HOME PARENTERAL NUTRITION

THE QUEBEC PATIENT PROFILE AND SYSTEMATIC REVIEW OF ANTIMICROBIAL LOCKS IN THE PREVENTION OF CATHETER RELATED BLOOD STREAM INFECTIONS

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Abstract

Background: Home parenteral nutrition (HPN) is a life-sustaining treatment for patients with chronic intestinal failure. Chronic intestinal failure is a rare condition with an estimated prevalence of 5 to 20 per million population (1). Patients with intestinal failure have insufficient bowel function to meet their nutritional needs with sole oral or enteral intake. On HPN, patients self-administer nutrients and fluids intravenously via central venous access, a complex process that is costly and puts patients at risk for several complications. One major complication is catheter related blood stream infection (CRBSI), which is associated with significant morbidity and mortality. No data currently exist on HPN patients in Quebec with little information available on local complications such as CRBSI and hospitalization rates.

Objectives: Our objectives were to establish a patient cohort to define the profile of HPN patients in Quebec and to review CRBSI in HPN. We aimed to evaluate CRBSI associated risk factors and prevention methods, namely antimicrobial lock use as prophylaxis.

Methods: We conducted a prospective cohort study enrolling active HPN patients in Quebec as part of the Canadian HPN Registry. We collected data on demographics, comorbidities, PN prescription and complication rates. After reviewing risk factors for CRBSI, we performed a systematic review on the use of antimicrobial locks as prophylaxis for catheter infection in the HPN population.

Results: The prevalence and incidence of HPN is 13 per million and 0.6 per million population in 2016 in Quebec. Demographics were comparable with the rest of Canada with the exception of greater proportion of short bowel syndrome and motility disorders in the PN population. Hospitalization rate was 1.05 ± 1.21 (range 0-6) per patient per year and mean CRBSI rate was 0.65 per 1000 catheter-year. Antimicrobial locks were not routinely used in Quebec. Our systematic review on the topic retrieved 23 studies (3 randomized controlled trials (RCT) and 20 observational studies) featuring important clinical and methodological heterogeneity and limited by moderate to high risk of bias. Our results are insufficient to establish the benefits of antimicrobial lock use.

Conclusion: HPN is rare in Quebec where there was a higher prevalence of short bowel syndrome and motility disorders, the latter driven by the presence of regional genetic dysmotility condition. Local CRBSI rate was low and comparable to national and international reports.

While our systematic review was inconclusive, we identified key methodological and study design characteristics useful to inform future studies on antimicrobial locks.

Résumé

Contexte clinique : La nutrition parentérale (NP) à domicile est un traitement pouvant prolonger la vie chez les patients atteints d'insuffisance intestinale. Il s'agit d'une condition rare avec une prévalence estimée de 5 à 20 cas par million de population(1). Les patients souffrant d'insuffisance intestinale ne peuvent répondre à leur apport nutritionnel par voie orale ou entérale due à une incapacité absorptive de leur tube digestif. Ainsi, en NP à domicile, les patients administrent eux-mêmes les nutriments et fluides par voie intraveineuse via un cathéter central. La NP est un processus complexe engendrant d'importants coûts et plusieurs complications, dont l'infection sur cathéter veineux central (ICC). Il n'existe cependant pas de données pour les patients sous NP à domicile au Québec, ni d'information sur les taux de complications.

Objectifs : Nos objectifs étaient de définir le profil provincial des patients sous NP, d'établir les taux de complications au Québec et d'évaluer l'une des complications les plus importantes de la NP, soient les ICC. Nous avons cherché à réviser les facteurs de risque et les méthodes de prévention des ICC, notamment avec les verrous antimicrobiens.

Méthodes : Nous avons effectué une étude prospective de la cohorte québécoise de patients sous NP dans le contexte du Registre Canadien de NP à domicile qui nous a permis d'obtenir des données sur la démographie, les comorbidités, les prescriptions de NP, ainsi que les complications au Québec. Après un survol des facteurs de risque pour les ICC, nous avons effectué une revue systématique de la littérature sur les verrous antimicrobiens en prophylaxie pour les ICC.

Résultats : La prévalence de NP à domicile était de 13 par million de population au Québec, avec une incidence de 0.6 par million en 2016. Le profil démographique était comparable au reste du Canada, avec cependant un plus haut taux de patients avec un syndrome de grêle court et de trouble de motilité intestinale. Le taux d'hospitalisation était de 1.05 ± 1.21 (écart 0-6) par patient par année et le taux d'ICC moyen était de 0.65 par 1000 cathéter-années. Les verrous antimicrobiens n'étaient que rarement utilisés au Québec. Notre revue systématique sur les verrous a inclus 23 études (3 études randomisées et 20 études observationnelles) avec une importante hétérogénéité clinique et méthodologique, et comprenant des risques de biais considérables (modérés à élevés). L'ensemble des résultats était donc insuffisant pour définir l'efficacité des verrous.

Conclusion : La NP à domicile était peu prévalente au Québec où on y retrouvait une plus grande proportion de patients avec un grêle court ou une dysmotilité intestinale, cette dernière étant expliquée par la présence d'une maladie génétique régionale affectant la motilité intestinale. Le taux d' ICC était faible et comparable aux taux canadiens et internationaux. Bien que notre revue systématique sur les verrous antimicrobiens en prévention des ICC n'était pas concluante, cette synthèse nous a permis d'identifier des éléments relatifs à la méthodologie qui pourront informer des études futures.

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Contribution of authors

Yidan Lu, MD

I have conceived the systematic review antimicrobial locks and the cross sectional study on the Quebec HPN population. I have set up the Canadian home parenteral nutrition Registry at each of the 3 sites, namely the Montreal General Hospital, St-Luc Hospital and Hôtel-Dieu de Québec and steered the ethics approval process. I performed the data collection at every site and proceeded to enter the data into the online Canadian Registry. Additional contributions include the data organization and statistical analyses for the cohort study. For the systematic review, I have performed data extraction, synthesis and analysis of the studies. I wrote this thesis and the manuscripts.

Alan Barkun, MD, MSc

Dr Barkun was the thesis supervisor. He oversaw the thesis organization and provided regular input in the study design and analysis, during periodic research meetings. He reviewed and critically revised the manuscripts and thesis.

Errol B Marliss, MD

Dr Marliss was my thesis co-supervisor. He provided regular input in the study design and analysis. He reviewed and critically revised the manuscripts and thesis.

Maida Sewitch, PhD

Dr Sewitch was my thesis co-supervisor. She provided regular input in the study design and analysis. She reviewed and critically revised the manuscripts and thesis.

Myriam Martel, MSc

Ms Martel has helped with the systematic review and the systematic search. She has also provided me with methodological input and helped me with statistical analysis. She has reviewed the manuscript for systematic review.

Chiara Saroli Palumbo, MD

Dr Palumbo has helped with the systematic search, data extraction and bias analysis for the systematic review. She has reviewed the manuscript for systematic review.

Abbreviations

Anti-TNF: anti-tumor necrosis factor

ASPEN: American Society for Parenteral and Enteral Nutrition

CDC: Centers for Disease Control and Prevention

CI: confidence interval

CRBSI: catheter related blood stream infections

ESPEN: European Society for Clinical Nutrition and Metabolism

HPN: Home parenteral nutrition

H2RA: Histamine 2 receptor antagonist

IQR: interquartile range

N: no

NA: not available

Obs: observational

PPI: proton pump inhibitor

PN: parenteral nutrition

RCT: randomized controlled trial

RR: relative risk

SD: standard deviation

SEM: standard error mean

Tx: treatment group

Y: yes

Chapter 1– Thesis introduction

1.1 Home parenteral nutrition

Parenteral nutrition (PN) is a life sustaining therapy that provides intravenous nutritional support for patients with intestinal failure. Such patients have compromised intestinal function leading to the inability to digest and absorb nutrients provided through oral and enteral routes. Patients with intestinal failure require parenteral nutrition; that includes a mixture of nutrients (proteins, carbohydrate, and lipids), fluids, electrolytes, vitamins and micronutrients tailored to patients' nutritional requirements, administered through a central venous catheter.

Patients that suffer from irreversible causes of intestinal failure, rather than a transient condition, require long-term PN. Long-term PN is typically administered at home, in the setting of a home parenteral nutrition (HPN) program. HPN is a complex process that is delivered in a highly specialized setting. Multi-disciplinary teams of physicians, nurses, nutritionists, and pharmacists are generally in place to provide patient training, education, support and disease monitoring. Patients are trained to administer PN autonomously at home, while being monitored periodically by the HPN team.

HPN remains infrequent, with an estimated prevalence between 5 to 20 per million (1), with reports ranging from 3.25 to 66 per million in Europe (2), and up to 120 per million in the US (3). A common etiology of chronic intestinal failure is short bowel syndrome caused by various conditions such as Crohn's disease, mesenteric ischemia, and surgical complications. Other causes include intestinal pseudo-obstruction, cancer and intestinal malabsorption (2). At least 45% of patients who start on HPN will continue to require life-long PN (4, 5). Patient survival has greatly improved since PN was first introduced in the 1960s, and now primarily depends on the patient's underlying disease. 10-year survival rates for non-malignant chronic intestinal failure range from 55 to 95% (6). The complexity and chronicity of HPN result in important resource utilization with annual costs of 100,000 to 150,000 USD per patient(3, 7).

1.2 Complications of HPN

While HPN is a life sustaining treatment, it is associated with numerous complications, and lower quality of life (8). Long-term metabolic complications include metabolic bone disease, nephrolithiasis, and hepatobiliary diseases such as cholestasis and liver failure (9). Additionally, HPN patients are at risk for infectious and mechanical catheter complications. Infectious etiologies include catheter related blood stream infections (CRBSI), site and tunnel infections, whereas mechanical causes vary from catheter thrombosis, occlusion, displacement and breakage (10, 11).

Among them, CRBSI are one of the most severe complications, and occur at rates ranging from 0.38 to 4.58 events per 1000 catheter-days (10). Catheter infections lead to frequent hospitalizations, and necessitate treatment with intravenous antibiotics, and even central catheter replacements. CRBSI are estimated to be responsible for 20 to 50% of HPN related mortality (12). Each hospitalization for CRBSI results in estimated costs of about 9170 USD per admission (13).

1.3 CRBSI prevention and antimicrobial locks

An episode of CRBSI can have serious implications that include loss of vascular access, sepsis and even death. Optimizing patient and staff education, hand-washing, sterilization and catheter handling techniques are fundamental to reduce the occurrence of CRBSI. Additionally, certain patient and PN characteristics have been identified as risk factors for CRBSI(10). Most of these risk factors cannot be modified. There is therefore a need to find additional methods to further reduce CRBSI.

Antimicrobial locks have been used to prevent CRBSI in PN patients. The technique consists of instilling a solution with antimicrobial properties into the PN catheter when not in use to prevent biofilm formation, and thus reduce the risk of microbial growth and CRBSI. This technique is easily applicable across different patient populations with indwelling central venous catheters. Several studies have been published in the PN population but yield variable results, and have not yielded clear recommendations on their use.

1.4 Demographics and CRBSI rate in the Quebec HPN population

Data on the demographics of HPN patients are available through registries and surveys from several European and American HPN cohorts (2, 3, 6, 14-19). The information they have provided has led to a better understanding of the different HPN centers' organization, and their patients. The results have highlighted a varied PN practice and reported heterogeneous patients populations across the centers.

A Canadian HPN Registry was established in 2004 to better characterize the HPN population of Canada, and to identify factors influencing survival, complications and PN-dependency(20).The Registry was the first to provide insight into the Canadian population. However, Quebec has remained absent from the Registry, and no data on the profile of Quebec HPN patients was available. Such information is important to better understand local patient demographics, PN practice and complications, including CRBSI rates, in order to tailor clinical practice and improve patient care.

1.5 Thesis objectives

The main objectives of this thesis were:

- to describe the Quebec HPN population
- to assess CRBSI rate in the Quebec HPN population
- to review risk factors for CRBSI in HPN
- to evaluate the role of antimicrobial locks solutions as prophylaxis against CRBSI in PN

We started by defining the profile of HPN patients in Quebec and described for the first time, their demographics and complication rates. This provided a better understanding of local patient characteristics and regional challenges. We enrolled all three HPN centers in Quebec into the Canadian National HPN Registry, and performed a cross-sectional study of Quebec HPN patients. This included indication for PN, PN requirements, catheter use, and complications. Globally, this initiative established a framework for prospective data collection including the building of a longitudinal dataset that captures the evolution of the patients over time.

We then evaluated the use of antimicrobial locks as a prophylaxis for CRBSI in HPN patients. Antimicrobial locks use has been supported by various publications, but results are conflicting and guidelines differ on their use. We performed a systematic review of the literature on CRBSI as prophylaxis exclusively in the parenteral nutrition population. We finally calculated CRBSI rates in Quebec and reviewed local practices on the use of antimicrobial locks.

1.6 Thesis overview

In **Chapter 2**, we present our findings from the Quebec cohort of the Canadian HPN registry in the manuscript entitled "Home parenteral nutrition in Quebec – data from the National Home Parenteral Nutrition Registry" (manuscript 1). In the **bridge section 1**, we review CRBSI and its risk factors in HPN. This section provides background information on CRBSI specific to HPN patients, and brings context to next chapter on CRBSI prophylaxis. In **Chapter 3**, we evaluate the use of antimicrobials locks as prevention for CRBSI in parenteral nutrition in a systematic review, with the manuscript entitled "Antimicrobial locks for the prevention of catheter-related blood stream infections (CRBSI) in patients on parenteral nutrition – a systematic review" (manuscript 2). Both manuscripts will be submitted to peer-reviewed journals. In the **bridge section 2**, we return to the Quebec HPN cohort while focusing on local complications rates. We defined Quebec complication rates, including hospitalization and CRBSI rates, and also reviewed local antimicrobial lock practice. In the final **Chapter 4**, we summarize our findings, discuss methodological challenges we encountered and offer insights for future research.

Chapter 2 –Home parenteral nutrition in Quebec – data from the National Home Parenteral Nutrition Registry

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ABSTRACT

Background: Home parenteral nutrition (HPN) is a life-sustaining treatment for patients with chronic intestinal failure. Patients on HPN self-administer fluids and nutrients intravenously at home, under the supervision of a multidisciplinary HPN medical program. HPN programs are established at three centers in the province of Quebec. Currently, no data exist on Quebec HPN patients.

Aims: Describe HPN patients in the province of Quebec via the Canadian National HPN Registry template. Determine the prevalence of HPN, patient characteristics and HPN related complication rates among Quebec patients, and perform a comparison with the general Canadian HPN population.

Methods: Retrospective study using prospectively collected data from a cohort of HPN patients that includes patient demographics, parenteral nutrition parameters and major complication rates. Patients were enrolled from December 2015 to September 2017 at three Quebec university-affiliated centers that offer HPN programs. Written consent was obtained. Descriptive analyses were performed using means and medians. Exploratory analyses for CRBSI risk factors were done using Chi-square and Wilcoxon rank sum tests. Comparison for the etiology of intestinal failure with the general Canadian HPN population was done using Chi-square or Fisher's exact tests.

Results: We have included 83 patients (33.7% male, mean age 55.2 ± 14.4 years, range 19 to 85). The most common etiology for intestinal failure was short bowel syndrome (SBS) (71.6%), followed by motility disorders (21%), mucosal disorders (4.9%) and tumours (2.5%). In the motility group, several patients shared the diagnosis of Chronic Atrial and Intestinal Dysrhythmia**,** a recessive founder genetic mutation highly specific to the French-Canadian population. The mean time on HPN was 9.8± 7.5 years (median 7.9, range 0.35 to 31.8), with 38.9 % on PN for over 10 years. We noted a mean of 0.21 catheter related blood stream infections (CRBSI) per patient per year, and estimated a CRBSI rate of 0.65 per 1000 catheter-days. There was a mean of 1.05 ± 1.21 (range 0-6) hospitalizations per patient per year, but only 25% resulted from PN complications.

Baseline characteristics were similar to Canadian data (age, female predominance) but greater prevalence of SBS (Chi-square statistic 28.013, $p<0.0001$) and intestinal motility disorders in Quebec (Chi-square statistic 16.325, $p<0.0001$) and fewer cancer patients (Fishers exact test $p<0.0001$).

Conclusion

The prevalence was 13 per million population in Quebec, identical to the estimated Canadian prevalence. Short bowel syndrome was the main etiology for intestinal failure. In contrast to the rest of Canada, there was a higher prevalence of motility disorders and fewer cancer patients. Complication rates were 0.65 CRBSI per 1000 catheter days and the mean hospitalization rate was 1.05 per patient per year.

INTRODUCTION

Home parenteral nutrition is a long-term treatment for chronic intestinal failure, a condition where there is insufficient functional intestinal mass resulting in impaired intestinal absorption. It is defined as "the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance"(21). Causes of intestinal failure are varied, and include short bowel syndrome, intestinal obstruction, dysmotility, and malabsorption from various etiologies.

HPN was first described in the 1970s, when its use was still experimental(22). It has now become the standard of care in patients with chronic intestinal failure. HPN remains a highly specialized treatment targeting a small population, with a prevalence that ranges between 3.25 to 120 patients per million (2, 3).

Patient data from HPN registries and surveys describe important regional variations. For instance 40% of US HPN patients receive PN for malignant conditions, whereas this percentage ranges from 5 to 81% in Europe (23). Differences between centers reflect heterogeneity of the patient populations, as well as differing practices and clinical approaches adopted at each HPN center. Regional patient data are thus important for accurate assessment of local patient profile.

The Canadian HPN Registry was established in 2004, and aims at characterizing the Canadian HPN population, as well as assessing their survival, complications and long-term outcomes(20). The Registry was the first of its kind in Canada and has now enrolled over 700 patients(20). It was prospectively validated (24) and has yielded important data on clinical practice. For instance it detected an excess in trace element supplementation in Canada(25) that subsequently led to practice modifications.

In Quebec, HPN is offered by three university-affiliated hospital centers (Hôtel-Dieu Hospital in Quebec city, Montreal General Hospital, and St-Luc Hospital in Montreal).which together provide care for all intestinal failure patients across the province. With a population over 8 million in Quebec, HPN patients data were however not available because provincial data had not been integrated into the Canadian HPN Registry. Moreover, the lack of regional data made it

challenging to precisely define the Quebec PN patient population, and identify clinically relevant practice improvement strategies. PN registries are useful to describe local patient profiles and document important outcomes such as survival and PN related complications. They further capture local clinical practices and may detect regional variations, as well as changes over time.

AIM

The main objective was to describe Quebec HPN patients. This included assessing the prevalence of HPN, and determining patient demographics and CRBSI rates.

METHODS

We recruited all patients followed at the three HPN centers in the province of Quebec from December 2015 to October 2017. The centers were Hôtel-Dieu Hospital (Centre hospitalier de l'Université Laval) in Quebec city, the Montreal General Hospital (McGill University Health Centre), and St-Luc Hospital (Centre hospitalier de l'Université de Montréal) in Montreal. After providing written consent, patients were enrolled in the Canadian HPN registry, a nationwide prospective registry for HPN patients. Inclusion criteria were the following: patients receiving parenteral nutrition or hydration at least once per week in the last 12 months, and age $\geq$ 18 years. Patients who discontinued PN for greater than 1 year were excluded.

Data collection

Information was obtained through a review of patient charts and electronic medical records. Data extraction was performed by a single investigator (Y.L.) using the standard Canadian HPN Registry form. The form included age, gender, diagnosis, anatomy, comorbidities, bloodwork, liver disease, medications, HPN regimen, hospitalization, line change, and Karnofsky score. Data collection occurred from December 2015 to September 2017.

Canadian HPN Registry

The Canadian HPN registry was created in 2004; it is a prospective registry with data collected every 2 years. Prior to the addition of Quebec patients, it was comprised of 8 centers from 5 provinces with over 799 patient entries. No Quebec patients had been enrolled prior to this

initiative. Data collection followed the same standard operating procedures as in other provinces and was uniform across all participating sites.

Relevant patient characteristic of the Quebec cohort are presented in Tables 1 to 6. When pertinent, we also performed comparisons using data from the Canadian HPN Registry. For the comparisons, we used data from active Canadian Registry patients (data collected between 2016-2018) if available, and otherwise used cumulative data from the full Canadian Registry (all patient entries since the start of the Registry). When the information was not available, we compared collected information with data from prior publications issued by the Canadian Registry (24, 25).

Statistical analysis

We performed a descriptive analysis of Quebec HPN patient characteristics using means and medians with standard deviations and ranges. We included patient demographics, underlying disease, time on PN, PN regimen, vascular access, medications, hospitalizations and catheter related blood stream infections. We recorded the total number of patients followed at each clinic at the time of data extraction, and calculated the percentage of patients enrolled in the Registry.

We compared the aetiologies of intestinal failure of the Quebec HPN population with Canadian data from the Canadian HPN registry using Chi-square or Fisher's exact test. We also performed an exploratory analysis to evaluate factors associated with CRBSI, using risk factors described in the HPN literature with Chi-square or Fisher's exact test for categorical variables, and Wilcoxon rank sum (Mann-Whitney U) test for continuous variables. STATA software was used for all analyses (STATA14.2, Texas, 2017). A threshold of $p=0.05$ was used to determine statistical significance.

Calculations

Time on PN was calculated using the documented time when a patient enrolled in the PN clinic and the time of data extraction. CRBSI rate was calculated using the number of CRBSI documented for each patient in the prior 12 months. If the patient was enrolled for less than 12

months, the actual duration was used. Duration was expressed in days and the denominator of 1000 catheter-days was used.

Ethics

Ethics approval was obtained at each site via the institutional review boards of the Centre hospitalier de l'Université Laval (CHUL), McGill University Health Centre (MUHC), and Centre hospitalier de l'Université de Montréal (CHUM). Written informed consent was obtained from patients prior to their enrolment into the Registry and data collection.

RESULTS

A total of 111 patients across 3 centers were receiving HPN in the province of Quebec at the time of data collection. This represented a point prevalence of approximately 13 HPN users per million population in Quebec, a value similar to the estimated Canadian prevalence (20, 26). A median of 5 (range 1-7) new patients were added per center in 2016, resulting in an overall incidence of 0.6 per million.

In total, 83 (74.8%) patients from Quebec agreed to enrolment in the Registry. Participation rates across centers ranged from 53% to 92%. The data presented below include only patients who consented to participation in the Registry.

Clinic organization

In Quebec, all 3 HPN centers were based in university-affiliated hospitals. Each center was led by a multidisciplinary team specialized in HPN. The overall organization generally consisted of physicians with expertise in PN, nurses, pharmacists and nutritionists. There was no standardized provincial protocol for the administration of HPN or patient monitoring. Individual PN suppliers varied, and were managed independently at each location. Nonetheless the overall PN clinic structure remained similar across the province.

Demographics and underlying etiology of intestinal failure

The mean patient age was 55.2 ± 14.4 years, with a predominance of females (66.3%). Patients had been on HPN for an average of 9.8 ± 7.5 years (Table 1). The vast majority had prior small

intestinal resections (70.3%) with a mean residual length of 77.3 ± 49 cm, and a comparable number also had prior colonic resections (61.2%) (Table 2).

The most frequent cause of intestinal failure was short bowel syndrome (71.6%), followed by motility disorders (21.0%). The remaining causes were mucosal disorders (4.9%) and tumors (2.5%) that included amyloidosis, radiation enteritis, autoimmune enteritis, and desmoid tumors.

Short bowel syndrome most commonly resulted from Crohn's disease, and mesenteric thrombosis (Table 3). Among motility disorders, the main etiology was primary chronic intestinal pseudo-obstruction (CIPO). In the Quebec population captured by the Registry, 47% of all motility disorders were from a genetic syndrome described almost solely among French Canadians. Chronic Atrial and Intestinal Dysrhythmia (CAID) syndrome is a condition caused by a homozygous founder mutation in the cohesion complex. Affected patients suffer from both sick sinus syndrome and CIPO. The genetic mutation in *SGOL1* has recently been described in a group of 16 French Canadians, with a geographic predominance in eastern Quebec (27).

Age and gender distributions were similar in Quebec and Canadian PN registry patients (Table 1). Short bowel syndrome was the primary cause of intestinal failure. In contrast, very few patients received HPN for malignancy related intestinal failure, a practice seen in certain Canadian centers. There were no cases of intestinal failure from surgical complications, or pancreatic disease. However, many cases classified under short bowel syndrome were often a result of surgical complications.

Statistically significant differences were detected in the distributions of certain etiologies when comparing Quebec HPN patients to those in the Canadian Registry (using all patient entries), with more short bowel syndrome in Quebec (Chi-square statistic 28.013, $p<0.00001$), more motility disorders (Chi-square statistic 16.325, $p=0.000053$) and less tumors (Fishers exact test $p< 0.00001$). The higher number of motility disorders is possibly driven by the regional prevalence of Chronic Atrial and Intestinal Dysrhythmia (CAID) syndrome.

Our findings contrast with the most recent Unites States HPN registry that reported the prevalence for short bowel syndrome at 28.6% and gastrointestinal cancers at 18.7%, and motility disorders at 11.1% (28). The US registry also noted high rates (7.2%) of intestinal failure from complications of bariatric bypass surgery, an indication not seen in the Quebec cohort.

Quality of life

Quality of life was measured by patients' HPN providers, using the Karnofsky Performance Scale (0-100). Scores of 80-100 suggested ability to work and care for self, 50-70: inability to work, but preserved self-care, and 10-40: inability to care for self (appendix 1). The mean Karnofsky score was 74.4 ± 15.3 (table 1). The majority (57.9%) of patients had a preserved quality of life with scores of 80-100, although 4% scored in the lowest category.

Parenteral nutrition prescription

Parenteral nutrition was administered most frequently (48.8%) using a 2-in-1 system dextrose-amino acid formulation. These patients either did not receive lipids, or had infusion of intravenous fat emulsions added via a separate bag. The 3-in-1 systems combining amino acids, dextrose and intravenous fat emulsions in the same container were used for 37.8% of patients. Overall, 13.4% of patients only required intravenous hydration with electrolytes, without any added lipids, amino acids, or dextrose (table 4). Almost all patients (90%) received additives to the PN bags such as multivitamins, vitamin K, and heparin. Details on trace elements are found in table 4.

Mean PN infusion frequency was 5.5 ± 1.7 days per week (median 6, range 2-7), over a mean 11.2 ± 2.5 hours (median 12, range 6-24). SMOFlipid® 20% (Fresenius Kabi) was the standard intravenous fat emulsion used, with only a few patients receiving Omegaven®. Parenteral nutrition provided a mean of 18.6 ± 11.6 kcal/kg/day (median 19.13), 0.81 g/kg/day of proteins and 50.4% of their calculated overall energy requirement. Only 4 (4.8%) patients solely relied on PN for caloric needs and had no oral intake.

Main differences with published Canadian data were the predominance of 2-in-1 delivery systems in Quebec (48.8% versus 3.3%), and overall lower calorie, protein, and trace element concentrations provided in the PN (Table 4) (24). In practice, the use of a 3-in-1 system that includes lipids within the same PN bag is less cumbersome to patients and favoured. Our findings highlight an important aspect of PN administration that can be improved provincially.

Catheter type and number of lumen

Vascular access for PN predominantly consisted of tunnelled catheters (88.8%) with a single lumen (92.5%) (Table 5). Peripherally inserted central catheters (PICCs) were used in a minority of patients (7.5%), often as a temporary vascular access in the context of CRBSI before re-insertion of a permanent catheter. Compared to global Canadian data, tunnelled catheters were significantly more common (Chi-square statistic 66.908, $p<0.00001$), and single lumen catheter use was also more frequent in Quebec (Chi-square statistic 63.964, $p<0.00001$). Moreover, Quebec PICC utilization rate was also lower than the rate reported among active Canadian Registry patients of 18%, as well as older Canadian data of 52.9% (24) and US values of 42.9% (28). Average vascular access duration was 4.0 ± 4.9 (95%CI 0.7 -27.1) years (Figure 1).

Complications

We documented a total of 84 hospitalizations among our patients in the prior 12 months, averaging at 1.05 ± 1.21 (range 0-6) hospitalization per patient. The mean CRBSI rate was 0.65 per 1000 catheter-year, corresponding to 0.21 event per patient per year. Only 25% of all hospitalizations result from a complication of PN. Line changes occurred at a rate of 0.31 per patient per year. Most patients (71.1%) did not require a line change.

Quebec CRBSI rates were notably lower than published Canadian rates of 0.97 per 1000 catheter days (24). However, they were comparable to the current rates seen among active Canadian Registry patients with 1.08 hospitalization and 0.31 CRBSI per patient per year.

Medication and teduglutide

We recorded medication use among PN patients (table 6). Close to one third of patients required immunosuppressors, narcotics, and anticoagulation. Antacids were used in 80% of patients, with

a predominance of proton-pump inhibitors (PPI). Teduglutide, a glucagon-like peptide 2 (GLP-2) analog for the treatment of short bowel syndrome was documented in 1 patient. Teduglutide has shown benefits in decreasing PN volume requirements in patients with SBS. Its low uptake in the Quebec cohort can be explained by several factors. First, it only became available in Quebec later relative to provinces like Ontario. Its approval also took place during the period of data collection for the Registry, and may be have been too early to capture it use. Together, the novelty of the medication, lack of experience with its use, high cost and potential side effects such as fluid overload, may have limited the uptake among clinicians in our cohort.

Exploratory analysis on CRBSI

We performed an exploratory analysis to identify factors associated with CRBSI in the Quebec patients using variables identified in the literature (10). We did not find any significant predictors of CRBSI.

DISCUSSION

This is the first report of Quebec HPN patients that can provide insight on local patient profiles and HPN program practice. Whereas HPN in Quebec was rare with a prevalence of 13 per million population, patients had received PN for a median time of 7.9 years. Our CRBSI rate of 0.65 per 1000 catheter-years remained on the lower range of rates reported in the literature of 0.38 to 4.58 (median 1.31)(10).

The Quebec cohort was comparable to the Canadian HPN population, with a predominance of female patients and a similar age distribution. Discrepancies were noted in the etiologies of intestinal failure, with more short bowel syndrome and motility disorders, but fewer malignancies. Differences were driven by local prevalence of certain conditions such as Chronic Atrial and Intestinal Dysrhythmia (CAID) syndrome and varying clinical approaches. For instance, palliative PN in the setting of incurable cancers were not routinely offered in Quebec.

Differences with Canadian data may also reflect changing practice over time. Indeed, in some instances we compared Quebec data with the full Canadian registry that encompasses older data

from the outset of the registry. The discrepancies may therefore be diluted by a change in practice over time rather than regional differences. For instance, our current data revealed low PN solutions manganese levels, whereas older Canadian data reported supra-therapeutic levels of manganese (25), which subsequently led to practice reassessment and manganese level adjustments.

This study that used the local Quebec registry has a few limitations. First, patient recruitment was incomplete because not all patients provided consent. Second, this first report used data from 2015 to 2017, and omitted older patient data that would have been useful to assess longitudinal outcomes; especially given the median time on PN was 7.9 (range 0.35 to 31.8) years. Comparisons with Canadian patients were limited by the availability of Canadian data. Low sample size and CRBSI rates decreased our power to detect predictors of infection. Lastly, combined Quebec data precluded the direct comparison between centers, as this was not the aim of the Registry.

The main strength of this registry was that it enabled us to describe HPN practice in Quebec (29). It provided an accurate reflection of local HPN practice because of the high participation rates across centers. Uniform definitions and measures were used, further strengthening our results by reducing the possibility for information bias. Furthermore, given the chronicity of the HPN, longitudinal participation in the Registry with data collection every 2 years, will permit the detection of trends and outcomes over time. Finally, this key benchmarking exercise provided a reference point for future studies and practice improvement. For instance, the current CRBSI rate of 0.65 per 1000 catheter days may evolve as we improve educational tools and introduce techniques such as antimicrobials locks to reduce catheter infection rates. By determining relevant and precise reference points, clinicians can target areas of practice that need improvement, and monitor progress.

Important practice parameters recorded in this study include quality of life (Karnofsky score), CRBSI rates, and hospitalization rates. Vascular access duration and time on HPN are also key surrogates of patient outcomes. Specific targets for improvement include a reduction of the proportion of patients on 2-in-1 delivery systems with separate lipids infusions, favouring instead

a 3-in-1 system, and eliminating the use of heparin locks (30). Finally, medications such as tedeglutide may completely alter practice and their use and impact must be closely documented.

Lastly, the local registry can be used to streamline care in Quebec. Indeed, the registry can promote exchanges between PN centers, allowing the benchmarking of best practice in HPN and also lead to the establishment of local practice standards.

CONCLUSION

In this report we have established the first profile of HPN patients in Quebec and local practice parameters. A total of 111 patients were enrolled in 3 different programs in Quebec, yielding a prevalence of HPN of 13 per million population. Compared to the rest of Canada, short bowel syndrome was also the main indication for HPN, but Quebec showed greater motility disorders and less cancer patients. Major complication rates are 0.65 CRBSI per 1000 catheter days and a mean hospitalization rate of 1.05 per patient per year, in keeping with national values. This is an important benchmarking experience in Quebec PN. The registry will be useful to provide longitudinal data and define practice standards.

TABLES AND FIGURES

Table 1. Patient demographics from Quebec home parenteral registry

Characteristics	Quebec patients	Active patients from Canadian Registry (n=289) (2016-2018)
	Mean ± SD or total (%)	**Median (Q1,Q3)**
Age (years)	55.2 ± 14.4 (median 50, min 19 max 85)	58 (47,67)
Time on PN (years)	9.8 ± 7.5 (median 7.9, min 0.35 max 31.8)	
Time on PN distribution (years)		
≤5	25 (32.0%)	
>5 to 10	22 (28.2%)	
>10 to 15	13 (16.7%)	
>15	18 (23.1%)	
BMI	23.0 ± 3.0	21.5 (19.7,24.3)
Male	28 (33.7%)	33.2%
Female	55 (66.3%)	66.8%
Quality of life		
Karnofsky score	74.4 ± 15.3	
Karnofsky score distribution		
Able to work and care of self: 80-100	44 (57.9%)	
Unable to work, able to care for self: 50-70	29 (38.1%)	
Unable to care for self: 10-40	3 (4.0%)	

Table 2. Small bowel and colon anatomy

Anatomy	Total (%) or mean ± SD
Small bowel intact	17 (20.7%)
Small bowel resection	65 (70.3%)
Residual small bowel length (cm)	77.3 ± 49 (n=39)
Colon intact	31 (38.8%)
Colon resection	49 (61.2%)
Ostomy bag	31 (37.5%)
Ostomy bag type	
Ileostomy	17 (54.8%)
Colostomy	7 (22.6%)
Jejunostomy	6 (19.4%)
Gastrostomy venting tube	1 (3.2%)

Table 3. Etiology of intestinal failure and short bowel syndrome

Etiology of intestinal failure	Total (%)
SBS	58 (71.6%)
Motility disorder	17 (21.0%)
Mucosal disorder	4 (4.9%)
Tumor	2 (2.5%)
Etiology of short bowel syndrome	**Total (%)**
Crohn's disease	28 (48.3%)
Mesenteric thrombosis	15 (25.8%)
Volvulus	7 (12.1%)
Surgical complication	4 (6.9%)
Other	4 (6.9%)

Table 4. Parenteral nutrition prescription

HPN prescription	Quebec patients	Canadian patients 2011-2014(24)
	Mean ± SD (range) (median)	**Median (Q1,Q3)**
Duration of infusion (hr/day)	11.2 ± 2.5 (6-24) (median 12)	12 (12, 13)
Infusion frequency (days/week)	5.5 ± 1.7 (2-7) (median 6)	7 (7,7)
Amino acid (g/kg/day)	0.81 ± 0.47 (0-1.70) (median 0.82)	1.3 (1.0, 1.6)
Dextrose (g/kg/day)	3.44 ± 3.18 (0-8.15) (median 3.18)	
Lipids (mL/kg/day)	1.81 ± 2.17 (0-5.89) (median 1.31)	
Total calories from TPN (kcal/day)	1099 ± 731	
Total volume from TPN (mL/day)	1642 ± 887	
Calories per kg (kcal/kg/day)	18.6 ± 11.6	25 (18.6, 30.6)
Volume per kg (mL/kg/day)	27.6 ± 14.7	
Method of delivery	**Mean (%)**	**%**
Hydration only	11 (13.4%)	
2-in-1	40 (48.8%)	3.3%
3-in-1	31 (37.8%)	94.6%
Oral intake and enteral nutrition	**Mean ± SD**	
Calories from oral intake (kcal/kg/day)	17.5 ± 11.4	
Total calories from oral intake (kcal/day)	1050 ± 678	
	Total (%)	**%**
Patients with no oral intake	4 (4.8%)	21.4%
Patients with enteral nutrition	0 (0%)	
Energy requirement	**Mean ± SD**	**Median (Q1,Q3)**
Calculated energy requirement (kcal/day)	1954 ± 566	
Calculated energy requirement per weight (kcal/kg/day)	32.0 ± 7.2	
Percent of energy from TPN (%)	50.4 ± 31.5	86.7 (67.7,98)
Percent of energy from oral (%)	49.6 ± 31.5	
Trace elements (umol/day)	**Mean ± SD (median)**	**Median**
Zinc	42.6 ± 27.86 (42.0)	76.50
Manganese	0.31 ± 1.44 (0.0)	7.80

Selenium	0.95 ± 0.73 (0.76)	0.76
Chromium	0.15 ± 1.30 (0.0)	0.19
Copper	10.67 ± 6.80 (11.24)	15.74
Iodine	0.13 ± 0.21 (0)	0.59
TPN additive	**Total (%)**	
Any TPN IV additive	72 (90.0%)	
Multivitamin IV	72 (88.9%)	
Vitamin K IV	45 (56.3%)	
Heparin IV	5 (6.0%)	
Other IV	1 (1.2%)	

Table 5. Vascular access

Vascular access method	Total (%)
Tunneled catheter	71 (88.8%)
Peripherally inserted central catheter (PICC)	6 (7.5%)
Implanted catheter	2 (2.5%)
Other	1 (1.2%)
Number of catheter lumen	
1	74 (92.5%)
2	5 (6.2%)
3	1 (1.3%)
Mean vascular access duration± SD (year)	4.0 ± 4.9 (95%CI 0.7 -27.1)

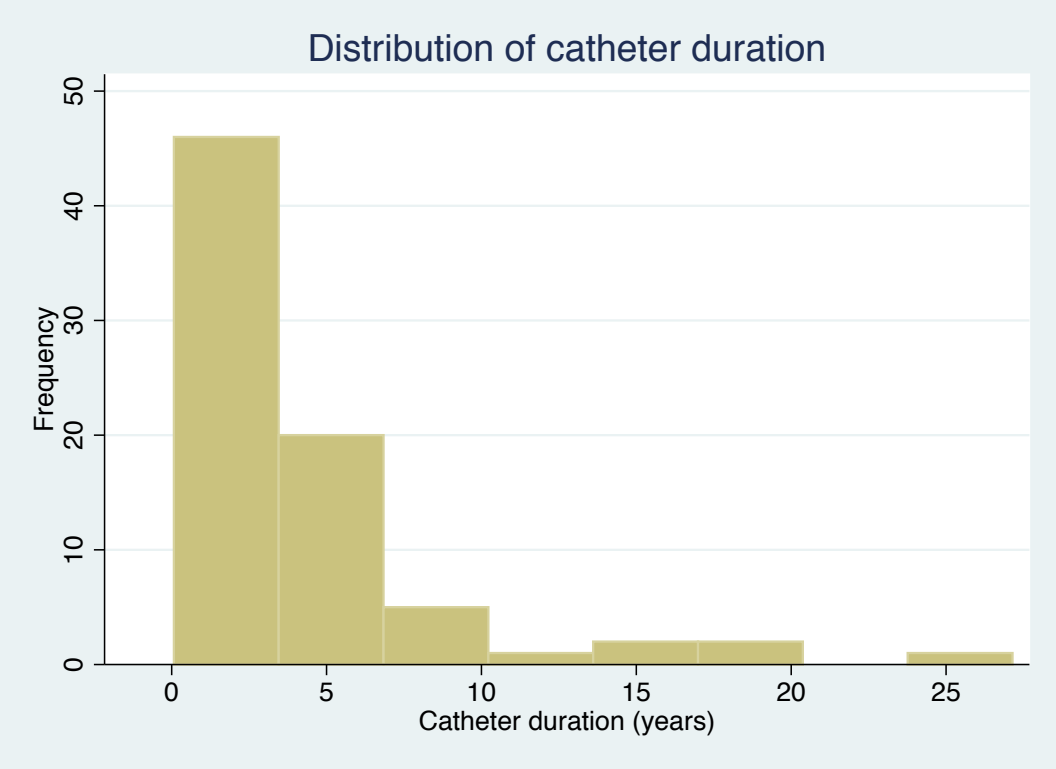
Table 6. Medications

Medications	Total (%)
Immuno-suppressors	25 (30.1%)
Anti-TNF	11 (13.2%)
Steroids	6 (7.2%)
Other	8 (9.7%)
Antidepressants	25 (30.9%)
Narcotics	25 (30.1%)
Sedatives	35 (42.2%)
Narcotics and sedatives	15 (18.1%)
Anticoagulation	28 (33.7%)
Antacids	66 (80.5%)
PPI	64 (77.1%)
Intravenous PPI	5 (7.8%)
H2RA	3 (3.6%)

Anti-TNF: anti-tumor necrosis factor, H2RA: Histamine 2 receptor antagonist, PPI: proton pump inhibitor

FIGURE

Figure 1. Central vascular access duration



Bridge section 1 – CRBSI risk factors, prevention and antimicrobial locks

Catheter related blood stream infections (CRBSI) represent the most common serious complication for patients on HPN. The reported CRBSI rates range from 0.38 to 4.58 events per 1000 catheter-days(10). In the Quebec population CRBSI rates were 0.65 per 1000 catheter-days. It is estimated that each episode of catheter infection increases health care costs by 50,000$ (31). CRBSIs are generally treated with antibiotic therapy, and often result in hospitalization and catheter removal. Furthermore, recurrent CRBSI is a criterion of failure of HPN and is considered an indication for intestinal transplantation (30).

The diagnosis of CRBSI requires a positive blood culture of the catheter tip, or detection of the same microorganism in blood cultures from the catheter and peripheral vein, in the context of clinical symptoms of infection where no alternative source is identified (1).

Risk factors have been described among various HPN cohorts. A systematic review that included 39 studies in the adult HPN setting reports several risk factors classified into patient characteristics, venous access, PN regimen and follow-ups. Increased CRBSI are noted in motility disorders, non-malignant conditions and Crohn's disease. Similar effects are seen in patients using opiates or sedatives, as well as patients with shorter residual bowel length. With regards to catheter characteristics, authors noted that larger catheter size, increased number of lumens, and both jugular catheter site and implanted catheters increase infection risk. Proper training and follow-up in a dedicated HPN program as well as access to specialized nurses are protective factors. Finally, the frequency of PN infusions also seems to impact CRBSI occurrence.

More recent studies report additional risk factors such as the presence of stomas and increased weekly PN infusions (32); frequency of lipid infusion, catheter use for blood sampling or infusion of medications (33); presence of ulcers, older age, anticoagulant use, public insurance coverage (34), male sex and underlying malignancy(35). A Canadian study identified socio-economic risk factors for CRBSI such as receiving social assistance or welfare (36). Many of these reports had small sample sizes and heterogeneous patient populations, which limit their

external validity. In 2011, the American Society for Parenteral and Enteral Nutrition (ASPEN) established a large HPN registry called SUSTAIN to collect data on adult and pediatric HPN (28). In a recent report, they have noted higher CRBSI rates in male, children, blacks and patients on Medicaid (28).

Aside from patient characteristics, parenteral nutrition itself has also been suggested as a risk factor for CRBSI though available data are insufficient to draw firm conclusions (37, 38). Furthermore heparin lock solutions, once routinely used, have been linked to greater infection rates due to biofilm formation (39). Both elements are important when extrapolating CRBSI data from other patient populations such as hemodialysis patients and older studies using heparin.

A detailed understanding of local patient profiles and complication rates are a fundamental step to improving patient care. Results from the Quebec cohort of the Canadian HPN registry in Chapter 2 provided baseline patient characteristics and established local CRBSI rates. While exploratory analyses did not detect any significant risk factors, we have identified several characteristics that may impact local CRBSI rates. Risk factors that are present in our patients include greater frequency of motility disorders, and the high prevalence of certain medication uses such as anticoagulants in 33.7%, narcotics in 30.9% and sedatives in 42.2%. Our CRBSI rates remain low. This may result from preferential use of tunnelled catheters (88.8%) with single lumen dedicated to PN (92.5%), and a predominantly female population (66.3%). Detailed CRBSI rates and hospitalization rates are discussed in the Bridge section 2.

Irrespective of risk factors, the fundamental principles in CRBSI prevention consist of patient and staff education, and proper hand-washing, sterilization and catheter handling techniques (30). Few other techniques such as catheter filters and routine line changes have been shown to reduce infection rates.

Antimicrobial locks, have been used in central venous catheters as a mean to decrease infection rates by instilling an antimicrobial agent in particular taurolidine and ethanol, when the catheter is not in use to reduce luminal biofilm formation. The most recent ESPEN chronic intestinal failure guidelines stipulate that taurolidine locking may be used as a preventative measure to

reduce CRBSI, particularly in high-risk patients with repeated CRBSI (30). Yet, the grading of the evidence was low. Indeed, several studies were conducted among HPN patients with variable results but there are no systematic reviews on the topic.

As such, in Chapter 3, we present a systematic review on antimicrobial locks as prophylaxis for CRBSI in PN patients.

Chapter 3 – Systematic review of antimicrobial lock solution as prophylaxis for catheter related blood stream infections

ANTIMICROBIAL LOCKS FOR THE PREVENTION OF CATHETER-RELATED BLOOD STREAM INFECTIONS (CRBSI) IN PATIENTS ON PARENTERAL NUTRITION – A SYSTEMATIC REVIEW

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Y. Lu, C.S. Palumbo, M. Martel, and A. Barkun equally contributed to the conception and design of the study; M. Sewitch and E. B. Marliss contributed to the conception of the study; Y. Lu, M. Martel, and C. S. Palumbo contributed to the acquisition and analysis of the data; Y. Lu, M. Martel, C. S. Palumbo, and A. Barkun contributed to the interpretation of the data; Y. Lu, M.

Martel, M. Sewitch, E. B. Marliss, and A. Barkun drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

ABSTRACT

Background: Catheter-related blood stream infections (CRBSI) in patients receiving parenteral nutrition (PN) may be prevented by the use of antimicrobial lock solutions.

Objective: To conduct a systematic review to assess antimicrobial lock solutions in preventing CRBSI in PN.

Data sources: We performed a systematic search of EMBASE, MEDLINE, CENTRAL, ISI Web of Knowledge to July 2017. Search terms included PN, citrate, ethanol, taurolidine, antibiotic and antimicrobial locks.

Study selection: We included randomized controlled trials (RCT) and observational studies evaluating antimicrobial locks compared to control solutions (heparin or saline) in preventing CRBSI in adult and pediatric PN patients.

Data extraction and data synthesis: Two reviewers independently performed study selection and data extraction. Study quality was assessed using the Cochrane Risk of bias tool and ROBINS-I for RCTs and observational studies, respectively.

Results: Overall, 23 studies (3 RCTs, 20 observational) were selected (601 patients); 12 assessed an ethanol lock solution, 10 taurolidine ± citrate, one vancomycin and one tobramycin.

All 17 studies in patients at high-risk for CRBSI showed lower rates in the antimicrobial lock group (significant in 16). In patients not at high-risk for CRBSI, 2/7 studies were positive and 5/7 did not detect significant differences between groups. All studies were at high risk of bias, and heterogeneity precluded pooling of data by meta-analysis.

Conclusion: Insufficient evidence was found to support the benefit of antimicrobial locks as prophylaxis for CRBSI in PN patients. High quality studies are needed, as most data were observational, with three heterogeneous RCTs precluding a meta-analysis.

INTRODUCTION

Parenteral nutrition (PN) is a treatment that provides intravenous nutrients, and fluids to patients with intestinal failure. PN is delivered through a central venous catheter, and is associated with several complications (9). Catheter-related blood stream infections (CRBSI) are the most common serious complication for patients on PN. Reported CRBSI rates range from 0.74 to 3 per 1000 catheter-days in the population of patients on chronic HPN (35). CRBSI are associated with increased morbidity, mortality and costs resulting from hospitalization (10, 12, 40). Antimicrobial locks have been used to try to prevent CRBSI. Locks involve instilling an antimicrobial solution into the catheter lumen, when not in use, to prevent bacterial colonization and biofilm formation, thereby reducing the risk of CRBSI. Some studies have supported the benefits of antimicrobial locks, but no clear recommendations exist on their use.

A 2011 multi-society guideline on the prevention of catheter-related infections concluded that study heterogeneity and methodological limitations in the published literature "preclude a general recommendation" for antimicrobial locks, though suggested it may be used in high-risk patients based on weak data (41). Earlier guidelines on PN from the European Society for Clinical Nutrition and Metabolism (ESPEN) were unable to provide a general recommendation on the use antimicrobial locks (42) for similar reasons. Since then eight new studies have been published (43-50).

The lack of consistent recommendations arises from the current limited and largely observational body of literature on the use of antimicrobial locks (10). Existing systematic reviews are not specific to PN patients, as they include heterogeneous populations such as hemodialysis, cancer, and critically ill patients (51, 52). The findings may therefore not apply to PN patients, a group that displays additional risk factors for CRBSI such as underlying intestinal motor disorders, the presence of stomas, as well as exposure to nutrient rich PN solutions (10, 41). We conducted a systematic review to assess the effectiveness of antimicrobial lock solutions versus controls (heparin or saline) in the prevention of CRBSI in adult or pediatric patients with a central venous catheter for the administration of PN.

METHODS

We conducted a systematic search of the literature to identify relevant articles.

Eligibility criteria

We included randomized controlled trials and observational studies of adult and pediatric patients receiving PN through a central venous catheter. The intervention of interest was antimicrobial lock solutions, namely ethanol, taurolidine, citrate, as well as antibiotics. We limited the intervention to the setting of CRBSI prevention. We excluded non-human studies, and studies in hemodialysis and cancer patients, antimicrobial-impregnated tubing or cleansing solutions, and locks for treatment of established infections. Heparin-containing or saline solutions were accepted as controls. The outcome measure was CRBSI per 1000 catheter-days.

Search strategy

We systematically searched the electronic databases (from earliest date to July 2017) EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), ISI Web of Knowledge for randomized controlled trials (RCTs) and observational studies on the use of antimicrobial locks in the prevention of CRBSI in patients receiving PN. We used the following medical subject headings and keywords: “parenteral nutrition” OR “total parenteral nutrition” OR “home parenteral nutrition” AND “citrates” OR “citric acid” OR “citrate” OR “citric acid” OR “sodium citrate” OR “alcohol” OR “ethanol” OR “thiadiazine” OR “ taurolidine” OR “taurolin” OR “tauroflex” OR “tauroline” OR “antibiotic lock” OR “antibiotic-lock” OR “antimicrobial solution” OR “antibiotic solution”, detailed in **Appendix 2**.The search was limited to PN, and to articles published in English or French. Studies published only in abstract form, and those with less than five patients were excluded.

Study selection

Two independent reviewers (CSP and YL) screened the titles and abstracts of studies. Studies meeting selection criteria or requiring clarification were retrieved in full, and assessed for eligibility. A third party (AB) resolved disagreements.

Data extraction

Two reviewers independently performed data extraction. We recorded patient demographics, antimicrobial and control solution details, as well as study design, and size, CRBSI rates, adverse events and follow-up.

Data synthesis and CRBSI risk level

We classified studies according to patient risk for CRBSI: 1) *high-risk* studies that enrolled only patients with recent or recurrent CRBSI, and 2) *non-high risk* studies that enrolled all-comers regardless of prior CRBSI. We compared CRBSI rates in treatment and control groups.

Heterogeneity

We planned to assess statistical heterogeneity between studies using the I^2 statistic with a I^2 value greater than 50% to suggest moderate to high statistical heterogeneity, provided that there are no major clinical and methodological heterogeneity.

Risk of bias in individual studies

Quality assessment was performed by two independent reviewers (CSP and YL) using the Cochrane Risk of bias tool (53) and RevMan (54) for randomized trials (**Appendix 3**), and the Risk of Bias in Non-randomized Studies – of Interventions assessment tool (ROBINS-I, version March 7, 2016) (**Appendix 4**) (55) for non-randomized studies.

RESULTS

The literature search identified 860 citations, 122 studies were reviewed in full, and 23 were selected (**Figure 1**). A total of 3 RCTs and 20 observational studies were included: 16 in patients at high-risk for CRBSI and 7 in non high-risk patients, totaling 601 patients. The 23 studies evaluated a total of 24 antimicrobial locks: 12 ethanol locks, 10 taurolidine (± citrate), one vancomycin and one tobramycin.

We found substantial study heterogeneity and issues with methodology quality. The three RCTs findings could not be pooled because of differing patient populations. The remaining observational studies were at moderate to critical risk of bias. For these reasons, we did not

perform a meta-analysis. Similarly, we did not assess statistical heterogeneity because of the important clinical and methodological heterogeneity.

We present key study characteristics, and summarize results stratified by patient risk level for CRBSI (high-risk and non high-risk), type of antimicrobial lock, and study design. Available data did not permit statistical assessment for publication bias, as the standard error was frequently not reported.

Description of included studies

Among the 23 included studies were 3 RCTs (2 open-label, 1 double-blind trial) and 20 observational studies. Details of the individual studies can be found in **Tables 1** and **2**. Most studies enrolled HPN patients; 2 also included hospitalized PN patients (56, 57). There were 11 pediatric (n=142 patients) and 12 adult (n=459 patients) studies.

Sixteen studies enrolled patients at high-risk of CRBSI as defined by a history of recent or frequent CRBSI. Seven enrolled non-high risk patients, namely, all-comers irrespective of prior CRBSI history. One study selected patients with ≤ 1 CRBSI/patient/year, and was classified as a non-high risk study. Definitions of CRBSI risk are listed in **table 3**.

The antimicrobial locks varied markedly between and within studies with different concentrations, volumes, dwell times and administration frequencies (**Table 1** and **Table 2**). The most commonly used locks were 70% ethanol or a mixture of taurolidine and citrate. The controls used either heparin-containing solutions (14 studies) or saline (5 studies).

CRBSI rate calculations were heterogeneous. The denominator was either mean or median catheter-days per patient, cumulative catheter-days, or not specified (43, 56, 58, 59). Only one study controlled for confounding, reporting an adjusted incidence ratio for heparin compared to taurolidine of 5.9 (95% confidence interval, 3.9–8.7) (60).

Duration of follow-up ranged from 97days (58) to 1086 days (61) (**Tables 4** and **5**), but was often unreported. Follow-up duration frequently differed between treatment and control groups within a study (**Tables 4** and **5**).

Risk of bias

Randomized controlled trials

The risk of bias assessments are found in **Appendix 3, Figures 2 and 3**. All RCTs featured elements at high risk of bias. Most notably, blinding was not performed or was incomplete, and sample sizes were small. Two studies adopted an open label design because the treatment and control lock solutions were deemed too dissimilar to cover due to the smell (62, 63). Another double blind RCT performed blinding but it was unlikely maintained due to the "distinct odor of ethanol" (58). Two studies were stopped early after an interim analysis (one showing efficacy (62) and one futility (58)), potentially biasing the treatment effect obtained. Importantly, the primary endpoint (CRBSI rate) in the study by Bisseling *et al.* failed to reach the adjusted statistical significance threshold of the interim analysis, and only the secondary endpoint (infection free survival) yielded significant differences. Moreover, sample sizes were low (range 30 to 38) in all trials. Two trials did not reach their power calculation targets (58, 62), and one did not provide such calculations (63).

Observational studies

The evaluation for bias for non-randomized studies using the ROBINS-I tool revealed moderate to critical risk of bias in all studies. Most were retrospective, employed a before-and-after design and did not control for confounding, although 1 had a prospective component (56). A single study controlled for confounding by providing an adjusted treatment effect (Olthof 2014)(60). The results are summarized in **Figures 4 and 5**.

Study results

We included 23 studies that report 24 separate outcomes. CRBSI rate in the treatment and control groups of each study are shown in T**ables 4 and 5**. All studies in high-risk patients showed lower CRBSI rates with antimicrobial locks, with all but one reaching statistical

significance (43). Of the seven studies in non high-risk patients, only two demonstrated statistically significantly fewer CRBSI in the treatment groups (60, 64) (**Figures 6 and 7**).

High-risk patients

Ethanol

No RCTs were identified. All 8 observational studies showed lower event rates in the treatment group (43-46, 59, 61, 65, 66), and all reached statistical significance, except one study that did not report such information (43). CRBSI rates ranged from 0.47 to 2.70 in the ethanol lock group and 3.53 to 10.3 in the control group.

Taurolidine

One open-label taurolidine RCT was identified (62). The primary endpoint of CRBSI rate was lower in the treatment group at 0.19 versus 2.02 per in controls (heparin), p=0.008. It also showed longer mean infection-free survival in the taurolidine arm (641 (95% confidence interval (CI): 556-727) days versus 175 (95% CI: 85-266) days in the control group, log-rank p<0.0001). The study was terminated early after an interim analysis showed significant benefits. Authors set an adapted statistical significance threshold of p<0.0056 rather than p<0.05. As a result, only the secondary outcome of infection free survival reached statistical significance (p<0.001), while the primary endpoint of CRBSI incidence rates did not (p=0.008).

The six observational taurolidine studies (47-50, 67, 68) showed fewer CRBSI in the taurolidine group compared to controls. Rates ranged from 0 to 1.1 in treatment group and from 2.02 to 10.8 events in controls.

Other antimicrobials

Among high-risk patients, both the vancomycin (43) and tobramycin (69) lock studies yielded statistically significant results favoring lock therapy.

Non high-risk patients

Ethanol

One RCT enrolled non high-risk patients (58). The study was underpowered and stopped early after an interim analysis.
All 3 observational studies were also negative. Mokha *et al.* reported rates of 4.59 versus 10.56 in treatment and control groups, respectively, p=0.57 (57). Ardura *et al.* reached statistical significant results only in the subgroup treated for longer than three months (56), and Mouw *et al.* did not perform statistical analyses due to low sample size (70).

Taurolidine
One open-label RCT by Klek *et al.* did not detect a benefit for taurolidine. The study specifically enrolled patients with infrequent CRBSI (<1 CRBSI per patient per year) (63). Overall rate was low, with only one event (0.273 per 1000 catheter-days) in the taurolidine plus citrate arm (p=1.000).

Two observational studies showed significantly lower rates in the taurolidine group (60, 64). One reported an adjusted infection incidence ratio of heparin compared to taurolidine locks of 5.9 (95% confidence interval, 3.9–8.7), after controlling for risk factors(60). This was the only observational study to control for confounding.

Studies using other types of antimicrobial locks in the non high-risk population were not found with our search strategy.

Complications
Nineteen of 23 studies documented the occurrence of complications during the follow-up period (**Table 6**).

One study (57) showed higher mechanical complications and catheter changes with ethanol. One taurolidine study documented lower catheter occlusions in the taurolidine group with 0.1 (95% CI 0.1-0.2) occlusions per access year versus 0.2 (95% CI 0.2-0.3) in controls (60). All other studies did not perform statistical testing for complications.

DISCUSSION

CRBSI is a serious complication of PN that results in considerable mortality and morbidity, and generates substantial costs. Patient and caregiver education, along with adequate hand washing and disinfection are paramount in CRBSI prevention (1, 71). Antimicrobial locks are easy to implement and have been used to prevent CRBSI. However, the evidence supporting the prophylactic use of antimicrobial locks in PN patients has been inconsistent

We retrieved 23 studies, including 3 randomized trials (**Tables 1 and 2**). This systematic review provides a structured summary of the existing literature and highlights important limitations when interpreting the data.

Among patients at high-risk for CRBSI, all but one study favored antimicrobial lock treatment, reaching statistical significance. However, for non high-risk patients, a minority (2/7 studies) reached this conclusion (60, 64). Notably, both RCTs did not detect a benefit for antimicrobial locks (58, 63) (**Figure 6 and 7**). Interestingly, in the non high-risk group, none of the 4 ethanol studies reached statistical significance.

Methodological considerations

While it appears that the beneficial effect of antimicrobial locks as prophylaxis for CRBSI may be better established in high-risk patients than in non high-risk populations, individual study characteristics and methodological issues need to be considered to appropriately interpret the results.

Methodologically, the overall level of evidence was low, with mostly observational studies at high risk of bias. Observational studies carry the risk of uncontrolled confounding that can bias results, especially true in retrospective before-and-after comparisons, which were used in most studies. Patient selection and treatment allocation were non-random, and determined by the clinicians introducing selection bias and confounding by indication.

Several risk factors for CRBSI (10) exist. Yet only one study (60) controlled for risk factors. Notably, one study did not control for oral antibiotic use occurring in 75% of their patients (56). Additionally, before-and-after designs cannot control for changes in practice over time that

influence outcomes, such as catheter manipulation techniques and CRBSI counseling. For instance, one study introduced locks along with a CRBSI "prevention bundle", making it impossible to extract individual effects attributable specifically to the treatment (56). The ROBINS-I risk of bias tool confirmed possible bias results with findings of moderate to critical risk among the observational studies.

The three randomized trials had limitations, including small sample size, and were at high risk for bias principally because of incomplete blinding, early trial discontinuation, and selective reporting of positive results. Practical challenges in maintaining blinding, such as the odor of ethanol, limited study design options. Multicenter trials with uniform definitions and lock solutions would allow reaching greater sample sizes.

Study characteristics and heterogeneity

There was substantial heterogeneity in study methodologies and clinical parameters precluding a meta-analysis. Overall treatment effect is difficult to ascertain and compare with such heterogeneity. Indeed, the definitions for CRBSI risk status (high-risk, and non high-risk) lacked standardization, and varied among studies.

Antimicrobial lock solutions differed between and within studies. For instance, lock composition, volume, frequency of use, and dwell times were heterogeneous, potentially affecting outcomes. Increased frequency of PN infusion days per week raises catheter manipulations risking line contamination, and results in shorter antimicrobial dwell times. The control solutions may also impact outcomes, as heparin has been associated with biofilm formation and increased infections (30, 39). The use of different controls limits the validity when comparing studies.

Discrepancies in the follow-up durations of treatment and control groups (**Tables 1 and 2**) can also bias results if CRBSI risk varies over time. Indeed, the measure of "events per 1000 catheter-days" assumes that the CRBSI rate remains constant over time regardless of follow-up duration, but this has to be confirmed. Different denominators (per catheter-days per patient or per total catheter-days) also preclude direct comparisons between studies. Equivalent total

catheter-days values can result from a small group of patients followed for a longer duration or a larger group of patients followed for a short duration. The interpretation of event rates in these settings are likely different, as a shorter follow-up period may not detect later events.

Comparison with other published studies

Our results are in contrast to the existing literature. To our knowledge, only one meta-analysis exclusively enrolled PN patients. This meta-analysis with four pediatric observational studies (61, 65, 66, 70) reported a mean CRBSI rate difference of 7.67 events per 1000 catheter days (95% CI 5.87, 9.47; p<0 .00001) favoring ethanol locks over heparin (72). However, the study combined high-risk with non high-risk studies, and included one study in which the authors had deferred statistical analyses due to its sample size of only 5 (70). Another meta-analysis of six taurolidine RCTs only included one PN study (62). It suggested significantly lower CRBSI rates with taurolidine compared to heparin locks (RR 0.34, 95% CI 0.21–0.55)(51), but patient risk status was not considered. A large meta-analysis with 23 trials assessing multiple antimicrobial lock solutions detected a reduction of 69% in CRBSI rates (RR 0.31, 95% CI0.24–0.40) with lock use (52). Again, this meta-analysis included mainly hemodialysis studies (16 studies), with only one PN study. Our systematic review exclusively assessing PN patients has yielded more variable results and questions whether the same benefits can be applied in this patient population. As PN solutions could be a risk factor for CRBSI (37, 38), the external validity of findings from the studies cited in non PN patients is limited, and extrapolation is not justified without equivalent data specifically in this patient group.

Current guidelines on central venous catheter care in PN are based on scarce evidence and expert opinion, and remain divided. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on intestinal failure state that “catheter locking with taurolidine may be used”, and do not recommend the use of 70% ethanol due to complication risks (1). In contrast the American Society for Parenteral and Enteral Nutrition (ASPEN) has suggested ethanol locks in high-risk pediatric patients (73).

Limitations and future implications

Our systematic review is limited by, small sample size studies, and heterogeneity among the included studies and low quality studies. These limitations reflect the challenges common to studies in patients with rare conditions.

Nevertheless, our review highlighted methodological issues that can serve to inform future research. Authors should strive for uniform definitions for CRBSI measures and patient risk status, and employ comparable antimicrobial solutions (i.e. similar concentration, volume, frequency of use and dwell time) and control solutions with saline (30, 39). The reporting of CRBSI should be standardized across studies to facilitate comparison. When randomized trials are not possible, investigators should aim to conduct high-quality prospective observational studies that minimize confounding. For instance, a multi-center approach combining several HPN cohorts could yield sufficient power to detect clinically relevant and statistically significant outcomes.

CONCLUSION

The results of our systematic review of 3 randomized trials and 20 observational studies on the use antimicrobials locks as prophylaxis for CRBSI in PN patients are inconclusive. Current data do not consistently demonstrate benefits attributable to antimicrobial lock use, particularly in non high-risk patients. Even in high-risk patients, the protective effects in reducing CRBSI need to be confirmed in future studies due to methodological limitations of the published studies.

Future research should also strive to answer additional, targeted questions such as the efficacy of individual antimicrobial locks and their safety profiles.

TABLES AND FIGURES

Table 1. Characteristics of studies in high-risk* patients for catheter-related blood stream infections

Study name	Year	Treatment (locks)	Participants	Study design	Number of partici-pants	Controls (locks)	Intervention details
Davidson (43)	2017	Ethanol[a]	Adult	Observational retrospective before and after study [b]	8	Not specified	70% ethanol, 3mL when catheter not used Dwell: average 12.3 ± 1.7 hours
John (44)	2012	Ethanol	Adult	Observational retrospective before and after study	31	Saline	70% ethanol,3mL Each infusion days Dwell: average 10 hours
Opilla (59)	2007	Ethanol	Adult	Observational retrospective before and after study	9	Saline	25%-70% ethanol, 3 mL 7 days/week (except 2 patients 1-2x/week) Dwell: 2-4 hours
Abu-El-Haija (45)	2014	Ethanol	Paediatric	Observational retrospective before and after study	7	Heparin	70% ethanol, volume to fill catheter Daily Dwell: minimum 4 hours
Pieroni (46)	2013	Ethanol	Paediatric	Observational retrospective before and after study	14	Heparin	70% ethanol, 1-2 mL Once a week Dwell: 2 hours
Cober (65)	2011	Ethanol	Paediatric	Observational retrospective before and after study	15	Not specified	70% ethanol, volume to fill catheter Daily Dwell: at least 2 hours
Wales (61)	2011	Ethanol	Paediatric	Observational retrospective before and after study	10	Heparin	70% ethanol, 1-3mL Daily Dwell: minimum 4 hours
Jones (66)	2010	Ethanol	Paediatric	Observational retrospective before and after study	23	Not specified	70% ethanol, volumeto fill catheter 3x/week Dwell: minimum 4 hours
Bisseling (62)	2010	Taurolidine	Adult	Open-label RCT	30	Heparin	2% taurolidine (Taurocept®), 5mL Lock frequency as per usual treatment
Saunders (49)	2015	Taurolidine + citrate	Adult	Observational retrospective before and after study	22	Saline	Taurolidine with citrate, tauroline, and TauroLock™ (taurolidine and 4% citrate) Lock frequency as per usual treatment
Al-Amin (47)	2013	Taurolidine + citrate	Adult	Observational retrospective before and after study	9	Heparin	TauroLock™ (2% taurolidine and 4% citrate), 1.5mL After each infusion Dwell: until next infusion

Study name	Year	Treatment (locks)	Participants	Study design	Number of partici-pants	Controls (locks)	Intervention details
							(around 12 hours)
Toure (48)	2012	Taurolidine + citrate	Adult	Observational retrospective before and after study	15	Saline	Taurolidine 1.35% and sodium citrate 4%, 3mL Frequency: 1-7x/week (after each infusion for 7/15 patients, and 1x/week for 8/15 patients) Dwell: until next infusion (around 12 hours)
Cullis (67)	2011	Taurolidine + citrate	Adult	Observational retrospective before and after study	7 [c]	Heparin	TauroLock™ (taurolidine and 4% citrate)
Jurewitsch(68)	2005	Taurolidine	Adult	Observational retrospective before and after study	7	Not specified	Taurolidine 2% (Taurolin®), 3mL Daily Dwell: 12 hours
Chu (50)	2012	Taurolidine	Paediatric	Observational retrospective before and after study	19	Heparin	Taurolidine 10U/mL, 0.7-1mL Daily Dwell: at least 12hr
Davidson (43)	2017	Vancomycin [a]	Adult	Observational retrospective before and after study	41	Not specified	Vancomycin 3-4mL Entire time catheter not in use
Onder (69)	2007	Tobramycin	Paediatric	Observational retrospective before and after study	5	Heparin	Tobramycin 5mg/mL, 0.15mL and TPA 2mg/mL, to fill remaining catheter volume Daily (alternating between 2 lumens) Dwell: 4 hours

Abbreviation: CRBSI: catheter-related blood stream infection

[*] Patients were defined as high-risk if they had recent or recurrent episodes of CRBSI

[a]The study included a subgroup with ethanol locks and a subgroup with vancomycin locks. The results are reported separately in the table. The study also assessed other antimicrobial locks (ciprofloxacin, cefepime, capsofungin, and gentamicin), but authors did not provide individual outcome data for these locks, and the results are not presented.

[b] Before and after study design refers to observational study comparing the outcome before and after the implementation of particular intervention in the same group of patients.

[c] There was a total of 49 patients in the study, however complete before and after data were only available for 7 patients

Table 2. Characteristics of studies in non high-risk patients* for catheter-related blood stream infections

Study name	Year	Treatment (locks)	Participants	Study design	Number of participants	Controls (locks)	Intervention details
Salonen (58)	2017	Ethanol	Adult	Blinded RCT	38	Heparin	70% ethanol, 3mL after parenteral nutrition infusion until next infusion
Mokha (57)	2017	Ethanol	Paediatric	Observational retrospective before and after study	13	Heparin	70% Ethanol, 1-3mL After each infusion Dwell: 2 to 4 hours
Ardura (56)	2015	Ethanol	Paediatric	Observational retrospective and prospectivebefore and after study	24	Heparin	70% ethanol, volume to fill catheter plus 0.1-0.2mL (max 3mL) Daily Dwell: 2 to 24 hours Administered by parents
Mouw (70)	2008	Ethanol	Paediatric	Observational retrospective before and after study	5 [a]	Heparin	70% ethanol, 0.5-2mL Daily Dwell: 4 to 14 hours
Klek (63)	2015	Taurolidine	Adult[b]	Open-label RCT	30	Saline	Group A: 2% taurolidine Group B: 1.35% taurolidine + citrate lock, volume not specified After each infusion Dwell: 12 hours
Olthof (60)	2014	Taurolidine	Adult	Observational retrospective study[c]	212	Heparin	2% taurolidine (Taurosept®) 1-7x/week, after each infusion
Hulshof (64)	2017	Taurolidine	Paediatric	Observational retrospective pre-post study	7[d]	Heparin	2% taurolidine (Taurosept®) Dwell: when parenteral nutrition was not administered

Abbreviations: RCT: randomized controlled trial

* Patients were defined as non high-risk if authors included all patients irrespective of prior CRBSI or only patients with infrequent CRBSI

[a]Study with total of 10 patients, however complete "before and after" data were only available for 5 patients

[b]The study was conducted specifically in low-risk patients defined as having less than 1 event per patient per year

[c] This was not a before and after study

[d]Study with a total of 23 patients, however complete “before and after” data were only available for 7 patients

Table 3. Definitions of high-risk and non high-risk patients for catheter related blood stream infections (CRBSI)

Study	Definition of high-risk patients
Davidson 2017(43)	No precise definition was provided, but authors refer to "high-risk patients"
John 2012(44)	Patients with at least 3 admissions for CRBSI in the past 1 year
Opilla 2007(59)	Patients with a history of recurrent CRBSI
Abu-El-Haija 2014(45)	Patients with at least 1 CRBSI
Pieroni 2013(46)	Patients with at least 2 CRBSI
Cober 2011(65)	Patients with any of the following 3 criteria: a) 2 previous catheter replaced because of CRBSI in the previous 18 months b) 2 previous CRBSI in current catheter that failed to clear with a full antibiotic course or were associated with the development of antibiotic resistance c) "Limited remaining catheter access"
Wales 2011(61)	Patients with at least 1 previous CRBSI
Jones 2010(66)	Patients with at least 1 CRBSI in the previous year
Bisseling 2010(62)	Patients with at least 1 CRBSI in the previous year
Saunders 2015(49)	Patients with any of the following 3 criteria: a) 2 or more CRBSI in the last 12 months b) More than 1 CRBSI in the presence of a persistent source of abdominal sepsis c) The presence of a "high-risk vascular access (e.g. chronic central venous occlusion in multiple vessels)"
Al-Amin 2013(47)	Patients with least 2 CRBSI in 6 months
Toure 2012(48)	Patients with at least 1 CRBSI in 12 months
Cullis 2011(67)	Patients with recurrent CRBSI
Jurewitsch 2005(68)	Patients with recurrent CRBSI
Chu 2012(50)	Patients with any of the following 2 criteria*: a) A history of recurrent CRBSI b) Previous removal of a catheter for overwhelming infections
Onder 2007(69)	Patients with any of the following 3 criteria:

	a) More than 2 CRBSI in 6 months b) More than 15 CRBSI per 1000 catheter-days c) History of a life-threatening CRBSI
	Definitions of non high-risk patients
Salonen (58)	All eligible new patients starting on home parenteral nutrition
Mokha (57)	All clinic patients
Ardura (56)	All clinic patients **
Mouw (70)	All clinic patients, with and without prior CRBSI
Klek (63)	Patients with less than 1 CRBSI per patient per year
Olthof (60)	All clinic patients
Hulshof (64)	All clinic patients

Abbreviations: CRBSI: catheter-related blood stream infections

* The authors included 4 patients without prior CRBSI in the high-risk category (and treated them with taurolidine locks): three were deemed vulnerable for complications in the event of a CRBSI, and one patient underwent lock therapy to match her twin and simplify care.

** In the initial period of the study (February 2012 to October 2012), authors included only high-risk patients with at least 2 CRBSI in the previous year, but as of October 2012, antimicrobial lock use was expanded to all patients.

Table 4. Summary of catheter related blood stream infection (CRBSI) rates (event per 1000 catheter-days) and follow-up in high-risk patients[*] for CRBSI

Study name	Type of lock	Study design	CRBSI rate		CRBSI rates favor Tx (Yes/No)	Statistically significant difference reached	Number of CRBSI		Follow-up per patient (days)		Total follow-up (catheter-days)	
			Tx	C			Tx	C	Tx	C	Tx	C
Davidson (43)	Ethanol	Obs	0.47	4.18	Yes	Not reported	NA	NA	NA	NA	NA	NA
John (44)	Ethanol	Obs	1.65	3.53	Yes	Yes (p=0.011)	12	96	NA	NA	7201	27210
Opilla (59)	Ethanol	Obs	2.7	8.3	Yes	Yes (RR CRBSI=0.325; 95% CI 0.17–0.64, p=0.001)	9	81	NA	NA	NA	NA
Abu-El-Haija (45)	Ethanol	Obs	1.4	10.3	Yes	Yes (P= 0.02)	11	19	Median 691 (IQR 198-782)	Median 181 (IQR 41-653)	3674	2155
Pieroni (46)	Ethanol	Obs	2.7	9.8	Yes	Yes (p<0.001)	27	60	Median 690 (IQR 120-1428)	Median 803 (IQR 92-3445)	NA	NA
Cober (65)	Ethanol	Obs	1.3	8	Yes	Yes (p<0.001)	Total= 5 Mean 0.2 (range 0-2) over 12 months	Total= NA Mean 2.9 (range 0-7) over 12 months	Mean 263 (range 23-652) (SD±190)	NA	NA	NA
Wales (61)	Ethanol	Obs	0.9	10.2	Yes	Yes (p=0.005)	3	91	Mean 227 ± 64	Mean 1086 ± 666	1821	9060
Jones (66)	Ethanol	Obs	2.1	9.9	Yes	Yes (p=0.03)	NA	NA	Median 215 (IQR 41-394)	Median 302 (IQR 207-596)	NA	NA
Bisselinig (62)	Tauroli-dine	Open-label RCT	0.19	2.02	Yes	**No**[a] for 1yr outcome of CRBSI incidence rate (P=0.008). **Yes**for 2ry outcome of mean infection free survival (<0.0001)	1	10	336 ± 51 Mean ± SEM (285-387)	353 ± 51 Mean ± SEM (285-387)	5370	4939
Saunders (49)	Tauroli-dine	Obs	0.99	5.71	Yes	Yes (p<0.0001)	12	42	NA	NA	12121	7351

Study name	Type of lock	Study design	CRBSI rate		CRBSI rates favor Tx (Yes/No)	Statistically significant difference reached	Number of CRBSI		Follow-up per patient (days)		Total follow-up (catheter-days)	
			Tx	C			Tx	C	Tx	C	Tx	C
	+ citrate											
Al-Amin (47)	Taurolidine + citrate	Obs	0	6.39	Yes	Yes (p=0.004)	NA	NA	NA	NA	NA	NA
Toure (48)	Taurolidine + citrate	Obs	1.09	6.58	Yes	Yes (p < 0.001)	6	36	365[c]	365[c]	NA	NA
Cullis (67)	Taurolidine + citrate	Obs	0.43	5.71	Yes	Yes (p<0.005)	NA	NA	NA	NA	5480	6737
Jurewitsch (68)	Taurolidine	Obs	0.8	10.8	Yes	Yes[b] (for infection free days, p=0.0156)	NA	NA	Range 90-1860	NA	5500	NA
Chu (50)	Taurolidine	Obs	1.1	8.6	Yes	Yes (p=0.002)	10	57	Range 61-1004	Range 243-365	9520	6630
Davidson (43)	Vancomycin	Obs	1.04	11.59	Yes	Yes (p<0.01)	NA	NA	NA	NA	NA	NA
Onder (69)	Tobramycin	Obs	14.3	26.5	Yes	Yes (p<0.05)	13	23	Mean 181.6 (range 98-257)	Mean 173.4 (range 103-242)	908	867

Abbreviation: C: control, CI: confidence interval, CRBSI: catheter-related blood stream infection, Obs: observational, RR: relative risk, Tx: treatment group, IQR: interquartile range, NA: not available, SD: standard deviation, SEM: standard error mean.

[*] Patients were defined as high-risk if they had recent or recurrent episodes of CRBSI

[a]The study stopped early after an interim analysis. Authors used an adapted significance level set at P-values <0.0056. Using the threshold of p<0.0056, the primary outcome of incidence rates did not reach statistical significance (p=0.008), and only the secondary outcome of mean infection-free survival reached statistical significance (infection-free survival of 175 (95% CI 85-266) days in the control arm (heparin), and 641 (95% CI 556-727) days in the taurolidine arm, log-rank p<0.0001)

[b] Statistical significance only reported for the outcome of infection free days (p=0.0156), and not for the outcome of CRBSI rates.

[c] Total catheter-days per patient

Table 5. Summary of catheter related blood stream infection (CRBSI) rates (event per 1000 catheter-days) and follow-up in non high-risk* patients for CRBSI

Study name	Type of lock	Study design	CRBSI rate		CRBSI rates favor Tx (Y/N)	Statistically significant difference reached	Number of CRBSI		Follow-up per patient (days)		Total follow-up (catheter-days)	
			Tx	C			Tx	C	Tx	C	Tx	C
Salonen (58)	Ethanol	Blinded RCT	1.54	0.32	No	No (p=0.9)	4	1	Median 107 (IQR 68-177)	Median 97 (IQR 47-229)	NA	NA
Mokha (57)	Ethanol	Obs	4.59	10.56	Yes	No (p=0.57)	13	13	Median 195	Median 101	2774	274
Ardura (56)	Ethanol	Obs	0.42	6.99	Yes	NA[a]	NA	NA	Median 266 (range 12-635)	Median 356 (range 90-510)	NA	NA
Mouw (70)	Ethanol	Obs	2.07	11.15	Yes	Not calculated due to low sample size	4	6	Range 91-741	Range 46-182	1936	538
Klek (63)	Taurolidine	Open-label RCT	**0.273**(Group A: 2% taurolidine) **0** (Group B: 1.35% taurolidine + citrate)	0	No	No (p=1.00)[b]	1 (Group A)	0	Group A 365.8; Group B 365 [c]	366 [c]	Group A 3658, Group B 3650	366
Olthof (60)	Taurolidine	Obs	NA [d]	NA	Yes	Yes (infection incidence ratio 95%CI 3.9-8.7 of heparin *vs* taurolidine) .	43	464	NA	NA	71112	147
Hulshof (64)	Taurolidine	Obs	4.3	12.7	Yes	Yes (RR 0.36, 95% CI: 0.20–0.65, p = 0.018)	NA	NA	Mean 466 (range 100-711)	Mean 659 (range 392-1043)	4307	461

Abbreviations: C: control, CI: confidence interval, CRBSI: catheter-related blood stream infection, Obs: observational, RR: relative risk, Tx: treatment group, NA: not available, N: no, Y:yes.

* Patients were defined as non high-risk if authors included all patients irrespective of prior CRBSI or only patients with infrequent CRBSI

[a] Statistical significance only reported for subgroup of patient on ethanol lock for > 3months. In this subgroup, CRBSI were 0.64 per 1000 catheter-days in the treatment group, and 7.01 in the control group, p=0.004)

[b] The study detected 1 infection (0.273 per 1000 catheter-days) in the taurolidine plus citrate arm, and none in the taurolidine or the control arm (p=1.000)

[c] Total catheter-days per patient

[d] Authors reported an adjusted CRBSI incidence ratio for heparin compared to taurolidine of 5.9 (95% confidence interval, 3.9–8.7) after adjusting for underlying disease, use of anticoagulants or immune suppressive, frequency of

HPN/fluid administration, composition of infusion fluids, place of catheter insertion and duration of HPN/fluid use before catheter creation.

Table 6. Reported complications in treatment and control groups

Study name	Type of lock	Complications		Description of complication
		Treatment	Control	
Salonen (58)	Ethanol	N	N	
Davidson (43)	Ethanol	NA	NA	[a]
John (44)	Ethanol	N	N	
Opilla (59)	Ethanol	N	N	
Mokha (57)	Ethanol	Y	N	Mechanical events: rate of 6.58 per 1000 catheter days in ethanol group and 0 in control group, p=0.008. Catheter replacement due to mechanical event: rate 5.05 per 1000 catheter days in ethanol group versus 0 in controls, p=0.01.
Abu-El-Haija (45)	Ethanol	Y	Y	Catheter thrombosis (requiring t-PA application): 1 (heparin) and 12 (ethanol), with corresponding rates of 0.46, and 3.27 per 1000 catheter days, p = 0.06. Catheter repair: 0 (heparin) and 23 (ethanol), with corresponding rates of 0 to 6.26 per 1000 catheter, p=0.25. Catheter replacement: median rate per 1000 catheter days of 0 (heparin) and 1.4 (ethanol), p=0.81
Pieroni (46)	Ethanol	N	N	
Cober (65)	Ethanol	Y	Y	Catheter repair (leakage or tear): 6.4 ± 10.0 (heparin) and 3.1 ± 5.2 (ethanol) per 1000 catheter days, p = 0.20
Wales (61)	Ethanol	Y	N	Catheter thrombosis: 2 in ethanol group
Jones (66)	Ethanol	N	N	
Ardura (56)	Ethanol	Y	N	Catheter occlusion: 1 in ethanol group
Mouw (70)	Ethanol	Y	N	Catheter thrombosis: 1 in ethanol group.
Klek (63)	Taurolidine	Y	N	Catheter occlusion: 1 in taurolidine group
Bisseling (62)	Taurolidine	N	N	
Saunders (49)	Taurolidine	NA	NA	
Al-Amin (47)	Taurolidine + citrate	NA	NA	
Toure (48)	Taurolidine + citrate	N	N	
Cullis (67)	Taurolidine	NA	NA	
Jurewitsch (68)	Taurolidine	N	N	
Olthof (60)	Taurolidine	Y	Y	Catheter occlusion: incidence rates of 0.2 (95% CI 0.2-0.3) per access year (heparin) and 0.1 (95%CI 0.1-0.2) per access year

Study name	Type of lock	Complications		Description of complication
		Treatment	Control	
				(taurolidine). Adjusted rate ratio of 1.9 (1.1–3.1) for heparin versus taurolidine after controlling for confounding. [b]
Hulshof (64)	Taurolidine	N	N	
Chu (50)	Taurolidine	N	N	
Davidson (43)	Vancomycin	NA	NA	
Onder (69)	Tobramycin	N	N	

Abbreviations: CI: confidence interval, CRBSI: catheter-related blood stream infection, N: no, NA: not available, Y: yes

[a] No complications were reported related to treatment or controls. However authors no that "during the last follow-up, it was noted that 12 patients had died. Of the 12 deaths, only 2 were attributable to complications related to HPN (CRBSI)."
[b] Authors adjusted for "underlying disease, anticoagulant use, immune suppressive use, HPN/fluid frequency per week, composition of infusional fluid, and duration of HPN/fluid use before creation catheter. Random effects for patients were incorporated to account for repeated vascular access periods within a patient".

FIGURES

Figure 1. PRISMA flow diagram

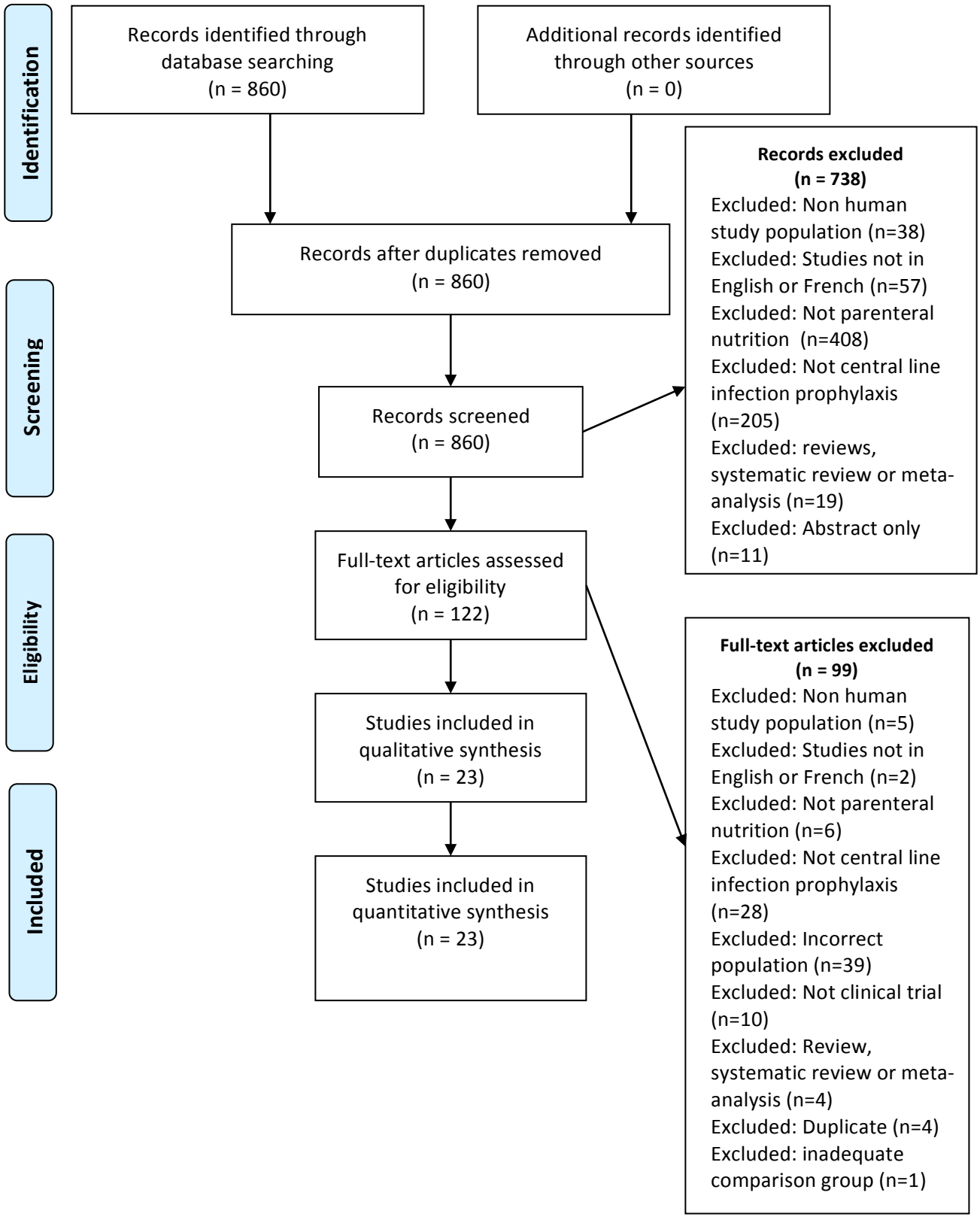
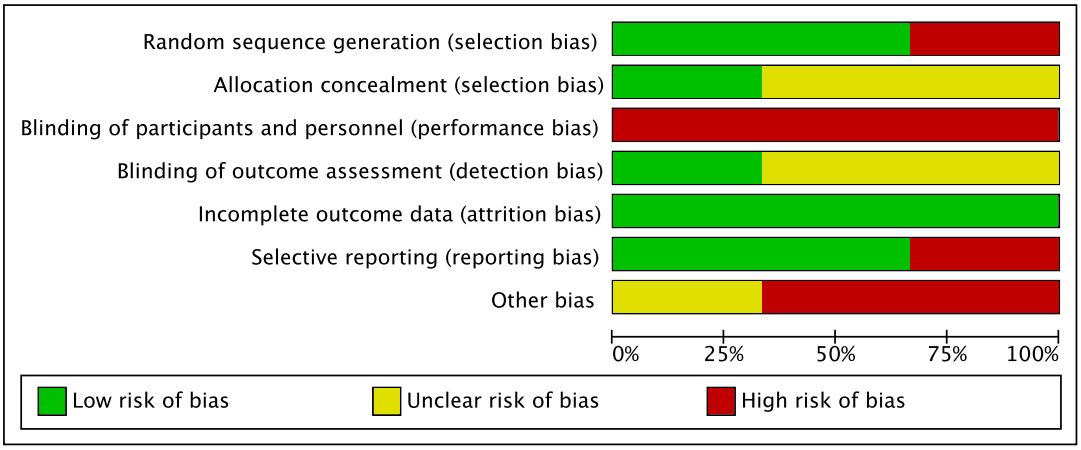
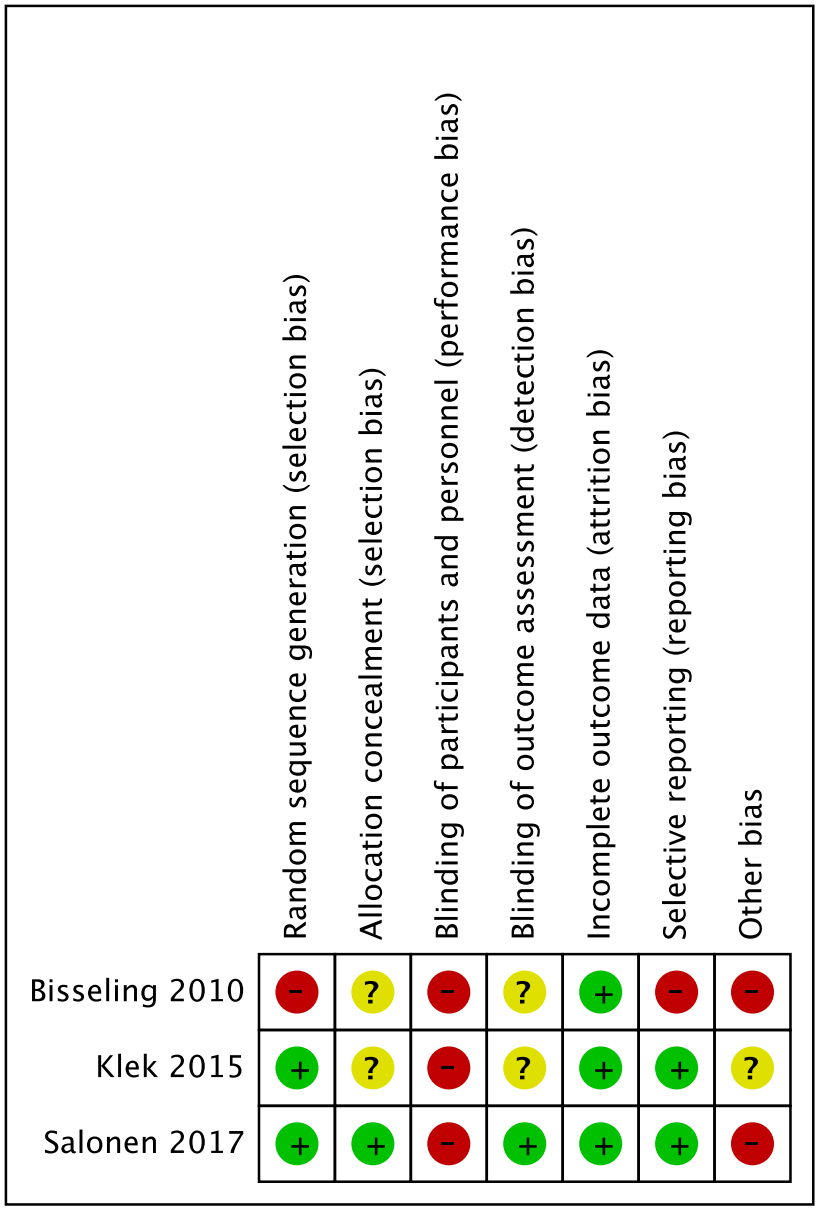


Figure 2. Risk of bias graph for randomized controlled trials



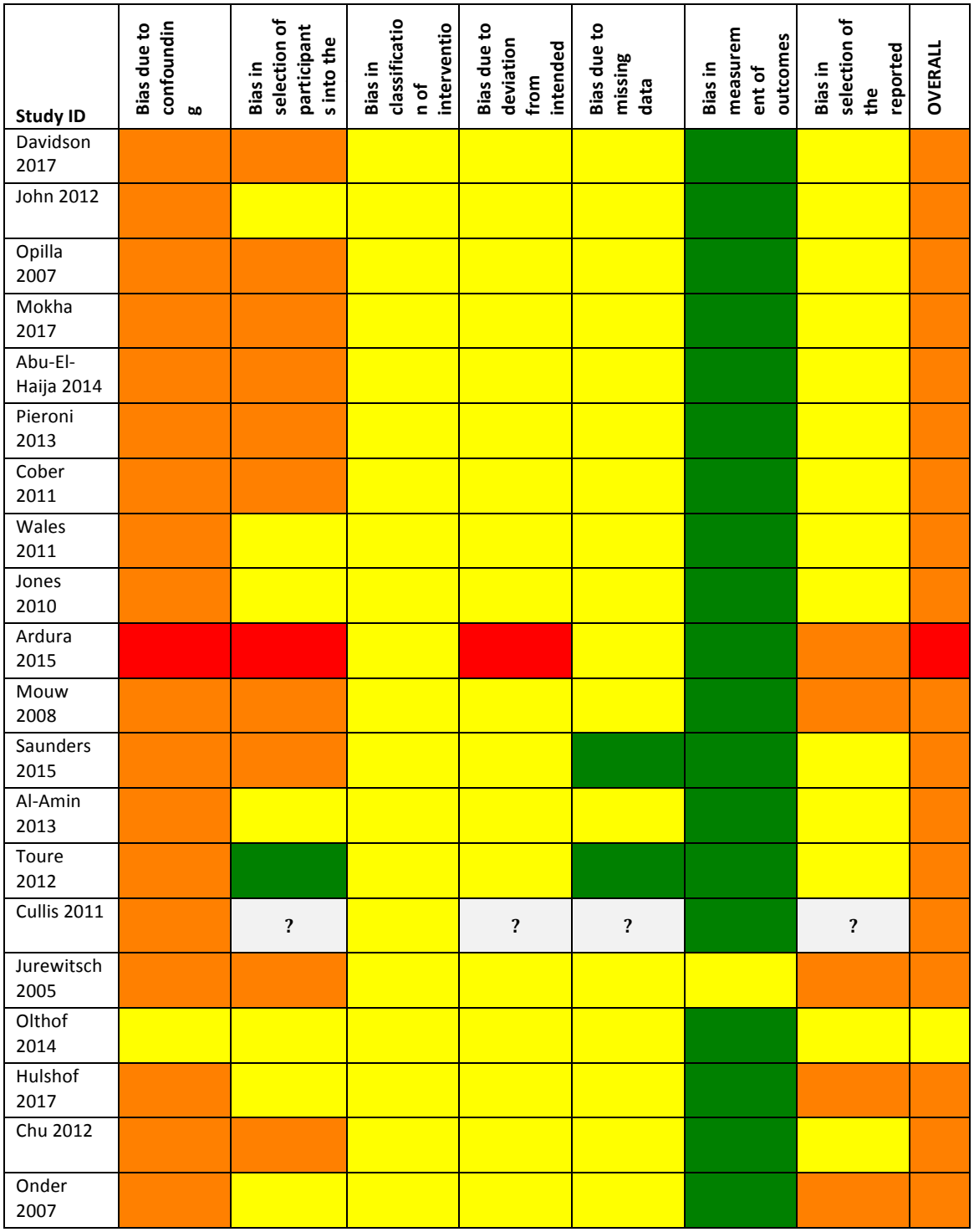
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across studies

Figure 3. Risk of bias summary for randomized controlled trials



Risk of bias summary: review authors' judgments about each risk of bias item for each study

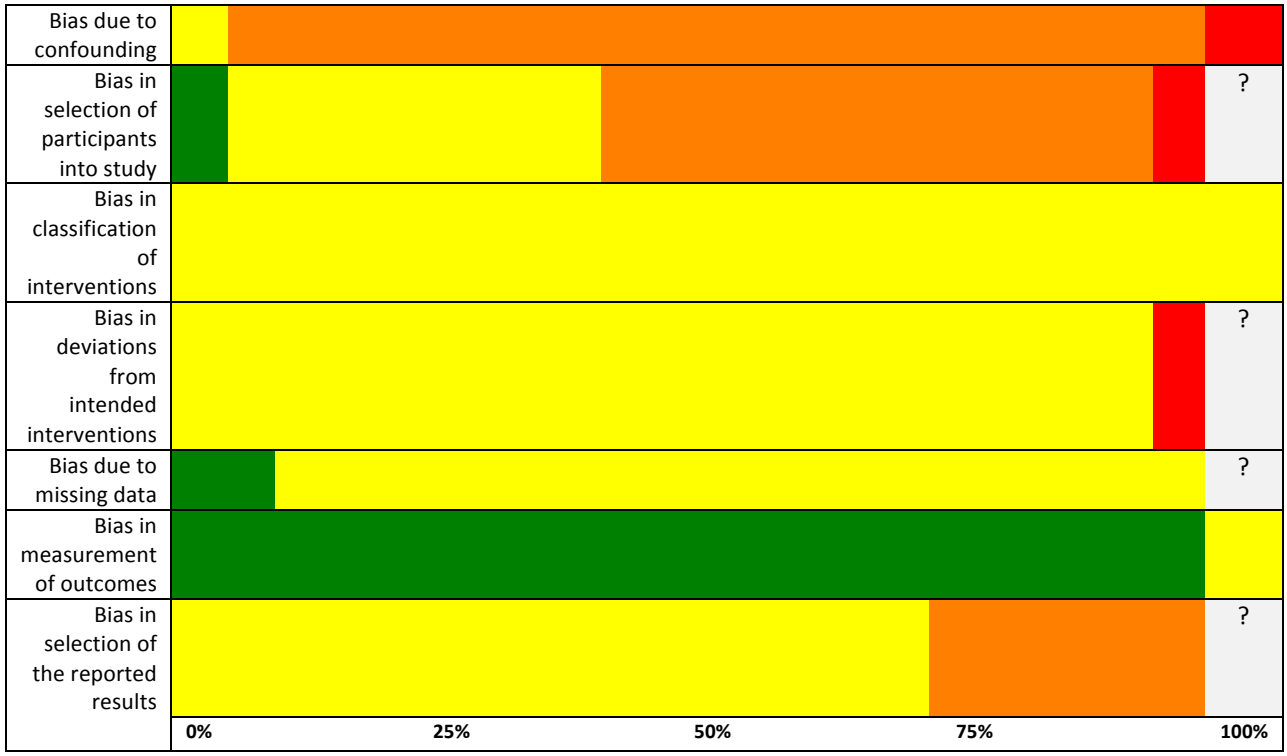
Figure 4. Risk of bias assessment for observational studies*



Legend	Low	Moderate	Serious	Critical	No information
Risk of bias assessment					**?**

* Risk of bias graph using review authors' judgements about each risk of bias item with color legend adapted from the Cochrane risk of bias tool for randomized trials(74).

Figure 5. Risk of bias summary for observational studies



Legend	Low	Moderate	Serious	Critical	No information
Risk of bias assessment					**?**

Figure 6. Summary of studies in high-risk patients for CRBSI

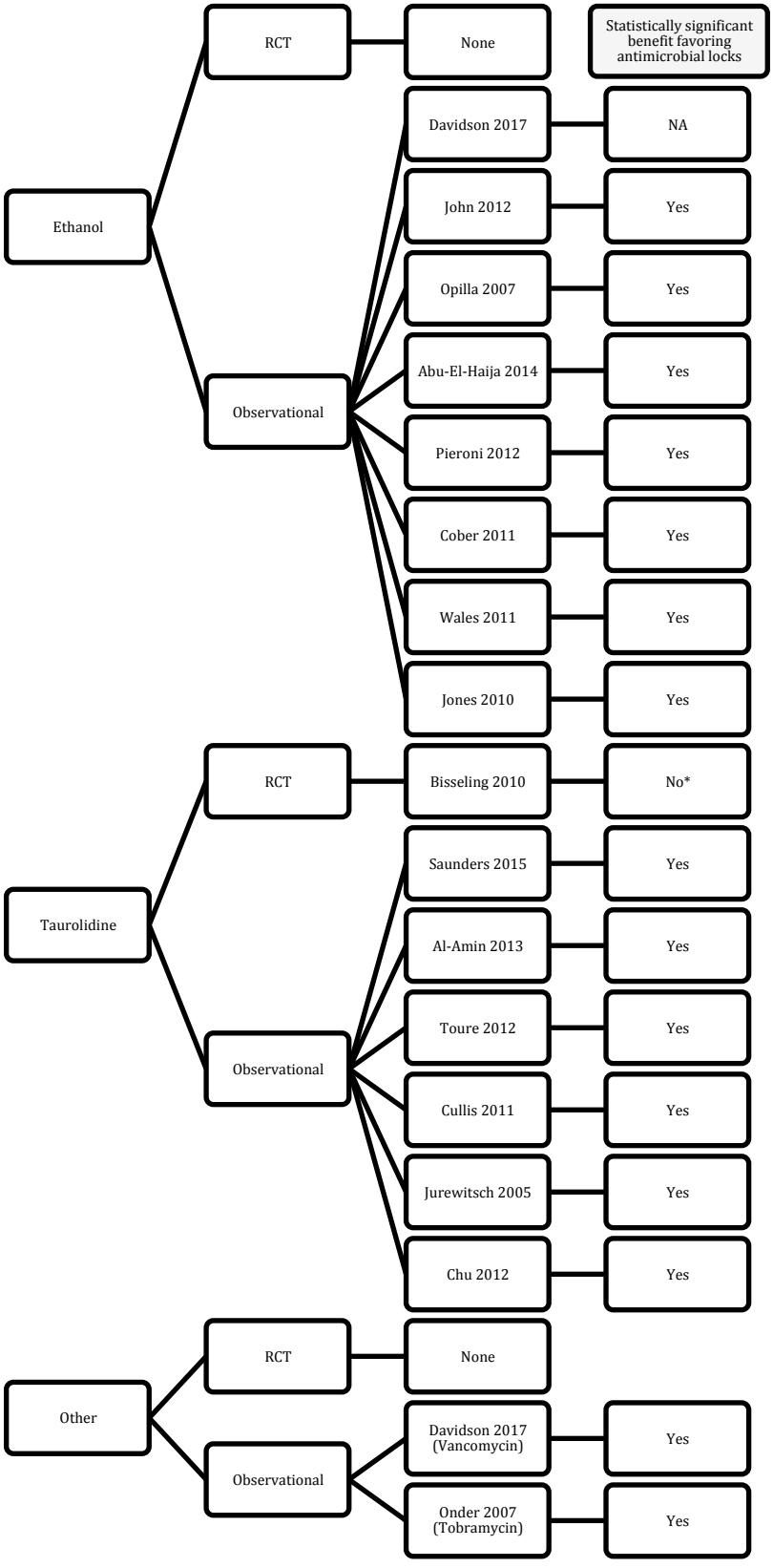
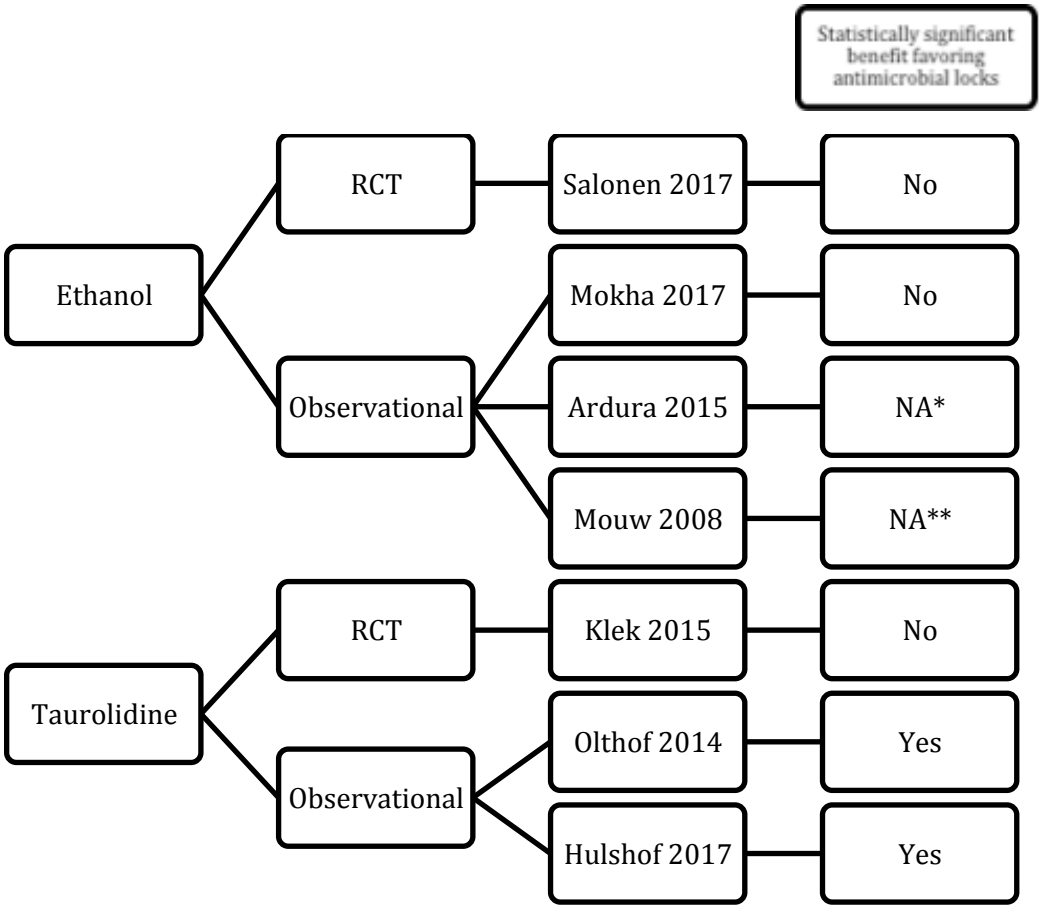


Figure 7. Summary of studies in non high-risk patients for CRBSI



*Statistical significance only reported for subgroup of patient on ethanol lock for > 3months. In this subgroup, CRBSI were 0.64 per 1000 catheter-days in the treatment group, and 7.01 in the control group, p=0.004)

** Not calculated due to low sample size

Bridge section 2 – Complications and CRBSI rates in Quebec HPN patients

The Canadian HPN Registry has allowed health care providers to gather important information on local HPN practice. The inclusion of Quebec patients permitted us to further evaluate PN at a provincial level and assess local quality indicators in the delivery of HPN. Full results and methodology of the Registry are described in Chapter 2. In this section, we consolidate important data gathered in the Quebec cohort (Chapter 2), and highlight the local complications rates including hospitalization and CRBSI rates. We also report on the use of antimicrobial locks as prophylaxis for CRBSI. The Quebec data we present on CRBSI and antimicrobial lock use further solidify the thesis by linking local data, with elements of the HPN literature described in Bridging section 1 and Chapter 3.

Hospitalizations

We documented a total of 84 hospitalizations among the 83 patients enrolled in the Quebec HPN Registry, encompassing 545 hospitalization days over 12 months. This represented at mean of 1.05 ± 1.21 (range 0-6) hospitalization per patient per year, with a mean length of stay of 8 days per patient. The majority of patients (57.5%) were hospitalized at least once, with 42.5% not requiring any hospitalization (Table 1). The average length of stay in patients with at least one hospitalization was 16.51 ± 14.20 (range 1-60) days. The distribution of hospitalizations is presented in Figure 1.

In Quebec, 25% of all hospitalizations were the result of a PN-related complication, accounting for 32.1% of all hospitalization days. Mean length of stay from PN-related complication was 12.5 ± 10.01 (range 1-31) days and 14.8 ± 15.59 (range 1-58) days in PN-unrelated complications. No significant differences were noted in length of stay between the two groups.

Direct comparison with Canadian data is difficult because older reports from Canadian HPN Registry were limited by validation issues (20), especially with regards to hospitalization data. They reported hospitalization rates of 1.10 ± 0.18 in 2006, and 0.92 ± 0.14 in 2009 (20). The majority of hospitalizations (54%) resulted from PN-related complications (26), and 62.7% of all patients required at least one hospitalization(26). Quebec hospitalization rates were similar, with

the exception of a lower proportion (25%) of hospitalizations due to PN-related complications. The discrepancy could be, in part, explained by differences in data collection, patient population as well as change in CRBSI rates over time.

CRBSI

It is estimated that 70% of all PN-related hospitalizations are attributed to CRBSI (1). Data on CRBSI at large suggest that each episode of CRBSI costs an additional 32,000 $ (31) to 55,600 $ (US dollars) per patient (75), and is linked to increased mortality (31).

We recorded a total 19 episodes of CRBSI over 12 months in the Quebec cohort, with 21.3% of all patients experiencing at least one infection. This corresponds to a mean of 0.21 infections per patient per year, or a rate of 0.65 events per 1000 catheter-days. The distribution of CRBSI is shown in Figure 2. In parallel, we noted 21 catheter changes with a rate of 0.31 per patient per year. Most catheter changes result from line infections, but indications include catheter breakage and thrombosis (Table 2).

The reported CRBSI rates in the literature vary. A systematic review by *Dreesen et al*. included 39 HPN studies and yielded a median CRBSI rate of 1.31 (range 0.38-4.58) per 1000 catheter-days. In subgroups with predominantly benign conditions, the rate was lower at 0.82 (range 0.19-2.41), *versus* 2.71 (range 1.9-6.8) in cohorts with > 50% of patients with malignancy. The included studies were published from 1984 to 2012 and were predominantly observational and retrospective. Another review has collected results from 27 HPN studies, conducted from 1989 to 2016 (76). They found CRBSI rates that ranged from 0.38 to 11.5. In the Unites States, the recent nationwide HPN Registry SUSTAIN Registry by the American Society for Parenteral and Enteral Nutrition's National Patient Registry for Nutrition Care, reported CRBSI data from 1046 patients across 29 centers dating from 2011 to 2014(28). The SUSTAIN Registry included both adult and pediatric patients and employed a uniform definition of CRBSI across all sites. The Registry reported 194 catheter infections affecting 112 patients (10.7% of all patients) with a global CRBSI rate of 0.87 and 0.35 per 1000 catheter-days in adults only (28).

The CRBSI rates in Quebec are slightly higher than the above US data, but lower than Canadian HPN Registry data, which reported rates of 1.58 during the period from 2005 to 2008, and 0.97 from 2011 to 2014 (24). Other Canadian reports have described line sepsis rates ranging from 0.89 (77) to 3.2 per 1000 catheter days(36).

There are several limitations when comparing CRBSI rates. First, the definition of CRBSI often varies. The Canadian Registry recorded an episode of CRBSI when the treating team made the clinical diagnosis, whereas the US SUSTAIN Registry used an *a priori* definition of a "bloodstream infection in patients with a central venous catheter […] not related to infections at other body sites" (28). The European Society for Clinical Nutrition and Metabolism guidelines suggest using Centers for Disease Control and Prevention (CDC) criteria for the adequate diagnosis of CRBSI, which includes a positive catheter tip culture or paired positive blood cultures from the catheter and peripheral vein in patients with clinical symptoms of sepsis(1). The CDC also includes quantitative culture (central line culture with at least 3-fold greater colony count) and differential time to positivity criteria (central line culture growth at least 2 hours before) (78). In practice, the use of quantitative and qualitative methods is often omitted, which can result in over-diagnosis (79) and contributes to the variability in reported CRBSI rates across centers.

Furthermore, CRBSI rates may vary according to the duration of PN with data suggesting higher CRBSI with longer PN treatment (28). Different follow-up duration can influence CRBSI rates, where shorter follow-up may not fully capture all events. Additionally, patient characteristics such as type of catheters, underlying disease and even socio-economic factors all influence infection rates(10). This highlights the importance of defining local complication rates to measure and monitor HPN care quality.

Antimicrobial lock use

The CRBSI rate in Quebec is low with 0.65 events per 1000 catheter-days. The benefits of antimicrobial locks are not well defined in low risk patients. Indeed, a randomized control trial using taurolidine locks in patients with less than 1 episode per patient per year did not detect any

benefit for lock use (80). Current ESPEN guidelines (30) recommend locks particularly among high-risk patients.

In Quebec, none of the 3 HPN clinics routinely prescribed antimicrobials locks for the prevention of CRBSI. A few patients with recurrent line sepsis were put on prophylactic antimicrobial locks on a case-to-case basis, with either ethanol or citrate. Taurolidine was not employed for practical reasons due to the lack of access in Quebec. This contrasts with the US data with ethanol locks use reaching 27.2% (28) in the SUSTAIN Registry, a population that included paediatric patients where ethanol lock use is more prominent. We do not have Canadian data on the topic, as lock use was not included in the national Registry.

The hospitalization and CRBSI rates in current Quebec HPN patients were low and comparable to national and international rates. Complication rates differ across cohorts because they result from a combination of varying risk factors. Indeed, they are influenced by local practice such patient education, nursing support, catheter handling and sterilization techniques, as well as patient characteristics and disease related factors such as underlying condition. Changes in practice over time can also influence outcomes. As such, longitudinal data will be key to periodically evaluate quality of care and possibly even identify local risk factors driving certain complications.

TABLES AND FIGURES

Table 1. Hospitalization rates

Hospitalizations in the last 12 months	Total (%) or mean ± SD (range)
Total number of hospitalizations	84
Distribution of hospitalizations	
0	34 (42.5%)
1	22 (27.5%)
2	15 (18.8%)
3	6 (7.5%)
4	2 (2.5%)
5	0 (0%)
6	1 (1.2%)
Mean number of hospitalizations per patient (mean ± SD (range))	1.05 ± 1.21 (0-6)
Mean hospitalization days per patient	8.13 ± 12.9 (0-60)
Total number of hospitalization days	545
Patients with at least one hospitalization	
Number of patients with at least one hospitalization	46
Mean percentage of hospitalizations from PN complications	28.2 ± 40.5
Mean hospitalization days	16.51 ± 14.20 (median 14, range 1-60)
Hospitalization from PN-related complications (% of total)	
Total number of hospitalizations	21 (25.0%)
Total hospitalization days for PN complication	175 (32.1%)
Mean hospitalization days (*excluding missing values)	
From PN–related complication	12.5 ± 10.01 (range 1-31)
From PN-unrelated complication	14.8 ± 15.59 (range 1-58)

Table 2. Vascular complications

CRSBI	Total (%) or rate
Total CRBSI	19 events
Patient with least one CRBSI	17 (21.3 %)
Distribution of CRBSI per patient	0: 63 (78.75%) 1: 15 (18.75%) 2: 2 (2.5%)
Average CRBSI rate	0.21 per patient per year
CRBSI rate in Quebec	0.65 per 1000 catheter days
Vascular access change (last 12 months)	
0	60 (71.1%)
1	17 (21%)
2	4 (4.9%)
Average vascular access change	0.31 per patient per year

Figure 1. Distribution of hospitalizations frequencies

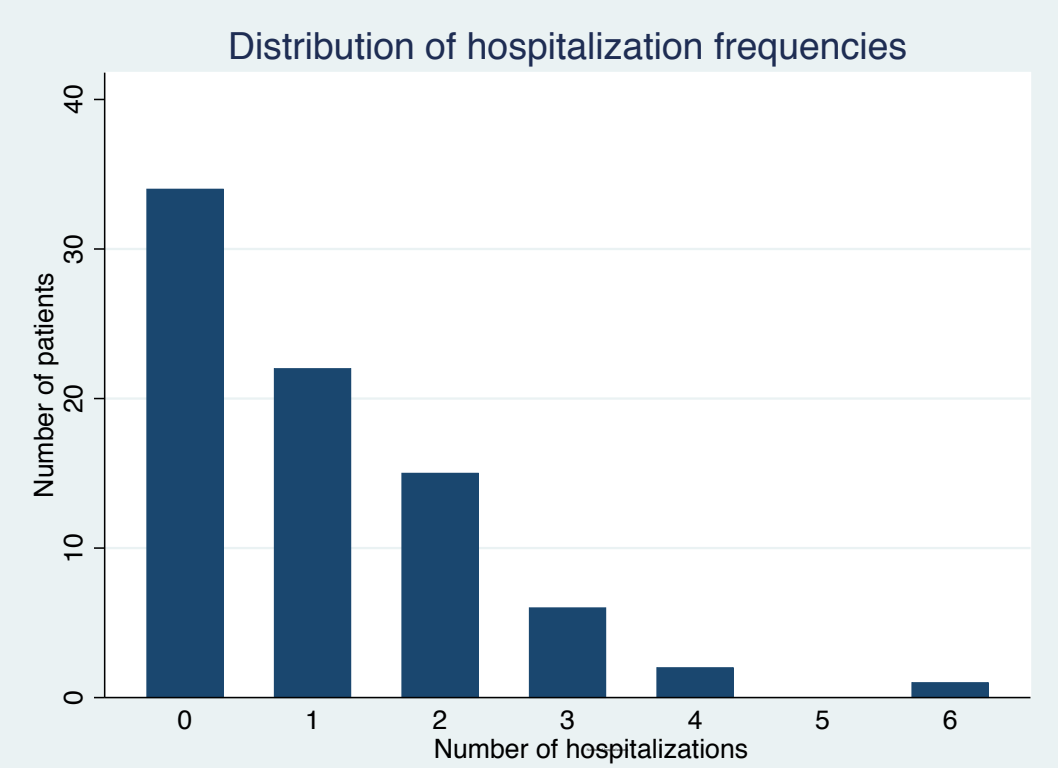
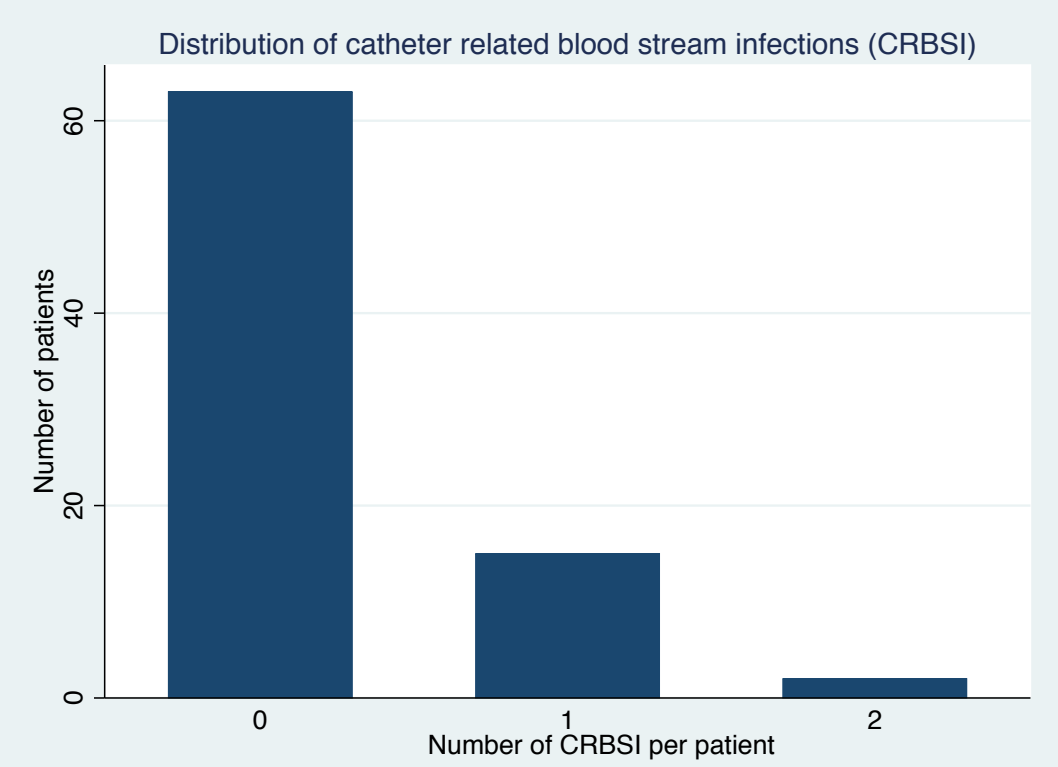


Figure 2. Distribution of CRBSI per patient



Chapter 4 – Summary and conclusions

Chronic intestinal failure is a rare condition treated with HPN, a highly specialized therapy with high costs and severe complications. The management of HPN is complex for several reasons. First, the technical requirements of patients performing their own intravenous infusions at home necessitate intensive education and close collaboration with a multi-disciplinary treating team. When infusion and catheter handling techniques are breached, there is an increased risk of complications such as catheter infections. Secondly, patients with intestinal failure have highly complex medical profiles with several comorbidities, and have different causes of intestinal failure such as Crohn's disease, intestinal pseudo-obstruction or malabsorption. Their care must therefore be individualized.

Some methodological aspects specific to the HPN literature influence how we interpret and use published data to guide our practice. The low prevalence of HPN is often a challenge in obtaining sufficiently powered studies and gather higher quality evidence to inform practice. Indeed, most studies in HPN are observational and have methodological limitations. As such, practice guideline recommendations are supported by lower level of evidence. Because of the above complexities, understanding local population data and complication rates are important in evaluating our practice and can guide the implementation of guideline recommendations.

This thesis makes 2 major contributions to the literature. First, we assessed the practice of HPN in Quebec, which is an essential step in understanding our patient population characteristics. Second we assessed CRBSI focusing on prevention, risk factors, and the use antimicrobial locks as prophylaxis.

We have defined for the first time the HPN patient demographics in Quebec. We confirmed the low prevalence and incidence of HPN, and described the general organization and practice in the Quebec clinics. In doing so, we integrated provincial data into the Canadian HPN registry, a structure that enables longitudinal follow-up and data collection. This will allow us to identify trends over time, as well as regional variations. Establishing our local practice parameters and complication rates is furthermore a fundamental step in the quality assessment process.

Our findings underscore the importance of understanding local population parameters in order to adapt care in intestinal failure, a condition where patient profiles tend to be heterogeneous and vary across cohorts. For instance, there is a higher proportion of motility disorders in Quebec, likely driven by the incidence of Chronic Atrial and Intestinal Dysrhythmia (CAID) syndrome, a local genetic condition. This may influence our CRBSI rates, as motility disorders are a known risk. Furthermore, the young age of onset should be taken into account looking at long-term outcomes such as PN dependence, quality of life, osteoporosis prevention and preservation of vascular access. We noted high rates of opioids and sedative use that should also prompt the evaluation of prescribing practices.

We were limited by small sample size, and did not have sufficient power to conduct additional statistical analysis such as assessing risk factors for CRBSI. Given the rarity of the chronic intestinal failure, this is a commonly encountered challenge for HPN research. Nonetheless, gathering local data is incrementally important in generating clinically relevant and pertinent information. Additionally, the use of a registry will provide longitudinal data that generates more statistical power to assess what are often rare outcomes.

A substantial focus of the thesis was on CRBSI, a major serious complication that can be prevented. We conducted a comprehensive review of CRBSI risk factors, performed a systematic review for antimicrobial locks and gathered detailed data on Quebec complication rates. This permitted us to review the current literature in HPN, particularly through the systematic review on antimicrobial locks, which identified 23 articles (3 RCTs and 20 observation studies). We were faced with limitations of the existing literature, featuring predominantly observational studies with not only the inclusion of studies with small sample sizes, but also displaying poorly, or uncontrolled confounding. In response, we suggest methodological recommendations that can serve to optimize study quality given the prevailing limitations. We suggest adopting uniform CRBSI rate measures, definitions of patient risk level, and comparable lock solutions. Moreover, the measurement of CRBSI rates with events per 1000 catheter-days, do not take time into account, and assume a stable infection rate regardless of PN duration. Until the effect of time on CRBSI rates is better established, authors may consider using a survival analysis to more confidently characterize and interpret CRBSI rates.

While our results of the systematic review were inconclusive, the use of antimicrobial locks - in addition to proper patient education and good catheter handing techniques - remains a promising strategy with the potential to prevent CRBSI. Its benefits may be more pronounced in certain patient groups, depending to risk level for CRBSI, but has yet to be confirmed.

HPN is well established in Quebec with a prevalence of 13 per million population, a median duration of 7.9 years, and CRBSI rates of 0.65 per 1000 catheter-days. Complication rates among Quebec patients are low, yet each complication leads to increased cost and health care utilization. In particular, risk factors for CRBSI are multifactorial and include patient characteristics, venous access, PN regimen and patient follow-up, as well as socio-economic factors. Antimicrobial locks may be beneficial in the prevention of CRBSI, but the current evidence is inconclusive. Future research should take into account certain methodological considerations such as using uniform treatment and outcome definitions, as well as assess the effect of antimicrobial locks in specific patient populations (at high-risk and non high-risk for CRBSI). By combining local patient data with high quality evidence, we will be able to evaluate the quality of our care and make informed decisions to improve HPN care in Quebec.

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Appendices

Appendix 1. Karnofsky performance scale

100 - Normal, no complaints, no evidence of disease
90 - Able to carry normal activity, minor signs/symptoms
80 - Normal activity with effort, some signs/symptoms
70 - Cares for self, unable to carry normal activity/active work
60 - Requires occasional assistance, able to care for most needs
50 - Requires considerable assistance, frequent medical care
40 - Disabled, requires special care and assistance
30 - Severely disabled, hospitalization indicated, death not imminent
20 - Hospitalization necessary, very sick, active supportive treatment
10 - Moribund, fatal processes progressing rapidly
0 - Dead

Appendix 2. Search strategy for systematic review

Search Strategy:

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1 PARENTERAL NUTRITION/ (39516)
2 (total adj1 parenteral adj1 nutrition).tw. (16886)
3 (home adj1 parenteral adj1 nutrition).tw. (2370)
4 Citrates/ (43038)
5 Citric Acid/ (36267)
6 Citrate$.tw. (80339)
7 (citric adj1 acid).tw. (19020)
8 (sodium adj1 citrate).tw. (5345)
9 Alcohol/ (205966)
10 Alcohol.tw. (439192)
11 ethanol/ (272063)
12 ethanol.tw. (209889)
13 Thiadiazines/ (1154)
14 Taurolidine.tw. (483)
15 taurolin.tw. (198)
16 tauroflex.tw. (12)
17 tauroline.tw. (9)
18 (Antibiotic adj1 lock).tw. (452)
19 Antibiotic-lock.tw. (448)
20 (antibiotic adj1 solution).tw. (660)
21 (antimicrobial adj1 solution).tw. (119)
22 or/1-3 (53046)
23 or/4-21 (783929)
24 22 and 23 (755)
25 remove duplicates from 24 (575)

Appendix 3. Cochrane risk of bias tool – criteria for judging risk of bias

SEQUENCE GENERATION **Was the allocation sequence adequately generated?**	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization* . *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgment or some method of non-random categorization of participants, for example: • Allocation by judgment of the clinician; Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information about the sequence generation process to permit judgment of 'Yes' or 'No'.
ALLOCATION CONCEALMENT **Was allocation adequately**	

concealed?	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgment of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgment – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS **Was knowledge of the allocated interventions adequately prevented during the study?**	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any one of the following: • No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;

	• Either participants or some key
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: • No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; • Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: • Insufficient information to permit judgment of a 'Yes' or 'No'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Were incomplete outcome data adequately addressed?**	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk

	enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgment of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome
SELECTIVE OUTCOME REPORTING **Are reports of the study free of suggestion of selective outcome reporting?**	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	Any one of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgment of 'NO' (i.e. high risk of bias).	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would have been expected to have been

	reported for such a study
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	Insufficient information to permit judgment of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.
OTHER POTENTIAL THREATS TO VALIDITY **Was the study apparently free of other problems that could put it at a risk of bias?**	
Criteria for a judgment of 'YES' (i.e. low risk of bias).	The study appears to be free of other sources of bias.
Criteria for the judgment of 'NO' (i.e. high risk of bias).	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Stopped early due to some data-dependent process (including a formal-stopping rule); • Had extreme baseline imbalance; or • Has been claimed to have been fraudulent; or • Had some other problem
Criteria for the judgment of 'UNCLEAR' (uncertain risk of bias).	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias

Taken from Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions.* Chichester (UK): John Wiley & Sons, 2008(53).

Appendix 4. The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

Version 7 March 2016

ROBINS-I tool (Stage I): At protocol stage

Specify the review question

Participants
Experimental intervention
Control intervention
Outcomes

List the confounding areas relevant to all or most studies

List co-interventions that could be different between intervention groups and that could impact on outcomes

ROBINS-I tool (Stage II): For each study

Specify a target randomized trial specific to the study

Design: Individually randomized / Cluster randomized / Matched (e.g. cross-over)
Participants
Experimental intervention
Control intervention

Is your aim for this study...?

1. to assess the effect of *initiating* intervention (as in an intention-to-treat analysis)
2. to assess the effect of *initiating and adhering to* intervention (as in a per-protocol analysis)

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding area (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

"Important" confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the area, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

<table>
<tr><td colspan="5">(i) Confounding areas listed in the review protocol</td></tr>
<tr><td>Confounding area</td><td>Measured variable(s)</td><td>Is there evidence that controlling for this variable was unnecessary?*</td><td>Is the confounding area measured validly and reliably by this variable (or these variables)?</td><td>OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control group?</td></tr>
<tr><td rowspan="2"></td><td></td><td></td><td rowspan="2">Yes / No / No information</td><td>Favour intervention / Favour control / No information</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="5">(ii) Additional confounding areas relevant to the setting of this particular study, or which the study authors identified as important</td></tr>
<tr><td>Confounding area</td><td>Measured variable(s)</td><td>Is there evidence that controlling for this variable was unnecessary?*</td><td>Is the confounding area measured validly and reliably by this variable (or these variables)?</td><td>OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control</td></tr>
</table>

				group?
			Yes / No / No information	Favour intervention / Favour control / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that "no statistically significant association" is not the same as "not predictive".

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

"Important" co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

		Favour experimental / Favour comparator / No information
(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important		
Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

Risk of bias assessment (cohort-type studies)

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.

Bias domain	**Signalling questions**	**Elaboration**	**Response options**
Bias due to confounding	1.1 Is there potential for confounding of the effect of	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial.	Y / PY / PN / N

	intervention in this study? **If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	There is no NI (No information) option for this signalling question.	
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, proceed to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI
	1.3. Were	If intervention switches are unrelated to the outcome, for example	NA / Y / PY /

	intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	PN / N / NI
	Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA / Y / PY / PN / N / NI
.	1.5. **If Y/PY to**	Appropriate control of confounding requires that the variables	NA / Y / PY /

	1.4: Were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	PN / N / NI
	1.6. Did the authors control for Controlling for post-intervention variables is not appropriate. Controlling for any post-intervention variables? mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias. **Questions relating to baseline and time-varying confounding**		NA / Y / PY / PN / N / NI
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time- varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomized trials and NRSI. Appropriate methods include those based on inverse-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	NA / Y / PY / PN / N / NI
	1.8. **If Y/PY to 1.7**: Were confounding	See 1.5 above.	NA / Y / PY / PN / N / NI

	areas that were adjusted for measured validly and reliably by the variables available in this study?		
	Risk of bias judgement	See Table 1	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is likely to have a dominant impact.	Favours experimental / Favours comparator / Unpredictable
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after	This domain is concerned only with selection into the study based on participant characteristics observed *after* the start of intervention. Selection based on characteristics observed *before* the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding). Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention **and** an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of	Y / PY / PN / N / NI NA / Y / PY / PN / N / NI NA / Y / PY / PN / N / NI

	the start of intervention? **If N/PN to 2.1:** go to 2.4 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention 2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	selection bias if selection into the study is related to both the intervention and the outcome.	
	2.4. Do start of follow-up and start of intervention coincide for most	If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses.	Y / PY / PN / N / NI

	participants?		
	2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be "No".	NA / Y / PY / PN / N / NI
	Risk of bias judgment	See Table 1	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly	Y / PY / PN / N / NI

		defined, and the answer is likely to be 'Yes'.	
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'.	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y / PY / PN / N / NI
	Risk of bias judgement	See Table 1	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias due to departures	4.1. Was the intervention	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by	Y / PY / PN /

from intended interventions	implemented successfully for most participants?	those administering the intervention?	N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. We distinguish between analyses where: (1) intervention switches led to follow up time being assigned to the new intervention, and (2) interventionswitches(includingcessationofintervention)wherefollowup time remained allocated to the original intervention. (1) is addressed under time-varying confounding, and should not be considered further here. Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow up. Was lack of adherence sufficient to impact the intervention effect estimate?	NA / Y / PY / PN / N / NI
	4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups.	NA / Y / PY / PN / N / NI
	4.4. **If N/PN to 4.1, 4.2 or 4.3**:	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust	NA / Y / PY / PN / N / NI

	Were adjustment techniques used that are likely to correct for these issues?	for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches.	
	Risk of bias judgement	See Table 2	
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	
Bias due to missing data	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study.	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the *intended* study sample is clear, which it may not be in practice.	Y / PY / PN / N / NI
	5.3 Were participants excluded due to	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.	Y / PY / PN / N / NI

	missing data on other variables needed for the analysis?		
	5.4 **If Y/PY to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed.	NA / Y / PY / PN / N / NI
	5.5 **If Y/PY to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used.	NA / Y / PY / PN / N / NI
	Risk of bias judgement	See Table 2	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null /

			Unpredictable
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves.	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements.	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls	Y / PY / PN / N / NI

	received?	being in place.	
	Risk of bias judgment	See Table 2	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in selection of the reported result	Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome *measurements* within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously	Y / PY / PN / N / NI

		scaled outcome converted to categorical data with different cut-points; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not pre- specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	
	7.3 ... different *subgroups*?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
	Risk of bias judgment	See Table 2	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions.	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Overall bias	**Risk of bias judgment**	See Table 3	Low / Moderate / Serious / Critical / NI
	Optional: What is the overall predicted direction of bias		Favours experimental / Favours

	for this outcome?		comparator / Towards null /Away from null / Unpredictable

Taken from: ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions(81).

Table 1. Reaching risk of bias judgements in ROBINS-I: pre-intervention and at-intervention domains

Judgement	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	No confounding expected.	All participants who would have been eligible for the target trial were included in the study *and* start of follow up and start of intervention coincide for all subjects.	Intervention status is well defined and based solely on information collected at the time of intervention.
Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial):	Confounding expected, all known important confounding domains appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.	Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.	Intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively.
Serious risk of bias (the study has some important problems);	At least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding.	Selection into the study was related to intervention and outcome; or Start of follow up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time.	Intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention);	Confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding.	Selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time.	(Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases.
No information on which to base a judgement about risk of bias for this domain.	No information on whether confounding might be present.	No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide.	No definition of the intervention or no explanation of the source of information about intervention status is reported.

Table 2. Reaching risk of bias judgements in ROBINS-I: post-intervention domains

Judgement	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	No bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued.	Data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias.	The methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status.	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts.
Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial):	Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention.	Proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis.	The methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status.	The outcome measurements and analyses are consistent with an *a priori* plan; or are clearly defined and both internally and externally consistent; and There is no indication of selection of the reported analysis from among multiple analyses; and There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.
Serious risk of bias (the study has some important problems);	Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.	Proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.	The methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status.	Outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention);	Substantial deviations from the intended intervention are present and are not adjusted for in the analysis.	(Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.	The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.	There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results.
No information on which to base a judgement about risk of bias for this domain.	No information is reported on whether there is deviation from the intended intervention.	No information is reported about missing data or the potential for data to be missing.	No information is reported about the methods of outcome assessment.	There is too little information to make a judgement (for example, if only an abstract is available for the study).

Appendix 5. Risk of bias of randomized trials

Bias	Author's judgment	Support for judgment
Bisseling 2010		
Random sequence generation	High risk of bias	A secretary performed the randomization by placing closed envelopes in a box.
Allocation concealment	Unclear risk of bias	Closed envelops were used, but authors do not mention using opaque envelopes
Blinding of participants and personnel	High risk of bias	This was an open label trial without any blinding.
Blinding of outcome assessment	Unclear risk of bias	This was an open label trial without any blinding, which may have affected the outcome assessment of CRBSI.
Incomplete outcome data	Low risk of bias	All patients were accounted for, and there was not missing data.
Selective reporting	High risk of bias	Authors mainly present the secondary endpoint (length of CRBSI-free interval) in the results section and only briefly discuss the primary endpoint (development of a CRBSI). Moreover, it is not mentioned that the primary endpoint did not reach the adapted statistical significance threshold ($p<0.0056$) set in the context of the interim analysis.
Other bias	High risk of bias	The study was stopped early after an unplanned interim analysis based on clinical observation showing strong benefits in the treatment group.
Klek 2015		
Random sequence generation	Low risk of bias	Quote: "All patients who met the eligibility criteria were assigned to 1 of 3 treatment groups using sealed envelopes containing computer-generated allocation numbers"
Allocation concealment	Unclear risk of bias	Sealed envelops were used, but authors do not mention using opaque envelopes
Blinding of participants and personnel	High risk of bias	This was an open-label trial without blinding. Quote: "The study could not be blinded because of significant differences in the appearance of the vials containing saline and taurolidine. Those differences could not be overcome by simple masking of the labels."

Blinding of outcome assessment	Unclear risk	This was an open label trial without any blinding, which may have affected the outcome assessment of CRBSI.
Incomplete outcome data	Low risk of bias	There was no loss to follow-up, and all patients were accounted for.
Selective reporting	Low risk of bias	All endpoints were pre-specified and reported in the results.
Other bias	Unclear risk of bias	The sample size was small and there was no power calculation to support the sample size used
Salonen 2017		
Random sequence generation	Low risk of bias	Quote: "The randomization list was generated using http://www. randomization.com and blinded using supplement codes. Blocks of six were used to ensure balance in between the groups during the study."
Allocation concealment	Low risk of bias	The authors used blinded supplement codes in the allocation.
Blinding of participants and personnel	High risk of bias	Although, the study was double-blinded, the authors mention that ethanol has a distinct odour, which can be detected by many patients hence blinding could have been broken.
Blinding of outcome assessment	Low risk of bias	The study was double blinded so there is a low risk for outcome assessment to be biased.
Incomplete outcome data	Low risk of bias	All patients were accounted for and there are no missing data.
Selective reporting	Low risk of bias	The primary endpoint was well defined and fully reported.
Other bias	High risk of bias	The study was halted early after an interim analysis. The study did not reach the targeted sample size from their power calculations. Quote: “Due to the publication of the ESPEN guidelines on chronic intestinal failure in adults advising against ELT, an interim analysis was conducted. Review of the above results led us to terminate the study early because the early results indicated further study would be unlikely to change the final outcome. “

CRBSI: catheter related blood stream infection