodological study quality using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. This tool covers the evaluation of participant selection, comparability of groups, and assessment of outcome. The questions in these domains were adapted to our research topic (adequate follow-up of  $\geq 30$  d, loss to follow-up  $\leq 20\%$ , adequacy of the method to diagnose CRBSI, and risk of bias due to study design) (Supplemental Figure 1). A maximum of 9 points could be awarded to each study, with higher points representing a lower risk of bias. A qualitative assessment determined the main exclusion criteria for CVC salvage attempts and the limitations of each study separately (Supplemental Table 2). Any disagreements on data extraction or bias assessment were

resolved through discussion with experts in the field (GJAW, CPB-R, SL, AB). None of the quality assessors were blinded. Study heterogeneity was assessed by the Cochrane  $Q$  test of heterogeneity and  $I^2$  statistic. We examined the presence of publication bias by producing a funnel plot with Egger's statistical test of successful catheter salvage as outcome against study size for each treatment.

### Definitions and outcomes

#### CRBSI definitions.

**CRBSI.** Based on the IDSA definition: positive blood cultures from catheter blood drawn from the catheter and a peripheral vein with a ratio of  $\geq 3:1$  (CVC vs. peripheral); and a differential period of CVC culture versus peripheral blood culture positivity of 2 h. Alternatively, and as per IDSA guidelines, a CRBSI was defined when the same organism was grown from  $\geq 1$  percutaneous blood culture and from the catheter tip (5).

**Central line-associated bloodstream infection.** This was defined based on the CDC guidelines (6, 14). At least 1 of the following criteria should be present: 1) positive blood culture from a known pathogen, or 2) positive blood cultures from common skin commensal organisms and symptoms of infection with no other potential source of infection. Studies with stricter criteria than central line-associated bloodstream infection (CLABSI), such as positive blood cultures from both catheter and peripheral vein, were categorized as CLABSI because they were broad enough to meet CLABSI criteria but not strict enough to meet the CRBSI criteria.

**No standard criteria.** Studies that did not provide a proper definition or reference to a standard definition for infectious catheter-related complications were categorized as "no standard criteria."

### Catheter salvage

#### 1) Catheter salvage rate.

Defined by CVC status (retained or removed), clinical resolution, and no recurrence within 30 d of the previous CRBSI date.

#### 2) Overall successful catheter salvage.

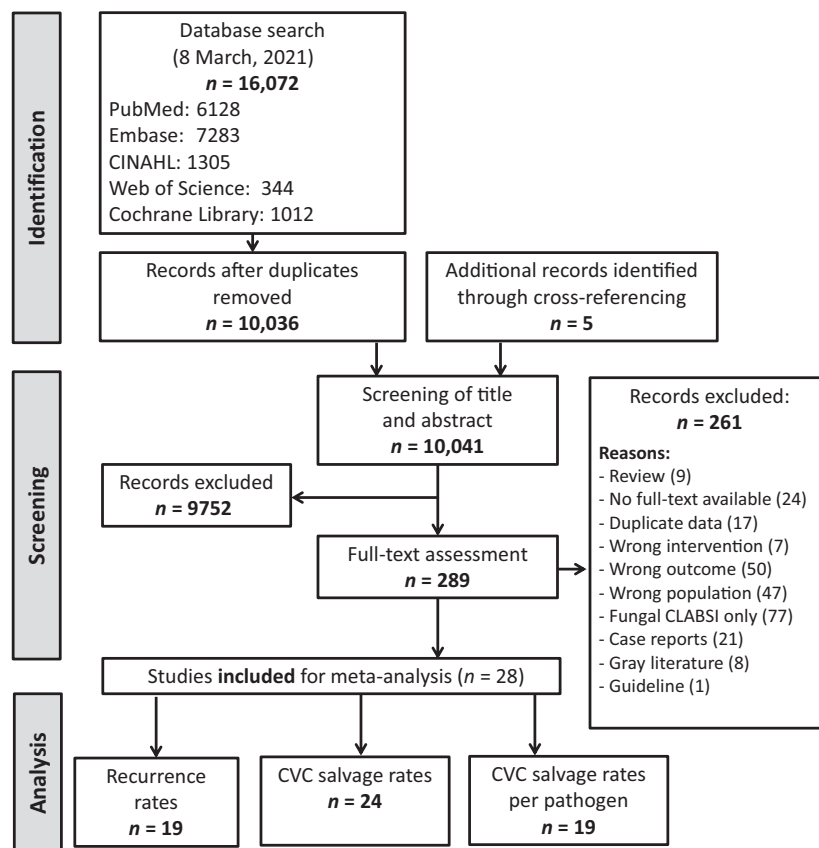
Calculation of catheter salvage rates, including all CRBSI cases (regardless of the reason for removal), according to Tribler et al. (24).

#### 3) Successful catheter salvage attempt rate.

Calculation of catheter salvage rates, including only attempted catheter salvage cases according to protocol and/or guidelines.

### Recurrence

- **Recurrence** was defined as any new CRBSI with the same microbial species and a comparable antibiogram occurring



**FIGURE 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. The flowchart represents the literature search and elements of the systematic review (identification, screening, and analysis). CINAHL, Cumulative Index to Nursing and Allied Health Literature; CLABSI, central line-associated bloodstream infection; CVC, central venous catheter; Embase, Excerpta medica database.

within 30–90 d of the previous CRBSI date. Recurrence data beyond 90 d were not extracted (unless representing the only measure of recurrence), because recurrence beyond this point is considered unlikely to be significantly influenced by the primary treatment (24, 25).

- *New infection* was defined as any new CRBSI with a different microbial species or different antibiograms from the former infection (24).

### Data synthesis and statistical analysis

Studies were divided into 3 treatment groups: 1) systemic antibiotic treatment only, 2) systemic antibiotics with the addition of ALT, and 3) CVC exchange. For most observational cohort studies, a direct comparison of treatments was not possible. Therefore, study results were synthesized between the 3 treatment groups by comparing the catheter salvage rates (displayed in proportions) with the treatments considered in that study (26). A mixed logistic effects model was built with a study-specific normal random effect that modified the mean log-odds for successful catheter salvage for the particular treatments. The treatment groups were included as a fixed effect and a study-specific random effect that modeled the studies' heterogeneity. The differences in salvage rates between the treatments were evaluated using ORs with 95% CIs, and *P* values from the Wald

test. For each treatment, each study was weighted by the number of patients receiving that treatment. The secondary outcomes were compared using the same methodology as described for the primary outcome. Heterogeneity was summarized for each of these outcomes using the  $\chi^2$  test and  $I^2$  statistics (27). Publication bias was investigated by Egger's regression test and funnel plots (28). The Statistical Package for the Social Sciences (SPSS version 23, IBM Corp.) was used for the mixed-effects logistics analysis. The R statistical platform (version 4.0.5, www.r-project.org) was used to generate the forest plots (Meta package) (29) and funnel plots (Metafor package) (30).

## Results

### Literature search

The initial search yielded 16,072 articles, but only 289 articles remained for full-text screening after deduplicating and exclusion by title and abstract (Figure 1). Five of these articles were found by screening the reference lists of relevant reviews. After full-text screening, 28 studies met the inclusion criteria for meta-analysis, representing 4911 CRBSIs (range: 8–1441) (15–17, 24, 31–54). All studies were published between 1981 and 2020. In addition, 16 case reports and 5 nonpublished studies were considered



suitable for a narrative review. **Supplemental Tables 3 and 4** summarize the list of included and most important excluded studies, including reasons for exclusion.

### Description of the studies

The majority of the 28 included studies were conducted in Europe ( $n = 21$ ) (15, 16, 24, 31–34, 36–39, 41–45, 48, 50–53) and the United States ( $n = 6$ ) (17, 35, 40, 46, 47, 54) (**Supplemental Figure 2**). Twenty-five studies were carried out in tertiary hospitals and/or specialized IF units (15–17, 24, 33–35, 37–54) and 2 studies were multicenter (31, 32). Twenty-two studies were conducted as single-arm studies (**Tables 1, 2**). The majority of these studies administered ALT in addition to systemic antibiotic therapy ( $n = 12$ ) (15–17, 32, 38, 40–45, 50) as standard care in their CRBSI management, whereas other studies only used systemic antibiotics ( $n = 10$ ) (24, 39, 46–49, 51–54). Five studies had a case-control design (33–37):

- One study compared CVC exchange with catheter retention and systemic antibiotic therapy (34).
- Two studies compared catheter removal with catheter retention and either ALT (33) or systemic antibiotics (35).
- Two studies compared systemic antibiotics with ALT (36, 37).

The remaining study was an RCT comparing ALT with placebo, both in addition to systemic antibiotic therapy (31).

Study duration ranged from 1 to >23 y and the patient follow-up time ranged from 7 to 540 d. A trend toward more ALT studies being published in the last decade was apparent (**Supplemental Figure 3**).

### Patient population

Across all studies, the included patients' median age was 53 y (IQR: 48–58 y) (missing = 9) (**Tables 1, 2**). Nineteen studies only included patients receiving parenteral nutrition (missing = 4). The median percentage of females was 50% (IQR: 40%–56%) (missing = 14). Eleven studies reported the percentage of oncological patients and 7 of these included >50% oncological patients (mean  $\pm$  SD: 67%  $\pm$  33%). The mean CRBSI rate was 1.06 per 1000 CVC days (range: 0.04–2.8 per 1000 CVC days).

### CRBSI and salvage definitions

Most studies defined CRBSIs according to the CDC (17, 35, 39, 43–45, 52) or IDSA (15, 16, 31, 32, 36, 50) guidelines; the other studies used either nonstandard definitions or did not report the definition used (33, 34, 37, 41, 48, 49, 51, 53, 54). Two studies reported a slightly modified definition, but were still considered as appropriate and were counted as using the CDC definition (24, 38). Reported salvage rates differed widely among studies: 9 studies reported overall salvage rates (17, 24, 34, 38, 40, 47, 49, 52, 54), whereas 18 studies reported successful salvage rates (e.g., exclusion of *S. aureus* for salvage) (15, 16, 31–33, 35–37, 41, 42–46, 48, 50, 51, 53) (**Supplemental Table 2**). One study did not mention the method of salvage (39). There was a wide variety of defining successful catheter salvage, varying

from solely negative blood cultures after completing antimicrobial therapy to clinical resolution and no recurrence within 90 d.

### CRBSI treatments

#### ALT.

All single-arm studies except 1 (40) used ALT in combination with systemic antibiotic treatment. Two case-control studies only administered systemic antibiotics to a selection of patients in the control group (33, 37). Antibiotic lock solutions with vancomycin as an empiric lock solution were used most frequently, which was later changed according to sensitivity. One study used a lock containing taurolidine (41). Heparin was frequently added as an anticoagulant in the lock solution. Dosage, concentration, and duration of lock solutions varied highly among studies (**Table 3**).

#### Systemic antibiotics.

The type of administered systemic antibiotics varied considerably among studies. Most studies mentioned empirical treatment according to IDSA guidelines with sensitivity-based adjustments. Several studies were unclear about administered antibiotics (17, 33–35, 39, 46, 47). Some studies used or reported notable percentages of inappropriate antibiotic treatments (32, 37) or administered extended broad-spectrum empirical antibiotic treatment (44, 48, 49), probably because those studies were performed in regions with a high prevalence of multiresistant bacteria.

#### Catheter exchange.

Only 1 case-control study used CVC exchange as the CRBSI treatment (34). Because a low number of included studies per subgroup induces the risk of problems with collinearity, the CVC exchange group was excluded from the meta-regression subgroup analysis (55).

### Efficacy of different treatment approaches

Successful catheter salvage rates per intervention type could be determined for 24 studies (15–17, 24, 31, 32, 34–42, 44–47, 49, 51–54). Four studies were excluded from the primary outcome: 2 studies only evaluated salvage rates for CRBSIs caused by CNS (43, 51) and the other 2 studies used ungeneralizable outcomes (33, 48). Nineteen studies reported on recurrence rates (15, 16, 24, 31–37, 39–44, 48, 51, 54).

### Primary endpoint: successful catheter salvage rates for CRBSI

**Figure 2** reports the results of the studies. **Figure 2A** shows a forest plot of pooled successful CVC salvage proportions for individual studies in each intervention type. The combined successful CVC salvage rate was 68% (95% CI: 64%, 72%). **Figure 2B** displays a subanalysis of studies using systemic antibiotics alone with a salvage rate of 60% (95% CI: 56%, 64%) compared with 73% (95% CI: 69%, 77%) for studies adding

TABLE 1 Data characteristics of ALT studies<sup>1</sup>

| Study, country                                   | Study period | Type of study   | CRBSIs, n | CRBSI rate | CRBSI definition     | Patient characteristics  | Salvage definition   | CVC salvage, %     | Follow-up       | Recurrence, %    | Infectious complications, n                                    |
|--|--------------|---|-----------|------------|----------------------|--|--|--------------------|-----------------|------------------|--|
| Alonso et al. (50), Spain                        | 2010–2017    | Retrospective chart review  | 217       | NR         | IDSA                 | Median age 58 y; 46.1% women; 32.9% (HPN); 96% oncologic; 57.9% venous port systems; 42.1% tunneled CVCs | Clinical resolution, negative follow-up BCs, no recurrence or complication     | NR                 | 90 d            | NR               | Death (1)  |
| Bond et al. (16), United Kingdom                 | 2012–2016    | Prospective observational cohort study                            | 134       | 0.31       | IDSA                 | Mean age 54 y; 63% women; 100% HPN; 100% tunneled CVCs   | No recurrence  | 67% (67 of 100)    | 180 d           | 4.5% (3 of 67)   | NR   |
| Clare et al. (38), United Kingdom                | 2004–2005    | Retrospective chart review  | 37        | 0.41       | CDC                  | 100% HPN; 100% tunneled CVCs   | Negative BC 48 h after completion of antimicrobial therapy                     | 81% (30 of 37)     | 16 d            | NR               | IE (1), infected thrombus (1)                                  |
| Dibb et al. (15), United Kingdom                 | 1993–2011    | Prospective observational cohort study                            | 297       | 0.38       | IDSA                 | 100% HPN; 98.3% tunneled CVCs  | Negative BC 48 h after completion of antimicrobial therapy and no recurrence   | 72.5% (180 of 248) | 30 d            | 4.4% (11 of 248) | IE (4), septic shock (20), metastatic infection (2), death (5) |
| Edakkanambeth Varayil et al. (17), United States | 1990–2013    | Prospective observational cohort study                            | 465       | 0.64       | CDC                  | Mean age 53 y; 40.4% women; 100% HPN; various types of CVCs  | Successful appropriate treatment, no recurrence                                | 70% (325 of 465)   | 28 d            | NR               | Death (8)  |
| Fernandez-Hidalgo et al. (42), Spain             | 1997–2006    | Retrospective chart review/prospective observational cohort study | 115       | NR         | IDSA                 | Median age 55 y; 84% women; 29% HPN; 40% tunneled CVCs   | Negative BC 30 d after completion of antimicrobial therapy                     | 82% (94 of 115)    | 30 d            | 6% (7 of 115)    | Septic shock (1)   |
| Fortún et al. (36), Spain                        | 2002–2005    | Retrospective chart review  | 48        | 0.50       | IDSA                 | Median age 52 y; 26% HPN; 77% venous port systems  | Clinical resolution, no recurrence   | 84% (16 of 19)     | 30 d            | 10.5% (2 of 19)  | Death (1)  |
| Guedon et al. (43), France                       | 1997–1999    | Retrospective chart review  | 34        | 0.30       | CDC                  | 100% HPN; 100% tunneled CVCs   | Clinical resolution and no recurrence  | NR                 | 60 d (CNS only) | 21% (3 of 14)    | NR   |
| Haag et al. (41), Germany                        | 2008–2010    | Retrospective chart review  | 24        | NR         | Nonstandard criteria | Median age 58 y; percentage HPN unknown; 100% oncologic; tunneled and venous port systems                | Clinical resolution, negative BC 72–96 h after start of therapy, no recurrence | 67% (16 of 24)     | 82 d            | 0% (0 of 24)     | None   |
| Krzywdwa et al. (40), United States              | 1988–1993    | Retrospective chart review  | 22        | NR         | Nonstandard criteria | Majority HPN; 100% tunneled CVCs   | Clinical resolution, negative BC posttreatment and 2 mo thereafter             | 68% (15 of 22)     | 60 d            | 32% (2 of 7)     | NR   |
| Lawinski et al. (33), Poland                     | 2005–2010    | Retrospective case-control study                                  | 352       | 0.87       | Nonstandard criteria | ALT group: mean age 55 y; 52% women; 100% HPN; 100% tunneled CVCs  | NR   | NR                 | 60 d            | 4% (4 of 100)    | NR   |
| Messing et al. (37), France                      | 1981–1985    | Retrospective case-control study                                  | 24        | 2.8        | Nonstandard criteria | 100% HPN; 100% tunneled CVCs   | Clinical resolution, negative BC after <7 d of treatment                       | 90% (20 of 22)     | 7 d             | 9% (1 of 11)     | None   |

(Continued)

TABLE 1 (Continued)

| Study, country                | Study period | Type of study                          | CRBSIs, <i>n</i> | CRBSI rate | CRBSI definition | Patient characteristics  | Salvage definition  | CVC salvage, %   | Follow-up | Recurrence, % | Infectious complications, <i>n</i>                                    |
|-------------------------------|--------------|--|------------------|------------|------------------|--|---|------------------|-----------|---------------|---|
| Rijnders et al. (31), Belgium | Unclear      | Randomized, placebo-controlled trial   | 44               | NR         | IDSA             | Mean age 49 y; percentage HPN unknown; 73% oncologic; 91% venous port systems and 9% tunneled CVCs | No death or recurrence  | 67% (14 of 21)   | 180 d     | 14% (3 of 21) | NR  |
| Santarpia et al. (44), Italy  | 1995–2006    | Retrospective chart review             | 169              | 2          | CDC              | Mean age 58 y; 55% women; 100% HPN; 84% oncologic; tunneled CVCs and venous port systems           | Clinical resolution after completion of antibiotic therapy (no recurrence of fever) | 74% (103 of 139) | 7 d       | 0% (0 of 139) | NR  |
| Santarpia et al. (45), Italy  | 2010–2012    | Retrospective chart review             | 94               | 1.74       | CDC              | Mean age 62 y; 47% women; 100% HPN; 74% oncologic; various CVCs                                    | Clinical resolution after completion of antibiotic therapy                          | 66.7% (22 of 33) | 28 d      | NR            | IE (1), septic pneumonia (3), septic shock (2), septic thrombosis (4) |
| Vidal et al. (32), France     | 2009–2011    | Prospective observational cohort study | 97               | NR         | IDSA             | Median age 63 y; 38.2% women; 44% HPN; 100% oncologic; 100% venous port systems                    | No recurrence and no death  | 77% (17 of 22)   | 84 d      | 18% (4 of 22) | Death (1)   |

<sup>1</sup> ALT, antimicrobial lock therapy; BC, blood culture; CNS, coagulase-negative staphylococci; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; HPN, home parenteral nutrition; IDSA, Infectious Diseases Society of America; IE, infective endocarditis; NR, not reported.

ALT. A low degree of heterogeneity at 23% ( $P = 0.21$ ) was seen in studies that used ALT and a moderate heterogeneity at 61% ( $P < 0.01$ ) in studies that only used systemic antibiotics. A sensitivity analysis performed by excluding the 2 studies (34, 53) having  $<10$  patients did not produce pooled salvage proportions that differed from those of the main analysis. Mixed-effects logistic regression analysis showed that the combination of systemic antibiotics with ALT was superior to systemic antibiotics alone (OR: 1.75; 95% CI: 1.21, 2.53;  $P = 0.003$ ). Additional multilevel regression analysis correcting for NOS score, follow-up duration, vascular access type, and type of salvage definition used did not affect these outcomes (adjusted OR: 1.79; 95% CI: 1.32, 2.43;  $P < 0.001$ ).

## Secondary endpoints

### Recurrence rates.

Figure 3 displays a forest plot of recurrence rates (displayed in proportions) per intervention type.  $I^2$  demonstrates moderate–high heterogeneity at 68% ( $P < 0.01$ ). Meta-regression analysis showed that recurrence was less common in studies that used the addition of ALT (weighted mean: 10%; range: 4%–29%) than in those that used systemic antibiotics alone (weighted mean: 15%; range: 7%–61%) (OR: 0.26; 95% CI: 0.11, 0.61;  $P = 0.002$ ) (CVC exchange group excluded).

### Successful salvage rates per pathogen category.

Successful catheter salvage rates per pathogen (divided into *S. aureus*, CNS, Gram-negative bacteria, polymicrobial, and other) were evaluable for 19 studies (15–17, 24, 32, 36, 38–40, 42–44, 46, 47, 50–54) and comprised of 3739 CRBSIs. CNS represented the majority of isolates (37%,  $n = 1388$ ), followed by Gram-negative bacteria (33%,  $n = 1238$ ) and *S. aureus* (9%,  $n = 340$ ). Of the CRBSIs, 12% were polymicrobial in origin ( $n = 448$ ). Supplemental Tables 5 and 6 report absolute numbers of CRBSIs per pathogen. Successful CVC salvage rates were compared by type of bacteria and separately per type of treatment (Figure 4). Weighted mean salvage rates in CNS cases were highest (75%; range: 68%–95%), followed by Gram-negatives (56%; range: 33%–92%). CRBSIs caused by *S. aureus* (54%; range: 25%–100%) and polymicrobial infections (54%; range: 36%–88%) had the lowest CVC salvage rates. Taking the type of treatment into account, successful salvage rates of various bacteria remained different, with the highest success rates for CNS followed by GNR and *S. aureus*. The ORs of successful salvage were as follows: CNS compared with *S. aureus*: 3.00; 95% CI: 2.33, 3.85;  $P < 0.001$ ; CNS compared with GNR: 2.19; 95% CI: 1.84, 2.60;  $P < 0.001$ ; and GNR compared with *S. aureus*: 1.37; 95% CI: 1.07, 1.76;  $P = 0.01$ . Among *S. aureus* and GNR infections, studies that added ALT achieved significantly higher successful CVC salvage rates than studies that solely used systemic antibiotics without an antimicrobial lock (Table 4).

### Other outcomes

Seventeen studies (15, 17, 32, 34, 36–39, 41, 42, 45, 47–52) reported on infectious complications (including infection-related death) with a weighted mean percentage of 13% (range:

TABLE 2 Data characteristics of systemic AB therapy studies<sup>1</sup>

| Study, country                        | Study period | Type of study                          | CRBSIs, n | CRBSI rate | CRBSI definition     | Patient characteristics  | Salvage definition  | CVC salvage, %     | Follow-up | Recurrence, %   | Infectious complications, n   |
|---------------------------------------|--------------|--|-----------|------------|----------------------|--|---|--------------------|-----------|-----------------|---|
| Benezra et al. (46), United States    | 1985–1986    | Prospective observational cohort study | 88        | NR         | Nonstandard criteria | Mean age 31 y; 48% women; percentage HPN unknown; 100% tunneled CVCs                         | Negative BC after completion of antimicrobial therapy                                       | 61.1% (33 of 54)   | 14 d      | NR              | NR  |
| Buchman et al. (47), United States    | 1973–1991    | Retrospective chart review             | 427       | 1.01       | Nonstandard criteria | 100% HPN   | Clinical resolution at 48 h and no recurrence   | 52% (155 of 298)   | 60 d      | NR              | Septic shock (1), renal failure (9), IE (3), septic emboli (6), death (7) |
| Campos et al. (51), Spain             | 1993–1998    | Retrospective chart review             | 8         | 1.37       | Nonstandard criteria | Mean age 46 y; 100% HPN; 36% oncologic; tunneled CVCs and venous port systems                | Negative BC 48 h after completion of antimicrobial therapy and no readmission or recurrence | 87.5% (7 of 8)     | 21 d      | 12.5% (1 of 8)  | None  |
| Caroff et al. (35), United States     | 2008–2012    | Retrospective case-control study       | 124       | NR         | CDC                  | 32% HPN; 100% oncologic; 16% tunneled CVCs, 26% venous port systems, and 58% PICCs           | No recurrence   | 87% (27 of 31)     | 60 d      | 1.9% (4 of 31)  | NR  |
| Cuerda et al. (52), Spain             | 1986–2001    | Retrospective chart review             | 69        | 0.04       | CDC                  | Median age 48 y; 35% women; 100% HPN   | Clinical resolution and no infectious complication  | 70% (48 of 69)     | 14 d      | NR              | IE (5), septic thrombophlebitis (1), septic embolism (1), Death (2)       |
| Fortún et al. (36), Spain             | 2002–2005    | Retrospective case-control study       | 48        | 0.50       | IDS-A                | Median age 58 y; 27% HPN; various types of CVCs  | Clinical resolution and no recurrence   | 65% (22 of 29)     | 30 d      | 10.3% (3 of 29) |   |
| Ladefoged et al. (34), Denmark        | 1967–1980    | Retrospective case-control study       | 48        | 0.3–0.6    | Nonstandard criteria | 100% HPN; tunneled CVCs or infant feeding tubes  | Clinical resolution, no recurrence, infection-related death or metastatic infection         | AB 71% (5 of 7)    | 60 d      | 29% (2 of 7)    | Osteomyelitis (1), septic arthritis (1)                                   |
| Leiberman et al. (53), United Kingdom | 1998–2017    | Retrospective chart review             | 171       | 1.35       | Nonstandard criteria | Median age 56 y; 59.8% women; 100% HPN; 13% oncologic; tunneled CVCs and venous port systems | No CVC removal within <30 d after treatment   | 61.87% (86 of 139) | 30 d      | NR              | NR  |
| Lorentsen et al. (39), Denmark        | 2005–2014    | Retrospective chart review             | 72        | 1.51       | CDC                  | Mean age 64 y; 55% women; 100% HPN; 28% oncologic; tunneled CVCs and venous port systems     | No recurrence   | 71% (20 of 28)     | 100 d     | 29% (8 of 28)   | IE (1), infective discitis (1), epidural abscess (1), endophthalmitis (1) |
| Miller et al. (54), United States     | 1983–1987    | Retrospective chart review             | 58        | NR         | Nonstandard criteria | Mean age 48 y; 52% women; 100% HPN; tunneled CVCs and venous port systems                    | Clinical resolution; negative BC at end of treatment; no recurrence                         | 55% (32 of 58)     | 60 d      | 12% (7 of 58)   | NR  |
| O'Keefe et al. (49), South Africa     | Not stated   | Unclear                                | 150       | 1.08       | Nonstandard criteria | Mean age 51 y; 100% HPN; tunneled CVCs and venous port systems                               | No recurrence   | 56% (84 of 150)    | 90 d      | NR              | None  |

(Continued)



TABLE 2 (Continued)

| Study, country                 | Study period | Type of study                        | CRBSIs, n | CRBSI rate | CRBSI definition     | Patient characteristics   | Salvage definition                       | CVC salvage, %      | Follow-up | Recurrence, %      | Infectious complications, n |
|--------------------------------|--------------|--------------------------------------|-----------|------------|----------------------|---|--|---------------------|-----------|--------------------|-----------------------------|
| Rannem et al. (48), Denmark    | 1970–1985    | Retrospective chart review           | 82        | 1.46       | Nonstandard criteria | Mean age 43 y; 60% women; 100% HPN; (non)tunneled CVCs                        | No recurrence                            | NR                  | 60 d      | 7.7% (2 of 26)     | None                        |
| Rijnders et al. (31), Belgium  | Unclear      | Randomized, placebo-controlled trial | 44        | NR         | IDSA                 | Mean age 47 y; percentage HPN unknown; 75% oncologic; 83% venous port systems | No death or recurrence                   | 43% (10 of 23)      | 180 d     | 39% (9 of 23)      | NR                          |
| Tribleret et al. (24), Denmark | 2002–2016    | Retrospective chart review           | 1441      | 1.83       | CDC                  | Mean age 57 y; 55% women; 100% HPN; 33.6% oncologic; various CVCs             | Retained CVC at discharge; no recurrence | 55.3% (744 of 1350) | 30 d      | 7.5% (101 of 1350) | NR                          |

<sup>1</sup>AB, antibiotic; BC, blood culture; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; HPN, home parenteral nutrition; IDSA, Infectious Diseases Society of America; IE, infective endocarditis; NR, not reported; PICC, peripherally inserted central catheter.

1%–30%) in the ALT group (11 studies) compared with 12% (range: 7%–29%) in the systemic antibiotic group (8 studies) and 5% (range not applicable) in the catheter exchange group (1 study). Incidence of infectious complication rates did not differ between the different interventions ( $P = 0.58$ ) (CVC exchange group excluded).

### Risk of bias

**Supplemental Table 7** provides an evaluation of the studies' quality and details the risk of bias within studies according to a modified NOS. Most studies had a low risk of bias, whereas 6 studies had a moderate (37, 41, 45, 46, 48) or high risk of bias (52). The overall median of the total NOS score was 6 out of 9. When the risk of bias was introduced as a covariate in the model for successful CVC salvage, its effect was not significant ( $P = 0.74$ ). The funnel plot showed that successful salvage rates did not differ between small and large studies that used ALT in addition to systemic antibiotics as treatment ( $P = 0.17$ ), indicating no evidence of publication bias (Figure 5). However, funnel plot asymmetry was present in studies that used systemic antibiotics alone, mostly due to the absence of larger studies with higher salvage rates ( $P = 0.002$ ).

### Narrative review of gray literature (unpublished studies) and case reports

The majority of unpublished studies on CRBSI treatment in HPN patients address the efficacy and safety of catheter salvage by ALT in addition to systemic antibiotic treatment. Haneda et al. (56) reported a high efficacy of ALT with vancomycin (25 mg/mL, twice daily for 10–14 d) in 7 HPN patients suffering from a total of 10 CRBSIs. The treatment success rate was 90%, although 1 patient developed a recurrent CRBSI within 30 d. The causative pathogens of the CRBSIs in this study were not reported. ALT with vancomycin was also successful in 8 of 9 cases of CRBSIs caused by *Bacillus cereus*, a pathogen for which the IDSA guidelines would advise catheter removal (57). A retrospective analysis of the addition of ALT in 10 hemato-oncological patients (8 received HPN) with a port-infection revealed a high rate of CVC removal after CRBSI (58). Although intraluminal treatment with antibiotics was not attempted in all patients, the CVC was removed in 7 of 10 cases (5 cases of CNS, 4 cases of Gram-negative bacilli, and 1 case of methicillin-susceptible *S. aureus*). Udvarhelyi et al. (59) examined the catheter retention time during the implementation of their catheter preservation protocol. The time to catheter replacement was prolonged by a mean of 118.7 d. Three patients presented with recurrent CRBSIs, 1 of whom developed endocarditis during the third recurring CRBSI. This led to the policy of CVC removal after the occurrence of a second CRBSI. The unpublished study of Ward et al. (60) found that catheter salvage was more likely to fail in CRBSIs with *S. aureus*. Patients were treated with either systemic antibiotics only or in combination with ALT. Attempted catheter salvage was successful in 79% of the cases. The additional use of ALT resulted in similar salvage rates as intravenous antibiotic therapy alone. Of note, catheter salvage was not attempted (5 of 29 cases) when additional complications were present, such as septic shock, endocarditis, and repeated

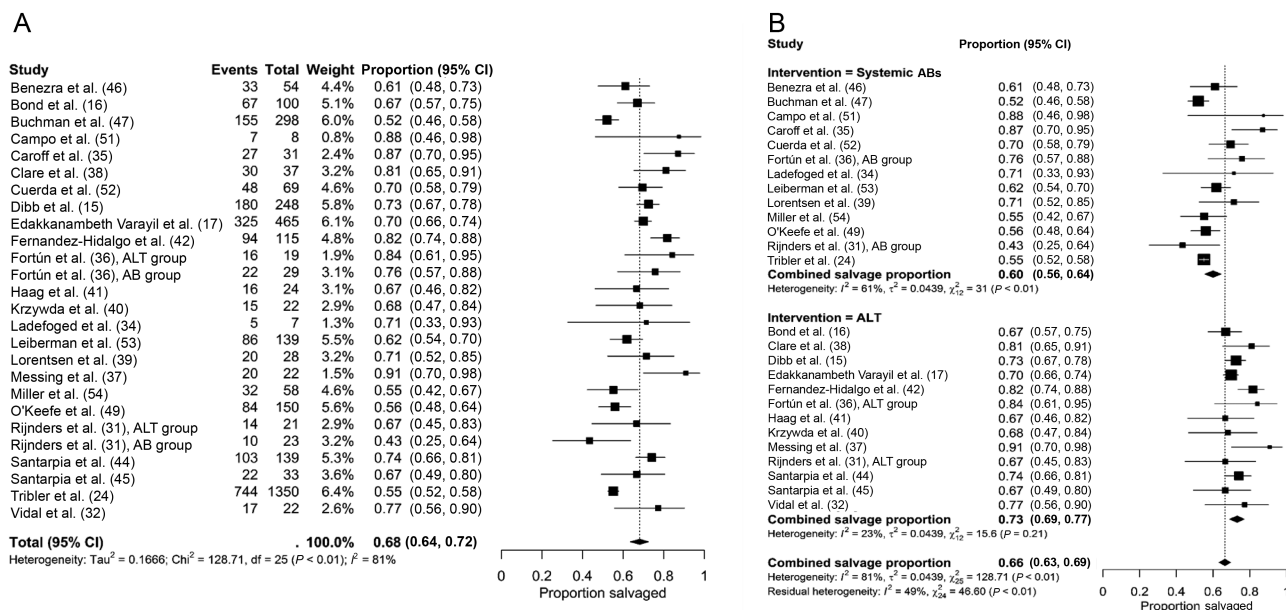
**TABLE 3** Type of ALT and comparison treatment per included study<sup>1</sup>

| Study ( <i>n</i> = 15), country                  | Lock protocol  | Lock solution   | Comparison treatment   |
|--|--|---|--|
| Bond et al. (16), United Kingdom                 | Referred to Dibb et al. (15).  | Referred to Dibb et al. (15).   | N/A  |
| Clare et al. (38), United Kingdom                | Duration not stated. Systemic ABs: not specified.  | Sensitivity-guided solutions (not further specified).   | N/A  |
| Dibb et al. (15), United Kingdom                 | 10 d for CNS; 14 d for all other pathogens. Systemic ABs: vancomycin, changed according to sensitivities if available. | Empirical: 4 mg vancomycin/mL; 5000 IU urokinase/mL. Changed according to sensitivities if available.   | N/A  |
| Edakkanambeth Varayil et al. (17), United States | Duration not stated. Systemic ABs: vancomycin and cefepime (7–14 d).   | Empirical: vancomycin lock.   | N/A  |
| Fernandez-Hidalgo et al. (42), Spain             | Up to 10 d. Systemic ABs: vancomycin or ciprofloxacin.   | GPC: 2 mg vancomycin/mL with 20 IU heparin/mL; GNR: ciprofloxacin or amikacin (2 mg/mL) with 20 IU heparin/mL.  | N/A  |
| Fortún et al. (36), Spain                        | Every 3 d and used for 8–12 h/d, for 10–14 d. Systemic ABs (not further specified).                                    | GPC: 2 mg vancomycin/mL with 20 IU heparin/mL. GNR: ciprofloxacin or gentamicin (2 mg/mL) with 20 IU heparin/mL.  | Systemic AB: vancomycin, dicloxacillin, ceftazidime, cefotaxime, cotrimoxazole (3–14 d). |
| Guedon et al. (43), France                       | 14 d. Culture-guided systemic ABs (22 of 34 cases).  | Empirical: 5 mg teicoplanin/2 mL.   | N/A  |
| Haag et al. (41), Germany                        | 3–4 d. Culture-guided systemic ABs.  | Taurolack Hep 100® (1.4% cyclo-taurolidine, 0.4% citrate solution, 100 IU heparin/mL).  | N/A  |
| Krzywda et al. (40), United States               | 3 cc of diluent, instilled with dwell time of 12 h; 5–17 d. No systemic ABs.   | Sensitivity-guided solutions (nafcillin: 250–500 mg; erythromycin: 200 mg; amphotericin: 1 mg; ceftriaxone: 250 mg; cefazolin: 200 mg; clindamycin: 300 mg; vancomycin: 100–250 mg; gentamicin: 40 mg). | N/A  |
| Lawinski et al. (33), Poland                     | 5 d. With or without systemic ABs.   | Day 1: 95% ethanol lock solution. Day 5: sensitivity-guided solutions (100 mg amikacin/mL; 40 mg teicoplanin/mL; 50 mg vancomycin/mL).  | CVC removal  |
| Messing et al. (37), France                      | 14–27 d with dwell time of 12 h. Group I ALT alone; Group II ALT with systemic ABs: methicillin.                       | Sensitivity-guided solutions ( <i>S. epidermidis</i> : 2 mg vancomycin/d; <i>Corynebacterium</i> spp.: 0.4 mg minocycline/d; GNR and <i>Micrococcus</i> spp.: 3 mg amikacin/d).                         | Methicillin treatment for 3 wk   |
| Rijnders et al. (31), Belgium                    | 7–14 d combined with systemic ABs according to IDSA guidelines.  | Ceftazidime for GNR and vancomycin for GPC in concentration of 500 mg/L with heparin.   | Heparin with systemic ABs according to IDSA guidelines                                   |
| Santarpia et al. (44), Italy                     | Once or twice a day for >7 d. Combination of 2 culture-guided systemic ABs.  | The same as the systemic AB with lowest MIC, diluted with 1–2 mL heparinized solution (500 IU/mL).  | N/A  |
| Santarpia et al. (45), Italy                     | 14–28 d (median 21 d). Culture-guided systemic ABs.  | Teicoplanin (20), daptomycin (9), or meropenem (4).   | N/A  |
| Vidal et al. (32), France                        | 1–14 d (mean 7 d). Systemic ABs: vancomycin and ceftazidime (2 cases).   | Vancomycin (11), amikacin (5), ethanol (5), or ceftazidime (2).   | N/A  |

<sup>1</sup> AB, antibiotic; ALT, antimicrobial lock therapy; CNS, coagulase-negative staphylococci; CVC, central venous catheter; GNR, Gram-negative rods; GPC, Gram-positive cocci; IDSA, Infectious Diseases Society of America; MIC, minimum inhibitory concentration; N/A, not applicable.

infections despite catheter salvage. The majority of the included case reports in this review related to cases with a complicated course of CRBSI including recurrent CRBSIs and rare causative pathogens. Also, the reported clinical outcomes differed widely.

Therefore, we decided not to combine these results in our meta-analysis. **Supplemental Tables 8 and 9** outline a summary of the patient characteristics and clinical outcomes of the included case reports.



**FIGURE 2** Forest plots of proportion (95% CI) of successful catheter salvage per study. (A) Overall successful central venous catheter salvage proportions. (B) Subanalysis per intervention type. The vertical lines represent the mean salvage proportion per intervention type, taking into account within-group variation. Mixed-effects logistic regression analysis showed that the combination of systemic ABs with ALT was superior to systemic ABs alone (OR: 1.75; 95% CI: 1.21, 2.53;  $P = 0.003$ ). AB, antibiotic; ALT, antimicrobial lock therapy.

## Discussion

This systematic review describes and compares the efficacy of 3 CRBSI management options for patients receiving HPN. These data show that successful catheter salvage can be achieved in the majority (68%) of HPN-dependent patients with a CRBSI, when catheter removal is not indicated. More importantly, the data indicate that ALT in addition to systemic antibiotics is superior to systemic antibiotic treatment alone for successful catheter salvage (OR: 1.75; 95% CI: 1.21, 2.53;  $P = 0.003$ ).

The benefit of ALT in tandem with systemic antibiotics has previously been described in a systematic review and meta-analysis in hemodialysis patients, which mainly comprised case-control studies (61). In line with our findings, the authors concluded that the addition of an antimicrobial lock solution is superior to systemic antibiotics alone; however, lack of good-quality clinical trials precluded firm conclusions from being drawn. Likewise, the yield of randomized controlled clinical trials in our systematic search was low, with only 1 RCT included (31). Although a notable nonsignificant difference in salvage success rates was observed between ALT and placebo groups (57% compared with 33%;  $P = 0.10$ ), this study was underpowered and ceased prematurely because of slow patient inclusion.

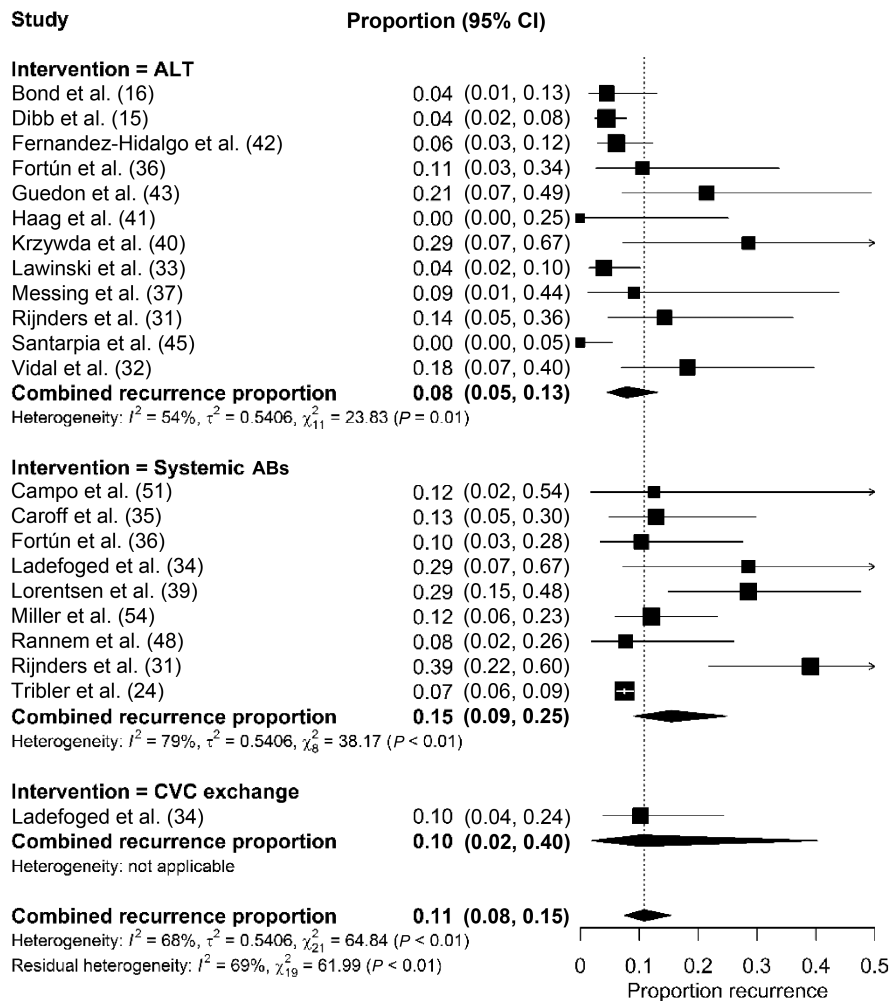
The IDSA guidelines for the diagnosis and management of CRBSI give 2 recommendations regarding the use of ALT as an adjunct therapy for catheter salvage: 1) it is advised that ALT is used (evidence B-II); 2) it is recommended to attempt catheter salvage in uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria, with the use of both systemic antibiotics

and ALT (B-II). These recommendations are in keeping with our findings, because the lowest catheter salvage success rates were found in CRBSIs caused by *S. aureus*. Nevertheless, the addition of ALT still resulted in higher catheter salvage success rates than systemic antibiotic treatment alone. Two studies showed that successful salvage rates of >75% could be achieved even in CRBSIs caused by *S. aureus* (16, 38). Caution may be required, however, because several of the included studies initially excluded catheter salvage in CRBSIs caused by *S. aureus* because of published guidelines and CVC removal within 72 h has been adopted as one of the key quality indicators for optimal *S. aureus* bacteremia management in antibiotic stewardship programs (62).

Only 1 study included in this meta-analysis used CVC exchange via a guidewire as CRBSI treatment (34). We did find 2 other studies that applied CVC exchange in patients receiving parenteral nutrition with our systematic search, but these only involved hospitalized patients (63, 64). In our opinion, catheter exchange via a guidewire is only indicated on the rare occasions when a hemodynamically stable HPN patient with CRBSI cannot be successfully treated with antimicrobial therapy and options to obtain venous access are extremely limited.

Some of the studies included in our analysis also attempted CVC salvage in patients with nontunneled and peripherally inserted central catheters (PICCs) (35, 48). It remains debatable as to whether CVC salvage for these devices is as appropriate as for tunneled CVCs and implanted ports, because nontunneled CVCs (including PICCs) themselves may carry a heightened risk of CRBSI acquisition (65–67).

CRBSIs caused by yeasts or fungi were not the scope of this review because CVC salvage is discouraged for these types of



**FIGURE 3** Forest plots of proportion of recurrence per study divided per intervention type. The vertical lines represent the mean successful salvage proportion per intervention type, taking into account within-group variation. Mixed-effects logistic regression analysis showed that recurrence of infection was less common in studies that used the combination of systemic ABs with ALT than in those that used systemic ABs alone (OR: 0.26; 95% CI: 0.11, 0.61;  $P = 0.002$ ) (CVC exchange group excluded). AB, antibiotic; ALT, antimicrobial lock therapy; CVC, central venous catheter.

infections by all major international guidelines (5, 12, 14, 68). In addition, there are limited clinical data to support the effectiveness of antifungal locks for patients with candidemia (69), and the use of such locks is currently not standard practice (5, 12).

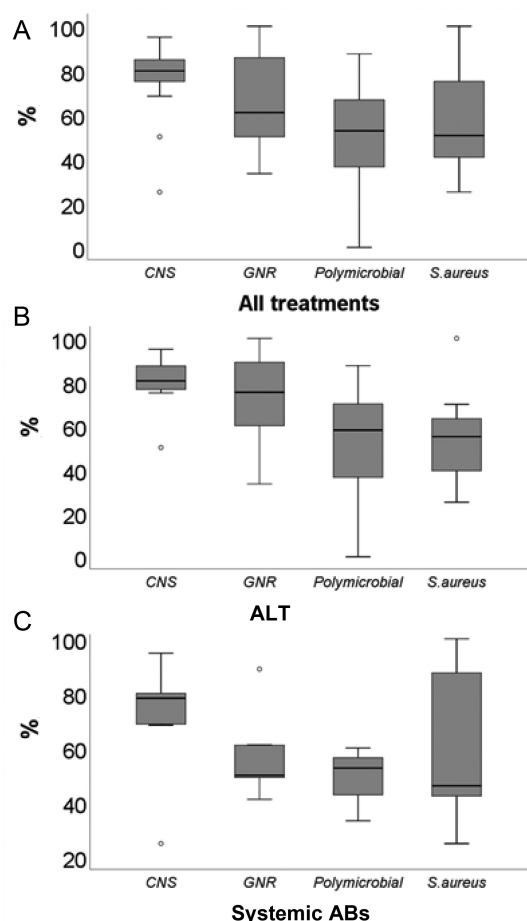
An important question that remains is the most effective composition and dose of the antimicrobial lock solution. There was wide variability in the reported concentrations and types of administered locks between the studies of this systematic review. Previous in vitro studies demonstrated that concentrations of lock solutions need to be  $\geq 5$  mg/mL, whereas several of the studies in this review used lower concentrations (15, 16, 36, 38, 42). It is also important to take reported dwell times into consideration which, unfortunately, were not reported in most of the included studies. Moreover, sufficient dwell time may be difficult to achieve if the catheter is used for parenteral nutrition infusion during the salvage protocol. Concerns also exist relating to the emergence of multiresistant bacteria resultant from antibiotic lock use, although data to support these concerns are currently lacking (70). Finally, limitations on lock

availability between different countries may limit the choice available.

A major strength of our systematic review is its strict adherence to the PRISMA and MOOSE guidelines: the protocol was prepublished (PROSPERO registry); an up-to-date and extensive systematic literature search was performed; a structured risk of bias assessment was undertaken by 2 independent authors using the NOS, which is widely supported in observational research; the complete data set was controlled for mistakes by a second investigator; and case reports/series were excluded from the meta-analysis to minimize selection bias.

There remain several limitations to the interpretation of our findings. The most important limitation is that only 1 RCT could be included (31). This finding in itself highlights the lack of RCTs in evaluating CRBSI management in HPN-dependent patients, despite these being the most serious complication for this vulnerable group of patients. In addition, assessment of study quality using the NOS tool showed that one-quarter of the studies had a moderate or high risk of bias although, notably, this did





**FIGURE 4** Boxplots of successful CVC salvage rates divided by the type of causative pathogen. (A) Overall CVC salvage rates. (B) CVC salvage rates for studies using ALT in addition to systemic ABs. (C) CVC salvage rates for systemic AB therapy-only studies. Circles denote outliers. ORs for CVC salvage (all treatments): CNS compared with *S. aureus*: 3.00; 95% CI: 2.33, 3.85;  $P < 0.001$ ; CNS compared with GNR: 2.19; 95% CI: 1.84, 2.60;  $P < 0.001$ ; GNR compared with *S. aureus*: 1.37; 95% CI: 1.07, 1.76;  $P = 0.01$ . AB, antibiotic; ALT, antimicrobial lock therapy; CNS, coagulase-negative staphylococci; CVC, central venous catheter; GNR, Gram-negative rods; *S. aureus*, *Staphylococcus aureus*.

not affect our results based on regression meta-analysis. Strong heterogeneity was present when pooling the successful salvage rates of all intervention groups together. In the subanalysis dividing studies per type of intervention, heterogeneity decreased substantially, but moderate heterogeneity was still present in the systemic antibiotic group. Another limitation was the wide variation in reporting successful catheter salvage outcomes. As outlined earlier, some studies only attempted salvage for CNS infections, whereas others attempted salvage of all CRBSIs, regardless of pathogen. Furthermore, in the absence of a universally agreed-on definition of successful CVC salvage, different approaches were used by different authors of the studies included in this review. In our opinion, successful catheter salvage is only achieved when all of the following criteria are met: clinical resolution, negative blood cultures performed  $\geq 48$ –72 h after antibiotic discontinuation (because of the long half-lives of several of the frequently used antibiotics), and no recurrence of infection with an identical strain for  $\geq 2$  mo.

**TABLE 4** ORs of successful catheter salvage (antimicrobial lock therapy combined with systemic ABs compared with systemic ABs alone) per type of infecting pathogen<sup>1</sup>

| Infecting pathogen           | OR (95% CI)       | <i>P</i> value |
|------------------------------|-------------------|----------------|
| <i>Staphylococcus aureus</i> | 2.00 (1.27, 3.13) | 0.003          |
| GNR                          | 2.02 (1.05, 3.87) | 0.035          |
| CNS                          | 1.14 (0.49, 2.67) | 0.757          |
| Polymicrobial                | 1.11 (0.50, 2.47) | 0.804          |

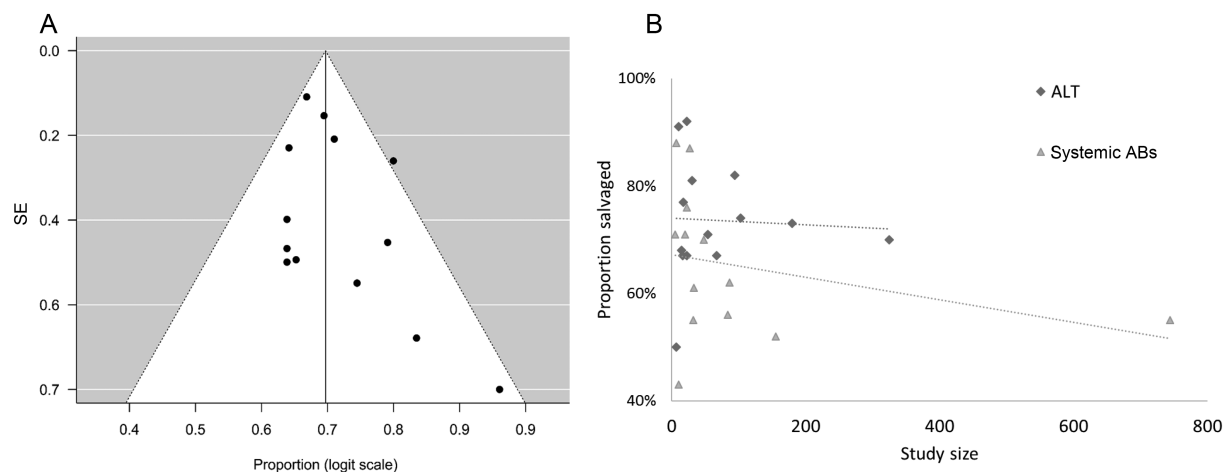
<sup>1</sup>AB, antibiotic; CNS, coagulase-negative staphylococci; GNR, Gram-negative rods.

Notably, only 2 studies fulfilled these criteria (40, 54). Although several studies performed control blood cultures at the end of antibiotic treatment, they only reported recurrence rates within  $<30$  d (15, 42, 46, 51). Furthermore, because different CRBSI definitions were used by studies, we endeavored to limit the impact of any potential misclassification bias by correcting for studies that used nonstandard definitions. In recent years, more ALT studies have been published and the approaches adopted to CRBSI diagnosis and management have also changed simultaneously in many centers; for example, there has been a recent paradigm shift toward shorter antibiotic treatment protocols for uncomplicated infections (71). These changes over time could lead to chronological time bias, resulting in a potential overestimation of the true benefit of the addition of ALT to systemic antibiotics. Funnel plots of published ALT studies showed no evident publication bias, but small studies were mainly included, and the few larger studies tended to have lower salvage rates. To overcome this issue, we weighted the analysis by study size and performed sensitivity analysis by excluding small studies of  $<10$  patients. A final limitation of note is that some of the included studies had a primary purpose other than the treatment outcome of interest for this meta-analysis, which could have led to a degree of reporting bias.

Despite the limitations outlined, this is the only meta-analysis that we know of on CRBSI management and catheter salvage in patients receiving HPN. Therefore, it is highly relevant to this population, where catheter preservation is the ultimate treatment goal. However, there is a clear need for additional high-quality clinical trials comparing the treatment options and also evaluating outcomes per pathogen. Additional topics that require well-designed research are studies assessing the most effective and safe ALT composition, as well as the optimal treatment duration and dwell time.

We conclude that the addition of ALT to systemic antibiotic treatment is associated with increased successful catheter salvage rates compared with systemic antibiotic treatment alone for CRBSI management in patients receiving HPN. Although most of the included studies were retrospective cohort in design, limiting the strength of our findings, it is important to recognize that larger prospective multicenter studies will ultimately be difficult to perform considering the rarity of this condition and the ethical barriers to enrolling patients with a life-threatening infection into a trial where they may not receive the best possible care. Hence, there is a need for more pragmatic and innovative clinical trials overcoming these issues, such as adopting an adaptive trial design (72), in order to reliably evaluate the true benefit of antibiotics for catheter salvage in this vulnerable group of patients.





**FIGURE 5** Funnel plots for examining publication bias. (A) Funnel plot of all the studies included for meta-analysis with SEs and salvage proportions. (B) Visual funnel plot of salvage rates and study size with trend lines per intervention type. Egger's regression test: ALT studies,  $P = 0.052$ ; systemic AB studies,  $P = 0.002$ . AB, antibiotic; ALT, antimicrobial lock therapy.

We appreciate the work of the investigators who published the studies we have reviewed, with a special thanks to Darren R Linkin, University of Pennsylvania, who also provided additional data and analyses upon request. We thank Pim Lepelaars for his help with data visualization.

The authors' responsibilities were as follows—MG and CP: conceptualized the study, performed the investigation, and prepared and wrote the original draft; MG, CP, CPB-R, GJAW, and RPA: outlined the methodology; MG and RPA: conducted the statistical analysis; MG, CP, AB, SL, and GJAW: performed the risk of bias assessment; MG: performed the visualization and is the guarantor of the article; MG, CP, AB, CPB-R, SL, and GJAW: reviewed and edited the original draft; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

## Data availability

The data used in the article that support the findings of this study are available from the corresponding author upon reasonable request.

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