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Use of Catheter Lock Solutions in Patients Receiving Home Parenteral Nutrition: A Systematic Review and Individual-Patient Data Meta-analysis

Yannick Wouters, MD[1]; Erna Causevic, BSc[1]; Stanislaw Klek, MD, PhD[2]; Hans Groenewoud, PhD[3]; and Geert J. A. Wanten, MD, PhD[1]

Abstract

Background: Use of catheter lock solutions (CLSs) as a strategy to prevent catheter-related bloodstream infections (CRBSIs) has been evaluated in recent clinical trials. Our aim was to identify the most effective CLS formulation in patients receiving home parenteral nutrition (HPN). *Methods:* We conducted a systematic review and individual-patient data meta-analysis (IPDMA). Prospective randomized clinical trials in adult HPN patients using CLS were identified from PubMed, EMBASE, Web of Science, CINAHL, Cochrane library, and ClinicalTrials.gov. Primary outcome was the number of CRBSIs per 1000 catheter days for each CLS. Other outcomes included time to CRBSI and identification of patients with a higher risk for CRBSIs. *Results:* In total, 1107 studies were screened for eligibility, of which three studies comprising 162 HPN patients and 45,695 catheter days were included in the IPDMA. CRBSI rates were significantly decreased in patients using taurolidine (rate 0.13; 95% confidence interval [CI], 0.05–0.32) when compared with saline (rate 0.74; 95% CI, 0.31–1.74; $P = .002$) or heparin (rate 2.01; 95% CI, 1.03–3.91; $P < .001$). The cumulative proportion of CRBSI-free patients using taurolidine, saline, and heparin after 1 year was 88%, 56%, and 14%, respectively. Three risk factors for CRBSIs were identified: type of CLS, intestinal dysmotility as underlying condition, and use of central venous catheters. *Conclusions:* Taurolidine was the most effective CLS formulation in HPN patients for the prevention of CRBSIs. We suggest discussing with patients the benefits and risks when starting taurolidine, especially in patients who are considered to have a higher risk for CRBSIs. (*JPEN J Parenter Enteral Nutr.* 2019;00:1–12)

Keywords

catheter lock solution; catheter-related bloodstream infection; central venous access device; ethanol; heparin; home parenteral nutrition; intestinal failure; saline; systematic review; taurolidine

From the [1]Intestinal Failure Unit, Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, the Netherlands; [2]General Surgery Unit, Stanley Dudrick's Memorial Hospital, Skawina, Poland; and the [3]Department of Health Evidence, Radboud University Medical Centre, Nijmegen, the Netherlands.

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Corresponding author:
Yannick Wouters, MD, MSc, Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Geert Grooteplein Zuid 10, 6500 HB Nijmegen, the Netherlands.
E-mail: Yannick.Wouters@radboudumc.nl

Introduction

Maintaining central venous access remains a major challenge in patients depending on long-term intravenous therapies, such as chemotherapy, hemodialysis, and home parenteral nutrition (HPN). HPN support is indicated in intestinal-failure patients who suffer from decreased intestinal absorption, usually due to the absence of functioning gut following extensive surgical resections (short-bowel syndrome) or due to disturbed gut motility.[1] These patients depend on long-term intravenous administration of nutrients and/or fluids via a central venous access device (CVAD), mostly a subcutaneously tunneled central-venous catheter (CVC).

Despite preventive hygiene protocols and CVAD training programs, catheter-related bloodstream infections (CRBSIs) remain the most daunting problem of HPN support, with incidences ranging from 0.25 to 2.99 CRBSIs per 1000 catheter days even in expert centers.[2,3] Some HPN patients appear more susceptible to develop CRBSIs, but exact criteria defining these high-risk patients are lacking from the literature.[4]

Development of CRBSIs most probably results from intraluminal colonization of CVADs by microbial pathogens, in particular Gram-positive bacteria derived from the skin that contaminate the catheter hub and subsequently form a biofilm.[5-7] Once developed, it is sometimes impossible to eradicate microbes within this impermeable biofilm by means of antibiotics.[8]

The key strategy to prevent CRBSIs remains to be strict adherence to aseptic protocols when handling CVADs. None of several other strategies, including use of antibiotic-coated or silver-impregnated catheters, antimicrobial cuffs, ointments of the catheter exit site, and eradication of skin pathogens, has so far been proven sufficiently effective.[9-11] An alternative strategy is the use of antimicrobial catheter lock solutions (CLSs) that are instilled in the CVAD when not in use. Especially in centers with a high background risk for CRBSIs or in patients with recurrent CRBSIs, these CLSs may be proven most effective. Several locking formulations have been studied, including anticoagulants, antiseptic agents, and antibiotics, mostly with disappointing results.[11] In addition, toxicity and side effects, including allergies as well as development of microbial resistance, remain a concern.

Historically, heparin has been the most commonly used CLS in HPN care, also because of the supposed need for anticoagulants. However, in vitro studies suggest that heparin might promote biofilm formation and that CVAD patency is not prolonged by heparin flushing as compared with saline.[11-13] In addition, based on its lower efficacy to prevent CRBSIs compared with alternative CLS, the use of heparin is no longer recommended in HPN patients.[11,14] The use of 0.9% saline as a CLS seems attractive because of its favorable safety and cost profile. Yet, as it applies to heparin, recent research has shown the inferiority to prevent CRBSIs when compared with taurolidine.[15] This latter antiseptic agent, derived from the amino acid taurine, displays broad antiendotoxic and antimicrobial effects against (myco)bacteria and fungal species, because of inhibition of microbial adhesion to biosurfaces and destruction of microbial cell membranes.[16-19] Finally, ethanol has been used as an alternative antiseptic CLS, also because taurolidine is not registered in many countries, including the United States. Although some efficacy in the prevention of CRBSIs over heparin has been suggested in low-quality studies, a recent randomized double-blinded study in pediatric patients with cancer or a hematological disorder did not show favorable outcomes when compared with heparinized saline, and CVAD occlusions requiring thrombolytic therapy were even more common with ethanol lock therapy.[20] Currently, European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on chronic intestinal failure do not recommend the use of ethanol, because of concerns for systemic toxicity and these mechanical CVAD complications. This view was further bolstered by the premature termination of a recent trial.[11,21-23]

The present study was sparked by the notion that several methodologically sound studies on CLS in the setting of HPN have been published recently that ask for an integral perspective that can be provided with an individual-patient data meta-analysis (IPDMA). Although the primary aim of this study was to assess the efficacy and safety of CLS to prevent CRBSIs, we also sought to identify HPN patients with an increased risk for such infections. We hypothesized that taurolidine is the most effective CLS to prevent CRBSIs in HPN patients.

Methods

Study Design and Participants

A study protocol was finished before study initiation and can be found elsewhere.[24] This international, collaborative systematic review combined individual-patient data from prospective randomized controlled trials published on CLS in HPN patients. Studies had to report CRBSI rates as primary or secondary outcome. At patient level, only adult intestinal-failure patients who received HPN and/or fluids via CVADs were included. To avoid bias, patients with an active malignancy or an untreated CRBSI at trial inclusion were excluded from the analyses. The preferred reporting items for systematic review and meta-analysis of individual participant data (PRISMA-IPD) guidelines were followed to report this study.[25]

Search Strategy and Selection of Studies

A broad literature search was conducted in PubMed, EMBASE, Web of Science, CINAHL, Cochrane Library,

and ClinicalTrials.gov from inception to August 1, 2018. We restricted our search to articles written in English or Dutch. The search was updated 1 month before the end of study to avoid missing recently published trials (last search January 8, 2019). The investigators were assisted by a clinical librarian in obtaining a correct and complete search syntax. The following search terms (and their synonyms) were combined: home parenteral nutrition, catheter, and lock solution. The full search strategy is listed in Table S1. Studies were screened based on title and abstract and were independently selected for full text by 2 investigators (YW and EC). Authors resolved any disagreements on study eligibility by discussion. A third investigator was adjudicator (GW) if no consensus was reached. We complemented our search with the reference lists of eligible articles. In case only a relevant abstract was available, contact with the original research team was made for additional information.

All primary researchers of the identified studies were invited by electronic mail to join the collaboration. The authors were asked to share their anonymized individual-patient data by an Excel file containing a list of predefined variables. The variables are listed in Table S2. The obtained databases were reanalyzed separately and checked for completeness and internal consistency, and the findings were confirmed with the original manuscript and author. In case primary researchers refused or could not share their trial data, aggregated data from the original article were independently retrieved by 2 investigators (YW and EC).

Ethical Statement

Each trial included in this study was approved by the institutional review board or ethics committee, and all patients provided written informed consent. In addition, the research ethics committee of the Radboudumc in Nijmegen, the Netherlands, approved the present study (reference number 2018–4162).

Study Quality Assessment

Each trial underwent a critical appraisal for relevance and internal validity. The quality of each study was independently assessed by 2 investigators (EC and MG) by using the Cochrane Collaboration tool for assessing bias in randomized clinical trials.[26] A third investigator (AH) was adjudicator when no consensus was reached.

Outcomes and Definitions

Primary outcome was the number of CRBSIs per 1000 catheter days for each CLS. Other predefined CRBSI-related outcomes included time to CRBSIs, distribution of bacteria (Gram-positive or Gram-negative) and fungi, CVAD salvage rates, drug-related antimicrobial resistance, and identification of patients at a higher risk for CRBSIs. In addition, we reported the number of CVAD occlusions and exit-site infections, drug-related adverse events, and cost.

A CRBSI was defined by clinical evidence of a systemic infection or sepsis and at least 1 positive blood culture from the CVAD and/or peripheral vein, in the absence of another apparent source of infection than the CVAD. CVAD salvage rate was defined as the proportion of CRBSIs successfully treated without the removal of a CVAD. A CVAD occlusion was defined as an obstruction of the CVAD with a failure to flush or aspirate or the inability to infuse sufficiently into the CVAD. An exit-site infection was defined as a local infection with erythema, induration, tenderness around the exit site, and/or purulent discharge from the catheter exit site.

Statistical Analysis

Continuous variables were presented as means with standard deviations or as medians and interquartile ranges, if not normally distributed. Drug formulations were categorized by their active component. For example, the taurolidine group consisted of patients using 2% taurolidine, 1.35% taurolidine-4% citrate, or 1.35% taurolidine-4% citrate-heparin (100 IU/mL).

Individual-patient data were used to compare CRBSI rates between CLSs, to analyze CRBSI-free survival, to identify patients at risk for CRBSIs, and to compare costs between CLSs. Differences in CRBSI rates between CLS were tested using a generalized estimating equation (GEE) Poisson regression model with clinical center as a clustering variable. We corrected for possible confounders by including significant different baseline characteristics or a change of $\geq$10% on unadjusted estimates by covariates in this model. Results were presented as rate ratios with 95% confidence intervals (CIs). CRBSI-free survival was studied using a Cox proportional hazards regression model with the marginal Cox model approach described by Lee et al to estimate coefficients and to adjust for clustering in clinical centers.[27] In addition, a GEE Poisson regression model was used to explore for predictors for CRBSIs. Potential risk factors included gender, age at start of study inclusion, underlying disease, diabetes status, type of CVAD, old or new CVAD, type (nutrition or fluids) and frequency of parenteral support, HPN experience, type of CLS, and history of CRBSIs. Independent risk factors for CRBSIs were used to stratify patients in the previously mentioned Cox proportional hazards model. Costs were based on Dutch prices and consisted of CLS costs and CRBSI resource use costs (hospitalizations, outpatient-clinic consultations, CVAD changes, and drug treatment).[28,29] The mean costs per patient were compared with a 1-way analysis of variance after correction for multiple comparisons and bootstrapping (1000 simulations). Other secondary outcomes, including CRBSI-causing microorganisms, CVAD salvage rates, antimicrobial resistance, CVAD occlusions, exit-site

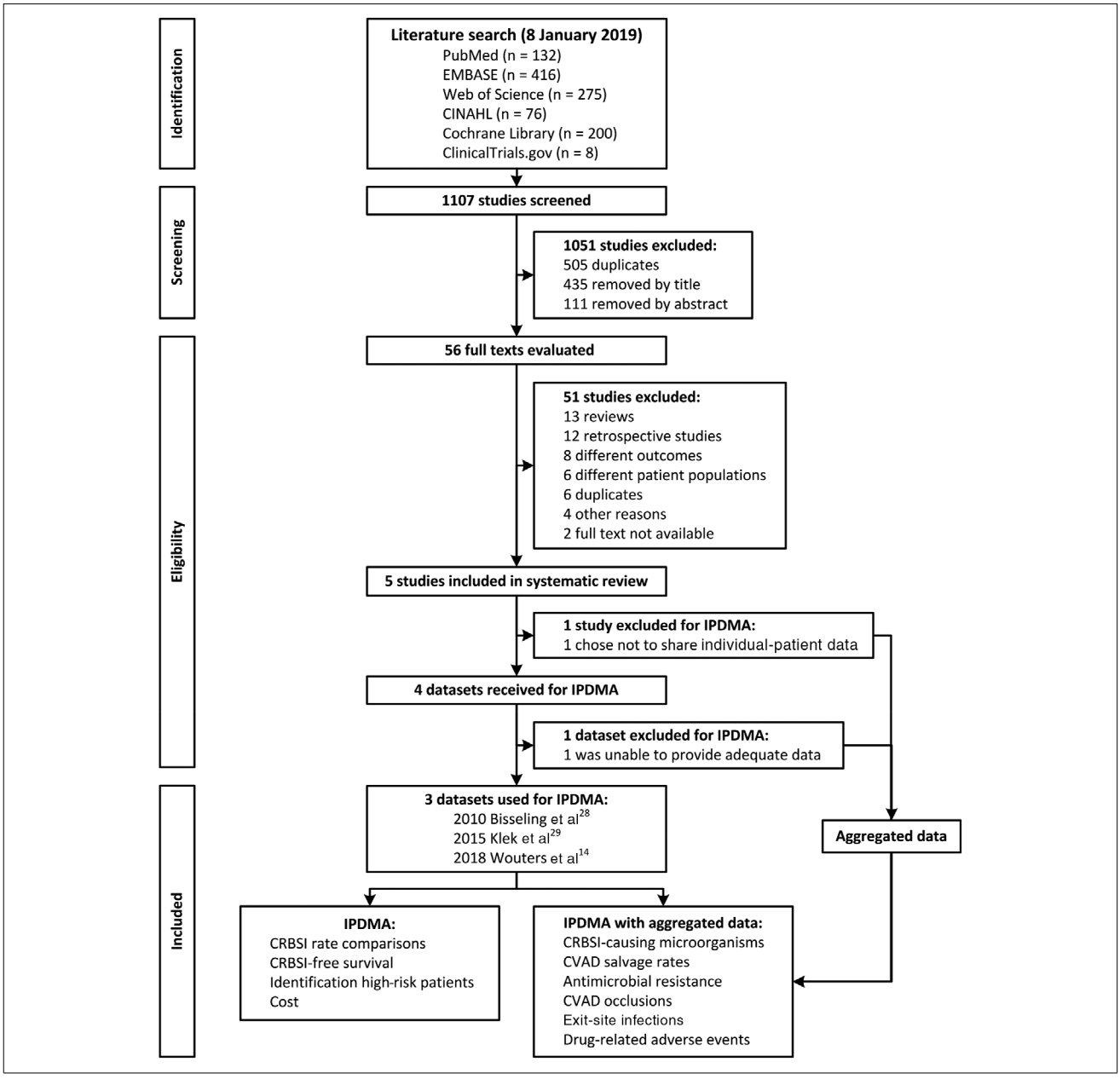

Figure 1. Search strategy for prospective randomized studies in adult home parenteral patients using catheter lock solutions. CRBSI, catheter-related bloodstream infection; CVAD, central venous access device; IPDMA, individual-patient data meta-analysis.

infections, and drug-related adverse events, were based on aggregated data and summarized using only descriptive statistical methods. In case studies did not report data on these outcomes, the studies were excluded from the relevant subanalyses.

If possible, publication bias was assessed using a funnel plot or Egger's regression method. A 2-tailed *P*-value $< .05$ was considered statistically significant. All statistical analyses were performed with SPSS statistical software package version 22.0 or SAS software package version 9.4.

Patient and Public Involvement

No patients were involved in the development of the research question, the outcome measures, or the design of the study, nor were they asked to advise on data interpretation or to write the results.

Results

In total, 1107 studies were screened for eligibility, of which 56 were evaluated for full text (Figure 1). Five studies

Table 1. Characteristics of Studies Fulfilling the Inclusion Criteria.

Study	Design	Follow-up	Patients	Major Inclusion Criteria	Control	Intervention(s)	Type of Data Available
Bisseling et al[30] (Netherlands, 2010)	Single-center, open-label	2 years	30	Adult HPN patients Benign underlying disease Recent history of CRBSI	Heparin (150 U/mL)	2% taurolidine	Individual-patient data
Klek et al[31] (Poland, 2015)	Single-center, open-label	1 year	30	Adult HPN patients Benign underlying disease ≥12 months HPN experience Tunneled catheter use	0.9% saline	2% taurolidine or 1.35% taurolidine-4% citrate	Individual-patient data
Salonen et al[23] (United States, 2017)	Single-center, double-blind	1 year	38	Adult HPN patients HPN naïve patients Tunneled catheter use	Heparin (100 U/mL)	70% ethanol	Aggregated data
Tribler et al[14] (Denmark, 2017)	Single-center, double-blind	2 years	41	Adult HPN patients No active malignancy ≥2 times per week HPN	Heparin (100 U/mL)	1.35% taurolidine-4% citrate-heparin (100 U/mL)	Aggregated data
Wouters et al[15] (Netherlands, 2018)	Multicenter, double-blind	1 year	105	Adult HPN patients Benign underlying disease ≥2 times per week HPN	0.9% saline	2% taurolidine	Individual-patient data

CRBSI, catheter-related bloodstream infection; HPN, home parenteral nutrition.

fulfilled the inclusion criteria and were selected for review (Table 1).[14,15,23,30,31] Of these, 1 refused to share participant data and was excluded from the IPDMA. The other 4 studies provided their individual-patient data. One study, however, was additionally excluded from the IPDMA because the provided data were not in agreement with the original manuscript, and the authors were unable to send the correct data. Thus, eventually 3 studies with 162 HPN patients and 45,695 catheter days were included in the IPDMA.[15,30,31] Patient characteristics of the 3 studies combined are shown in Table S4. The 2 excluded studies were screened for aggregated data and integrated, where possible, in the analyses (Figure 1).

Quality Assessment and Publication Bias

Quality assessment of each study and across studies is presented in Figure S1 and Table S3, respectively. Two of 5 studies were open-label trials and considered to be high risk for performance and detection bias. Of 1 blinded study, detection bias still may have occurred, and risk of bias was considered unclear. All but 1 study had an unclear risk regarding incomplete reporting of outcome data (attrition bias). Of 1 study, selective reporting may have occurred (unclear risk), and risk for other bias was considered high. The low number of studies did not allow for a funnel plot or regression-based assessment for publication bias.

Catheter-Related Bloodstream Infections

Main outcomes of the IPDMA are demonstrated in Figure 2. The CRBSI rate for taurolidine (rate 0.13; 95% CI, 0.05–0.32) was significantly lower when compared with saline (rate 0.74; 95% CI, 0.31–1.74; $P = .002$) or heparin (rate 2.01; 95% CI, 1.03–3.91; $P < .001$). The CRBSI rate in the saline group was significantly decreased when compared with heparin (rate ratio 0.37; 95% CI, 0.17–0.80; $P = .01$). In a sensitivity analysis, we examined the effects of studies of which we were not able to collect individual-patient data, by combining the results of our IPDMA with the aggregated data of the 2 excluded studies. CRBSI rates of the taurolidine and saline groups did not change, but the CRBSI rate of the heparin group decreased to 1.19 (95% CI, 0.55–2.57) (Table S5).

The cumulative proportion of CRBSI-free patients using taurolidine, saline, and heparin after 1 year was 88%, 56%, and 14%, respectively (Figure 3). Type and frequency of CRBSI-causing microorganisms are presented in Table 2 and Table S6, respectively. Most CRBSIs (34 [72%]) were monobacterial of origin, and except for patients using saline as CLS, the majority of these bloodstream infections (21 [62%]) were caused by Gram-positive bacteria (mainly *Staphylococcus* species). In total, 5 (11%) polybacterial bloodstream infections and 5 (11%) fungemia were

CLS	Study	Patients	CRBSIs	Days	CRBSI rate (95%CI)	Adjusted CRBSI rate (95%CI)[b]
Heparin	Bisseling *et al.*	14	10	1,814	5.51 (2.76-9.67)	2.01 (1.03-3.91)
Saline	Klek *et al.*	10	0	3,660	0 (0-0)	0.74 (0.31-1.74)
	Wouters *et al.*	50	18	12,493	1.44 (0.85-2.23)	
Taurolidine	Bisseling *et al.*	16	1	5,110	0.20 (0.01-0.86)	0.13 (0.05-0.32)
	Klek *et al.*	20	1	7,300	0.14 (0.01-0.60)	
	Wouters *et al.*	52	5	15,318	0.33 (0.11-0.76)	

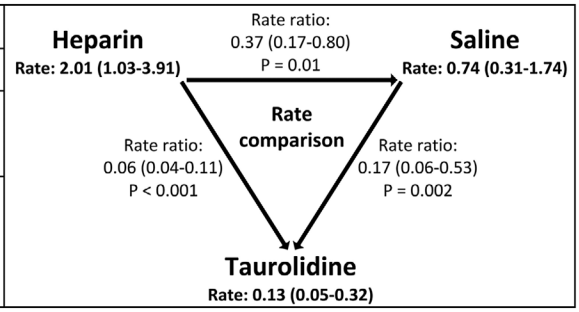

Figure 2. Comparison of Adjusted CRBSI Rates per CLS[a]. Presented data were obtained from individual-patient data of 3 studies (Bisseling et al, Klek et al, and Wouters et al).[15,30,31]. CI, confidence interval; CLS, catheter lock solution; CRBSI, catheter-related bloodstream infection; CVAD, central venous access device. [a]Rates are expressed as number of CRBSIs per 1000 catheter days. [b]CRBSI rates were adjusted for center, history of CRBSIs, type of CVAD, and type of infusion fluids.

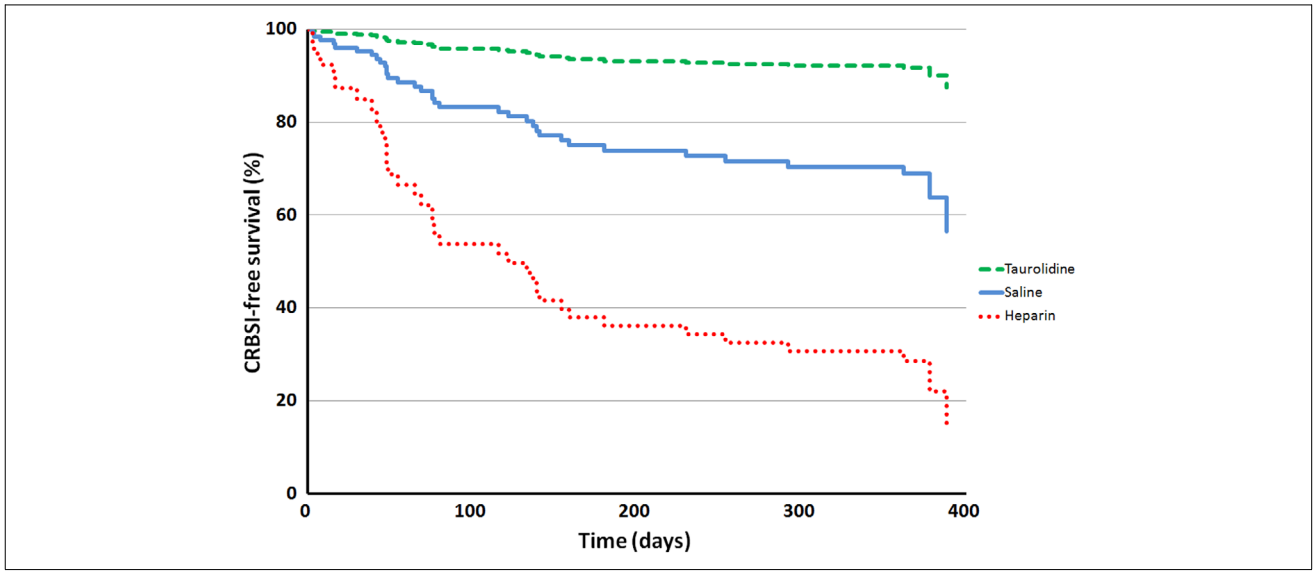

Figure 3. Survivor functions for the 3 treatment groups. Results of a Cox proportional hazards model adjusted for center clustering, representing the time to CRBSI with CVADs locked with taurolidine (striped green line), saline (continuous blue line), or heparin (dotted red line). The cumulative proportion of CRBSI-free patients after 1 year was 88% in the taurolidine group, 56% in the saline group, and 14% in the heparin group. Presented data were obtained from individual-patient data of 3 studies (Bisseling et al, Klek et al, and Wouters et al).[15,30,31] CRBSI, catheter-related bloodstream infection; CVAD, central venous access device.

reported. CVAD salvage rates varied per CLS (0%–56%) and are shown in Table 2. None of the studies reported signs for drug-related antimicrobial resistance.

Patients at Risk for CRBSIs

Three main risk factors for CRBSIs were identified (Table 3). First, the type of CLS (eg, heparin or saline) was independently associated with a higher risk for CRBSIs when compared with taurolidine. Secondly, patients with a motility disorder as underlying condition had a higher risk for CRBSIs when compared with short bowel syndrome patients (rate ratio 3.51; 95% CI, 2.25–5.47; $P < .001$). Finally, patients using subcutaneous port systems had a lower risk for CRBSIs when compared with CVCs (rate ratio 0.33; 95% CI, 0.25–0.44; $P < .001$).

Subsequently, patients were stratified for these 3 risk factors in an overall CRBSI-free survival model (Figure 4). The highest cumulative proportion of CRBSI-free survival after 1 year (97%) was reached in short bowel patients with a subcutaneous port while using taurolidine. In contrast, the lowest cumulative proportion (2%) was found in

Table 2. Secondary Outcomes.

Type of CRBSI[a]	Ethanol (n = 18)	Heparin (n = 55)	Saline (n = 60)	Taurolidine (n = 108)
Monobacterial bloodstream infection	1	15	14	4
Gram-positive (%)	1 (100)	11 (73)	6 (43)	3 (75)
Gram-negative (%)	0 (0)	4 (27)	8 (57)	1 (25)
Polybacterial bloodstream infection	1	2	1	1
Isolated fungemia	2	1	1	1
Unknown[b]	0	0	2	1
Total	4	18	18	7
CVAD salvaged after CRBSI				
No—no. of CVADs (%)	4 (100)	13 (72)	8 (44)	4 (57)
Yes—no. of CVADs (%)	0 (0)	5 (28)	10 (56)	3 (43)
Total	4	18	18	7
CVAD occlusions[c]				
No—no. of patients (%)		28 (80)	57 (95)	98 (91)
Yes—no. of patients (%)		7 (20)	3 (5)	10 (9)
CVAD occlusion rate (95% CI)[d]		0.80 (0.32–1.65)	0.19 (0.04–0.54)	0.27 (0.13–0.49)
Exit-site infections[c]				
No—no. of patients (%)		28 (80)	55 (92)	97 (90)
Yes—no. of patients (%)		7 (20)	5 (8)	11 (10)
Exit-site infection rate (95% CI)[d]		0.80 (0.32–1.65)	0.31 (0.10–0.72)	0.29 (0.15–0.53)
Drug-related adverse events				
Dizziness	0	1	0	1
Dysgeusia	0	0	0	9
Erythema catheter exit site	0	0	0	1
Flushing	0	0	1	0
Heartburn or acid reflux	0	1	0	0
Nausea, vomiting, and anorexia	0	0	0	2
Paresthesia or tingling sensations	0	1	0	3
Reduced catheter patency	0	0	1	0
Total	0	3	2	16
Adverse event rate (95% CI)[d]	0 (0–1.41)	0.25 (0.05–0.74)	0.12 (0.01–0.45)	0.40 (0.23–0.66)

Presented data were obtained from aggregated data of 5 studies (Bisseling et al, Klek et al, Salonen et al, Tribler et al, and Wouters et al).[14,15,23,30,31]

CI, confidence interval; CRBSI, catheter-related bloodstream infection; CVAD, central venous access device.

[a]A detailed overview of microorganism-causing CRBSIs is shown in Table S6.

[b]A positive blood culture was reported; however, the microorganism involved was not documented.

[c]All patients (n = 18) from the ethanol group and 20 patients from the heparin group were excluded from the analyses, because CVAD occlusions and exit-site infections were not reported in the study of Salonen et al[23] For both CVAD occlusions and exit-site infections, the generalized estimating equation Poisson regression model did not converge because of the low number of events, which prohibited comparisons between treatment groups. Therefore, only descriptive aggregated data are shown.

[d]Rates are expressed as number of events per 1000 catheter days.

patients with a motility disorder while using heparin via a CVC.

CVAD Occlusions and Exit-Site Infections

The number of CVAD occlusions and exit-site infections per CLS are presented in Table 2. In 20% of patients using heparin, a CVAD occlusions or exit-site infection occurred, respectively. The frequency of CVAD occlusions and exit-site infections (5%–10%) was lower in patients using saline or taurolidine.

Drug-Related Adverse Events

All 21 reported adverse events were mild to moderate and no anaphylactic-like reactions were observed (Table 2). Most adverse events were reported in patients using taurolidine and consisted of dysgeusia (n = 9) or paresthesia (n = 3). Heparin-related adverse events included dizziness,

Table 3. Multivariable Poisson Regression Analysis of Factors Associated With CRBSIs.

Variable		Rate ratio (95% CI)	*P*-Value
Gender	Female	*Reference*	
	Male	0.74 (0.43–1.27)	.28
Age at start of HPN	Years	0.99 (0.97–1.02)	.50
Underlying disease	Short bowel syndrome	*Reference*	
	Motility disorder	3.51 (2.25–5.47)	<.001
	Other underlying diseases	1.31 (0.34–5.11)	.70
	Motility disorder	*Reference*	
	Other underlying diseases	0.37 (0.10–1.41)	.15
Type of CVAD	Central venous catheter	*Reference*	
	Subcutaneous port system	0.33 (0.25–0.44)	<.001
Type of CLS	Heparin	*Reference*	
	Saline	0.18 (0.10–0.31)	<.001
	Taurolidine	0.04 (0.02–0.08)	<.001
	Saline	*Reference*	
	Taurolidine	0.20 (0.07–0.58)	.003

Presented data were obtained from individual-patient data of 3 studies (Bisseling et al, Klek et al, and Wouters et al).[15,30,31] Potential risk factors included: gender, age at start of HPN, underlying disease, diabetes status, type of CVAD, old or new CVAD, type (nutrition or fluids) and frequency of parenteral support, HPN experience, type of CLS, and history of CRBSIs. Risk factors that showed a *P*-value of ≤.2 in the univariable Poisson regression model were included in the final multivariable model.
CI, confidence interval; CLS, catheter lock solution; CRBSI, catheter-related bloodstream infection; CVAD, central venous access device; HPN, home parenteral nutrition.

heartburn, or paresthesia. Flushing and a reduced catheter patency were reported to be related to saline. No adverse events were reported in patients using ethanol.

Cost of CLSs and CRBSI Resource Use

Total mean costs were significantly increased in patients using heparin (€18,252) when compared with saline (€3429, $P = .001$) or taurolidine (€3156, $P < .001$) (Table S7 and Figure S2). There was no difference in mean costs between saline and taurolidine ($P = .91$). In a sensitivity analysis, which was adjusted for extreme costs, similar results were observed, although there was a trend toward cost reduction in patients using taurolidine (€1834) when compared with saline (€3429, $P = .09$).

Discussion

This is the first comprehensive IPDMA in the field of HPN that provides an extensive overview of prospective outcomes under influence of various CLS. Our results demonstrate that taurolidine is the most effective CLS to reduce CBRSIs when compared with heparin or saline.

Besides the type of CLS, 2 additional factors were found to be associated with CRBSIs: the patient's underlying disease and the type of CVAD. CRBSI rates were significantly increased in patients with motility disorders when compared with short bowel patients. Such outcomes have been previously reported by others, and a recent robust HPN cohort has shown increased overall CVAD-related complication rates in motility-disorder patients as well.[32-34] Previously, small-bowel bacterial overgrowth and subsequent translocation of gut flora have been suggested as the route of infection in these patients.[32,35-37] Another explanation may be that these patients are more frail than expected, which impairs their quality of catheter care. Although more than half of patients with a motility disorder do not have a clear underlying pathologic mechanism, these patients still have a poor survival when compared with other severely affected HPN patients, such as short bowel–syndrome patients.[11,38] In addition, absence of adequate coping behavior and substance abuse, especially of opiates, may also play a role in these patients.[39]

The use of subcutaneous port systems was independently associated with a decreased risk for CRBSIs when compared with CVCs. The currently available literature on this topic remains controversial and is mainly based on retrospective studies in adult patients with CVADs, not always necessarily inserted for the purpose of HPN support. This is exemplified by the equivocal results of studies: 5 reported a protective effect on CRBSIs in patients using subcutaneous port systems, 3 found the opposite, and 5 did not observe a difference between the 2 CVAD types.[32,40-51] Recent guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) state that subcutaneous port systems are primarily intended for low-frequency and intermittent venous access.[52] The authors suggest that subcutaneous port systems are associated with the lowest risk for CRBSIs mainly because of reduced CVAD manipulations and that presence of an indwelling needle for continuous or frequent access would offset the reduced infection benefit. These data

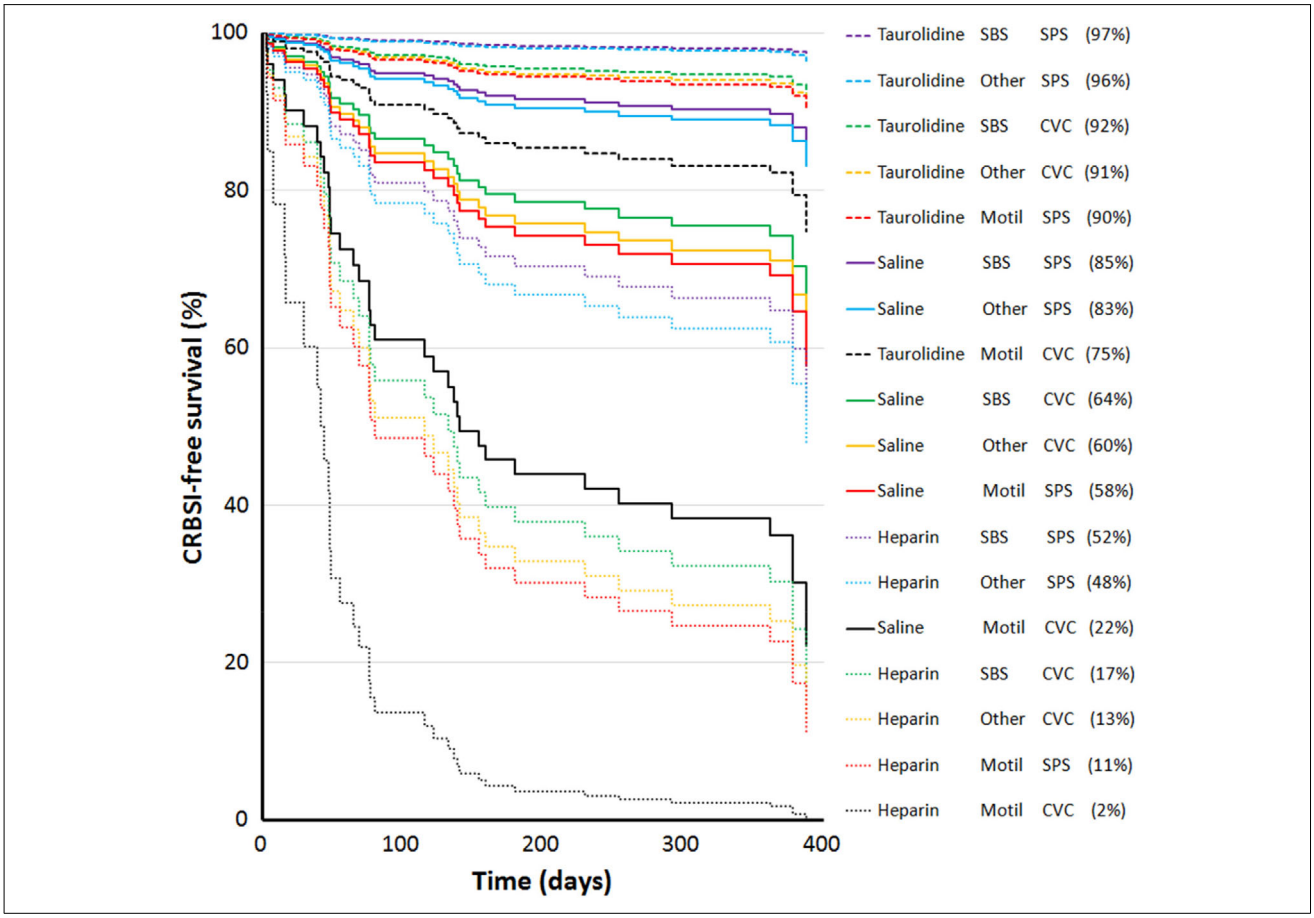

Figure 4. Survivor functions of patients stratified for risk factors for CRBSIs. Results of survivor functions according to a Cox proportional hazards model adjusted for center clustering with stratification for risk factors for CRBSIs (Table 3): (1) type of lock solution (taurolidine [striped line], saline [continuous line], or heparin [dotted line]); (2) underlying disease (SBS, motility disorder, or other underlying diseases); (3) type of central venous access device (CVC or SPS). Presented data were obtained from individual-patient data of 3 studies (Bisseling et al, Klek et al, and Wouters et al).[15,30,31] CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; motil, motility disorder; other, other underlying diseases; SBS, short bowel syndrome; SPS, subcutaneous port system.

are mostly based on patients receiving chemotherapy rather than HPN.[11] In the present study, however, the median number of manipulations between both CVCs and subcutaneous port systems did not differ. In addition, it is unlikely that 9 peripherally inserted CVCs in the CVC group affected the outcomes, as none experienced a CRBSI. Although our results suggest that subcutaneous port systems seem favorable in HPN patients, it is important to note that other (patient-specific) factors play a role as well when selecting a CVAD, such as the duration of HPN, preferred access sites, a center's experience, and the patient's preference.[11,53]

We selected several other potential risk factors for our analyses (eg, gender, type [nutrition or fluids] and frequency of parenteral support, and history of CRBSIs), based on previous (retrospective) studies.[7,54] None of these factors was eventually univariably associated with CRBSIs in this study. We cannot rule out that our study was underpowered to identify these factors. The fact that we identified 3 risk factors in a still relatively large, prospective, and heterogeneous cohort with patients from various international centers suggests that these risk factors are strongly associated with CRBSIs. Obviously, additional prospective studies are needed to validate our findings.

Based on the explored risk factors, we stratified patients in a Cox proportional hazards model. It was striking that the simplest modifiable factor, that is, the CLS, was responsible for the largest difference in CRSBI-free survival after 1 year. The use of taurolidine potentially increased CRBSI-free survival by 12% to 45% in patients having no additional risk factors than the CLS when compared with 53% to 73% in patients having 2 additional risk factors. These results seem highly relevant for clinical practice, as it may provide a solid foundation for patient-specific, targeted preventive strategies.

In most patients, the CLSs were well tolerated. Drug-related adverse events were only mild to moderate, and no anaphylactic-like reactions were reported. These data are strengthened by a recent, large long-term HPN cohort study, which found no evidence for serious side effects with taurolidine.[51] At first glance, taurolidine seems less safe due to an absolute higher number of adverse events. However, it is important to incorporate the treatment time on the CLS as well. Most patients in the heparin and saline groups had a relative short follow-up period due to the higher incidence of CRBSIs and their subsequent withdrawal from trials. Indeed, the number of adverse events per 1000 days of CLS use seemed similar between the CLSs (Table 2).

Previous studies found a cost-reduction in patients using taurolidine, when compared with heparin or saline.[14,15] Here, we only found a trend toward cost reduction. Although cost-effectiveness remains an important issue, especially in centers with a very low background risk for CRBSIs, the prevention of any CRBSI episode is crucial in light of CRBSI-associated morbidity and mortality. Even a single episode of CRBSI may have devastating consequences, for instance, in case of infection-related thrombosis that results in complete loss of vascular access (eg, following occlusion of the superior vena cava). As long as there is no evidence for detrimental effects of taurolidine (eg, no development of microbial resistance), we would support the use of prophylactic locking as standard practice.[17,30,55-57] In our view, this notion outweighs the argument that in expert HPN centers with a low risk for CRBSIs, many/most patients would use such locks in vain. In case of a drug-related adverse event, it may be necessary to perform a (blinded) rechallenge in a controlled environment.[51] If symptoms persist, a switch to another CLS should be performed. Our results suggest that saline may be the best second option, also because of its safety profile.

The use of individual-patient data from prospective randomized studies has a number of strengths. The IPDMA allowed to adjust for heterogeneous trial and patient data by predefining outcomes and by adjusting for study/center effect modifications and other potentially confounding patient factors. This likely resulted in a more precise estimation of outcomes, such as CRBSI rates per CLS, and generated new outcomes of interest as well, such as CRBSI-free survival and the identification of patients at risk for CRBSIs. In addition, we were able to compare saline vs heparin, for both of which head-to-head comparisons in HPN patients were lacking so far.

This study has limitations as well. The quality of the present study is largely based on the individual quality of included studies. Limitations of these clinical trials may apply to this study as well. In addition, although we assembled the largest prospective cohort of HPN patients on CLS to date, the number of included studies/patients remains low. Eventually only 3 studies were included in the IPDMA, which particularly hampered inclusion of patients using heparin from the 2 excluded studies. Also, because of the low number of CVAD occlusions and exit-site infections, we were unable to statistically compare these complications between CLSs. A final limitation is that we categorized CLSs based on their active component. Especially for taurolidine, there are several formulations available with different taurolidine concentrations and with or without concomitant anticoagulants. It is possible that these formulations differ in efficacy. For example, earlier, we showed in vitro that growth of microbes was detected earlier in lower taurolidine concentrations, whereas citrate or heparin did not inhibit growth of clinical isolates.[58] As such, the combined CRBSI rates reported in this study may not be representative for every single formulation. It would be valuable to determine which taurolidine formulation is most effective in future studies. This will, however, require robust randomized trials with large patient groups, and it is questionable whether such large trials will be performed in the setting of HPN.

In conclusion, this study showed that the use of taurolidine as CLSs was most effective in HPN patients for the prevention of CRBSIs. Adverse events were reported to be relatively infrequent and only mild to moderate. Risk factors for CRBSIs included the type of CLS, the underlying disease, and the type of CVAD used. We suggest discussing with patients the benefits and risks when starting taurolidine, especially in those who are considered at a higher risk for CRBSIs.

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Statement of Authorship

Y. Wouters, H. Groenewoud, and G. J. A. Wanten contributed to conception/design of the study; Y. Wouters, E. Causevic, S. Klek, H. Groenewoud, and G. J. A. Wanten contributed to acquisition, analysis, or interpretation of the data; Y. Wouters and E. Causevic drafted the manuscript; Y. Wouters, E. Causevic, S. Klek, H. Groenewoud, and G. J. A. Wanten critically revised the manuscript; and G. J. A. Wanten agrees to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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