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Randomized Control Trials

Taurolidine lock reduces *recurrent* catheter-related bloodstream infections in patients with chronic intestinal failure: A randomized, placebo-controlled trial in a real-world clinical setting

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Background & aims: *Recurrent* catheter-related bloodstream infections (CRBSIs) are a frequent, severe, and costly complication of home parenteral support (HPS) in patients with chronic intestinal failure (CIF). While taurolidine-containing catheter locks have shown potential in preventing CRBSIs, real-world data on their effectiveness in reducing *recurrent* infections remain limited.
This study aimed to assess the efficacy and safety of a 1.35% taurolidine-containing catheter lock solution compared to standard-of-care 0.9% saline for the secondary prevention of *recurrent* CRBSIs in adult CIF patients.
Methods: In this double-blind, placebo-controlled trial, adult CIF patients were age-matched, stratified by prior CRBSI incidence rates, and randomly assigned to use either a 1.35% taurolidine or a 0.9% saline lock for two years. The primary outcome was the difference in CRBSI occurrence between the two treatment groups, analyzed using the Andersen-Gill model with exact p-values obtained through a permutation test.
Results: A total of 61 CIF patients were randomized, with 31 assigned to the 1.35% taurolidine lock (17,809 treatment days), and 30 to the 0.9% saline lock (18,692 treatment days). Six CRBSIs occurred in the taurolidine group compared to 27 in the saline group, corresponding to incidence rates of 0.35 and 1.46 per 1000 central venous catheter (CVC) days, respectively. Taurolidine use significantly reduced the rate of *recurrent* CRBSIs by 77% compared to saline (HR 0.23, 95% CI; 0.09–0.62, p-exact = 0.009). Furthermore, taurolidine significantly lowered the rate of CVC removals due to CRBSIs by 91% compared to saline (HR 0.09, 95% CI; 0.02–0.43, p-exact = 0.002). The Number Needed to Treat (NNT) was 892 treatment days (97.5% robust CI; 124–1660, $p = 0.022$).
Conclusions: This study demonstrates that the use of 1.35% taurolidine significantly reduces the rate of *recurrent* CRBSIs and CVC removals due to CRBSIs compared to 0.9% saline in adult patients with CIF reliant on HPS.
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1. Introduction

Chronic intestinal failure (CIF) is the rarest form of organ failure, affecting approximately 80 individuals per million [1]. Patients with CIF depend on long-term home parenteral support (HPS), preferably administered through a subcutaneously tunneled, single-lumen central venous catheter (CVC) [2]. While HPS

Abbreviations: CIF, chronic intestinal failure; CRBSI, catheter-related bloodstream infections; CVC, central venous catheter; HPS, home parenteral support; IF, intestinal failure.

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is life-sustaining, the presence of a long-term CVC poses a significant risk of catheter-related complications [2–4]. Among these, catheter-related bloodstream infections (CRBSIs) are particularly concerning, as they lead to increased morbidity, mortality, and substantial healthcare costs [5,6]. CRBSIs account for 30–70% of hospital admissions among patients with CIF [7,8]. Recurrent CRBSIs often necessitate multiple CVC replacements, which increases the risk of compromised central venous access and HPS failure - a condition that is fatal without intestinal transplantation [2,5,9].

The development of CRBSIs involves a combination of catheter-, microbial-, and patient-related factors [10–14]. The primary pathogenic mechanism involves contamination at the catheter hub, which leads to intraluminal colonization and biofilm formation [2,15]. Microorganisms detaching from the biofilm can enter the bloodstream, causing CRBSIs [16]. Strict adherence to aseptic techniques during CVC insertion and handling remains the primary preventive strategy [2,12], however, CRBSIs remain a persistent threat to CIF patients [2,17]. To enhance prevention, catheter locking with various solutions containing antibiotics, anticoagulants, and antiseptics has been explored, but many of these solutions were abandoned due to ineffectiveness, adverse events, or the development of microbial resistance [5,18–20].

Historically, heparin was widely used as a catheter lock solution. However, evidence shows that heparin may promote *Staphylococcus aureus* biofilm formation, thereby increasing the risk of CRBSIs [21]. As a result, heparin is no longer recommended, and 0.9% saline is now preferred [3]. Taurolidine, an antiseptic agent, has emerged as a promising alternative. It prevents biofilm formation by inhibiting microbial adhesion to the luminal surface of CVCs [22–25]. Additionally, it exhibits broad-spectrum activity against bacterial and fungal pathogens by disrupting microbial cell membranes and neutralizing toxins [24]. Although several studies in CIF patients have demonstrated taurolidine's effectiveness in preventing CRBSIs, robust evidence from well-powered, prospective, blinded, and placebo-controlled RCTs remains limited [26,27]. Furthermore, there is still ongoing debate about which patients benefit most from taurolidine locks, and whether use should be limited to high-risk patients [28], or considered for the broader CIF population.

Most previous studies have focused on time-to-first-event endpoints for their primary and secondary analyses. However, this approach overlooks the recurrent nature of CRBSIs. Recurrent event analysis, which captures all occurrences of the same event type within the study period, offers a more comprehensive and real-world evaluation of treatment effects, greater statistical power, and a more accurate estimation of disease burden [29,30].

Recognizing these advantages, we designed the current study to evaluate the efficacy of 1.35% taurolidine compared to the standard-of-care 0.9% saline for the secondary prevention of *recurrent* CRBSIs and CVC removals in adult patients with CIF relying on HPS. In this context, secondary prevention refers to preventing *recurrent* CRBSIs in patients who have already experienced at least one episode, distinguishing it from primary prevention, which aims to prevent the first occurrence. Additionally, the study assessed other catheter-related complications and adverse events to provide a comprehensive understanding of taurolidine's clinical impact.

2. Material & methods

2.1. Study design and settings

This single-center, double-blind, randomized, placebo-controlled trial was conducted at the tertiary referral Intestinal Failure (IF) unit at Rigshospitalet, Copenhagen, Denmark. Recruitment took place between June 2019 and March 2020, with a two-year follow-up completed in March 2022. Potential participants were identified through the Copenhagen Intestinal Failure Database [31] and screened for eligibility during routine outpatient visits or hospital admissions. The CRBSI definition in the database combines microbiological and clinical data, rather than relying on strict microbiological criteria [32].

2.2. Participants – Inclusion and exclusion criteria

Eligible patients were adults aged 18–85 years with CIF of any etiology, who received HPS through a pre-existing subcutaneously tunneled, single-lumen CVC (e.g., Broviac or Hickmann catheter). Inclusion required a history of at least one CRBSI, indicating susceptibility to recurrent infections, and a minimum of three weeks since completing antibiotic treatment for the most recent episode. Exclusion criteria included pregnancy, lactation, or known hypersensitivity or allergy to the formulation of the taurolidine-containing catheter lock solution. Although prior use of taurolidine was not an exclusion criterion, none of the enrolled patients had received it as part of routine care, as it was not standard practice in our department at the time of inclusion. However, 16 patients had been exposed to taurolidine during a clinical trial conducted at our center between 2013 and 2016 [33]. Written informed consent was obtained from all participants prior to enrollment.

2.3. Randomization and blinding

Prior to randomization, patients were stratified by prior CRBSI incidence rate (≤ 4 or > 4 CRBSIs per 1000 CVC days) and matched by age (Supplementary Methods). This stratification was intended to minimize the risk of uneven distribution of the few patients with the highest risk between the two treatment groups. Group A included patients with a prior CRBSI incidence of ≤ 4 per 1000 CVC days, while Group B comprised ultra-high-risk patients with > 4 CRBSIs per 1000 CVC days. No stratification was performed based on the type of microorganisms responsible for previous infections. Within each group, patients were randomly assigned (1:1) to use either 1.35% taurolidine or 0.9% saline for two years.

Randomization was conducted externally by the Regional Pharmacy of the Capital region, Denmark, using an electronic randomization system [34] with a computer-generated permuted block scheme. To ensure balanced allocation of the two catheter lock solutions within each treatment group, the scheme included 15 blocks of 6 patients in Group A and 5 blocks of 6 patients in Group B, based on the expected recruitment distribution. Blinding was maintained for patients, investigators, and site personnel throughout randomization, treatment, data collection, and outcome consensus. Unblinding occurred in stages: initially, participants were unblinded only to anonymized group labels (Group X and Group Y), without revealing which specific catheter lock solution (taurolidine or saline) they had received. Full unblinding of treatment assignment occurred only after all statistical analyses were completed.

2.4. Study treatment and CVC procedures

The active treatment consisted of TauroLock™-Hep100, a catheter lock solution containing 1.35% (cyclo)-taurolidine, 4% sodium-citrate, and 100 IU/mL heparin (TauroPharm GmbH, Germany). This formulation was chosen to reflect clinical practice at the time of study design when heparin was the standard-of-care in our department. During the study preparation phase, the department transitioned to 0.9% saline as the new standard-of-care which was used as placebo, in accordance with ESPEN recommendations [35]. Both active treatment and placebo ampoules were identical in appearance, odor, and administration method.

Patients or caregivers were trained to instill the assigned catheter lock solution at home, following the IF Unit's standardized protocol [36]. Before each HPS infusion, the CVC was flushed with 10 mL of sterile 0.9% saline. After the infusion, the CVC was again flushed with 10 mL of saline, followed by instillation of 2 mL of the assigned catheter lock solution. The solution was left in the catheter lumen with a minimum dwell time of 4 h to ensure antimicrobial efficacy. During this period, the CVC was not assessed. If multiple HPS infusions were required in a single day, the lock solution was instilled only after the infusion with the longest interval before the subsequent one, to ensure the required 4-h dwell time. After other infusions, the CVC was locked with saline only. Before each new infusion, the lock solution was flushed out with 10 mL of saline. The frequency of administration followed the patient's HPS schedule, with a minimum of three instillations per week.

CVC insertions were performed by anesthesiologists, with placement confirmed by chest X-ray. Patients were followed every three to six months in our outpatient clinic, with additional visits and hospitalizations as needed. During follow-up visits, concomitant medications, CVC function, exit-site condition, signs of CRBSI, and adverse events were assessed. CRBSIs were treated according to departmental guidelines. CVC removal was indicated in cases of severe sepsis or septic shock; persistent or recurrent symptoms despite appropriate antibiotic therapy; infection with fungi or virulent bacteria; complicated infections (e.g., endocarditis, osteomyelitis); tunnel infections; recurrent CRBSI with the same pathogen; or catheter-related thrombosis. For admissions to local hospitals, physicians were instructed to follow our IF unit's guidelines, although antibiotic regimens followed the local guidelines. Complete medical records and discharge summaries were retrieved for all admissions. Patients remained in the study for the entire two years, after which they were censored. Compliance with the treatment protocol was assessed by counting unused catheter lock ampoules.

2.5. Outcomes

The primary outcome was the difference in CRBSI occurrence between the 1.35% taurolidine group and the 0.9% saline group, assessed by the hazard rate of *recurrent* CRBSIs and the incidence rate expressed as CRBSIs per 1,000 CVC days. Predefined secondary outcomes included time to first CRBSI, and the incidence of catheter-related complications (e.g., local infections, catheter occlusions, and catheter-related venous thrombosis), CVC removals, and adverse events.

2.6. Definition of catheter-related complications

A CRBSI was suspected when patients exhibited clinical signs of systemic infection (i.e., a body temperature > 38.5°C or < 36°C, chills, hypotension (systolic blood pressure < 90 mmHg or a decrease in systolic blood pressure > 40 mmHg), tachycardia (> 90 beats per minute), elevated white blood cell count (> 12×10^9/L) and/or an increase in C-reactive protein), in the absence of any identifiable source of infection other than the CVC, consistent with ESPEN guidelines [2,12]. Paired blood cultures were collected simultaneously from the CVC and a peripheral vein to assess the differential time to positivity. In cases of negative blood cultures, resolution of symptoms following CVC removal was considered indirect evidence of CRBSI, consistent with our clinical assessment approach. All suspected CRBSI episodes were confirmed by consensus among study investigators (CTN, PBJ, ST, and CEM), based on both clinical and microbiological evaluation, rather than relying solely on microbiological criteria. Only episodes in which the CVC was identified as the primary source of infection were included in the analysis. CRBSIs secondary to exit-site infections or other extraluminal sources were excluded. This approach aligns with the mechanism of action of catheter lock solutions, which specifically target intraluminal colonization and biofilm formation.

Local infections included *exit-site* and *tunnel* infections. *Exit-site infections* were defined by erythema, induration, drainage, and tenderness within two centimeters of the catheter exit site, whereas *tunnel infections* occurred further along the subcutaneous tunnel [37].

Mechanical complications of the CVC included occlusions (e.g., inability to flush, failure to aspirate, or insufficient infusion), displacement (e.g., visible cuff or accidental removal), and defects (e.g., breakage or silicone degradation).

2.7. Protocol amendment

Recruitment challenges related to the COVID-19 pandemic prevented the study from reaching the planned sample size determined by the power calculation. In consultation with our statistician, the treatment period was extended from 18 to 24 months. This amendment was approved by the Danish Research Ethics Committee in June 2020 (protocol amendment no.73659).

2.8. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (ISO 14155:2011) and Good Clinical Practice guidelines. Approval was obtained from the Danish Research Ethics Committee (journal no.: H-19000051) and the Danish Data Protection Agency (journal no.: VD-2019-170). Written informed consent was obtained from all participants prior to enrollment.

2.9. Statistical considerations and analyses

2.9.1. Power calculation

Sample size calculations assumed a 70% reduction in CRBSI rate in the 1.35% taurolidine group compared to the 0.9% saline group. Using a two-tailed α error of 5%, 80% power, and a significance level of 5%, the required sample size was 44 patients per group. To account for a 30% anticipated drop-out rate, 18-months of follow-up was planned. These calculations were based on a CRBSI incidence rate of one episode per 1000 CVC days, as observed in previous studies of our cohort [33,38]. Due to recruitment challenges during the COVID-19 pandemic, the study was underpowered for subgroup analysis and the entire cohort was analyzed.

2.9.2. Baseline characteristics

Categorical variables are presented as counts and percentages, with comparisons using the Chi-square tests. Continuous variables are reported as means with 95% CIs for normally distributed data and as medians with IQRs for non-normally distributed data. Comparisons were conducted using the t-test for normally distributed data and the Wilcoxon rank-sum test for non-normally distributed data. Statistical significance was defined as $p < 0.05$.

2.9.3. Survival model

The Andersen-Gill (AG) model [29,30] with robust standard errors was employed to estimate hazard ratios (HRs) and compare CRBSI rate between treatment groups. This model is an extension of the Cox proportional hazards model and specifically designed to handle recurrent events. Censoring occurred at patient withdrawal, discontinuation, study completion, or death. The period at risk of CRBSI included days from randomization during which the patients had a subcutaneously tunneled CVC, no CRBSI, and was not receiving intravenous antibiotics.

P-values were calculated using the permutation test [39,40], a non-parametric method that reshuffles treatment assignments within randomization strata to generate the null distribution for the test statistic. The exact p-value represents the proportion of permuted test statistics that are as extreme or more extreme than the observed value. We applied this method to ensure robust statistical inference given the limited sample size.

2.9.4. Incidence rates

Incidence rates were calculated as episodes per 1000 CVC days at risk of CRBSI. A random-effects Poisson regression model was used to compare incidence rates between treatment groups, reporting incidence rate ratios (IRRs) with robust 97.5% CIs.

2.9.5. Number needed to treat (NNT)

The random-effects Poisson regression model was also used to calculate NNT, expressed as treatment days required to prevent one CRBSI, with robust 97.5% CIs.

2.9.6. Time to first event

We estimated the cumulative incidence of time to first CRBSI using the Aalen-Johansen estimator, and applied Gray's test to compare groups while accounting for the competing event of death. The AG model with robust standard errors was used to estimate HRs, and permutation tests were applied to calculate exact p-values, consistent with the recurrent event analysis. CVC days were defined as the number of days a patient had a CVC from randomization until the first occurrence of CRBSI, death, discontinuation, or end of treatment.

All statistical analyses were performed using RStudio, version 4.2.2.

3. Results

3.1. Study population

A total of 61 patients were enrolled and followed for 2 years. Of these, 31 patients received taurolidine, and 30 patients received saline as their catheter lock solution. The median age was 63.3 years (IQR: 52.6–75.6). Baseline characteristics and potential risk factors for CRBSIs were similar between the two groups (Table 1).

Prior to enrollment, the study population had received HPS for a total of 171,877 CVC days, with a median of 2277 CVC days per patient (IQR: 1513–3349). The median CRBSI incidence rate prior to the study was 1.3 episodes per 1000 CVC days, with no significant difference between the taurolidine and saline group ($p = 0.27$) (Table 1).

3.2. CRBSIs

During the study, 33 CRBSIs occurred during 36,363 CVC days, resulting in an overall incidence rate of 0.91 episodes per 1000 CVC days. In the taurolidine group, 6 CRBSIs occurred in 6 patients over 17,750 CVC days, while 27 CRBSIs occurred in 12 patients during 18,613 CVC days in the saline group, yielding incidence rates of 0.34 and 1.46 episodes per 1000 CVC days, respectively ($p = 0.003$). Notably, no recurrent CRBSIs were observed in the taurolidine group during the study period. The unadjusted HR was 0.23 (95% CI; 0.09–0.62), corresponding to a 77% reduction in CRBSI rate with the use of taurolidine compared to saline (p-exact = 0.009). After adjusting for baseline CRBSI incidence rate, taurolidine still significantly reduced the rate by 68% (HR 0.32, 95% CI; 0.14–0.72, p-exact = 0.009).

The NNT to prevent one CRBSI with taurolidine use was 892 treatments days (Robust 97.5% CI; 124–1660, $p = 0.022$).

There was no significant difference in time to first episode of CRBSI between the taurolidine and saline groups (Supplementary Table 1).

3.3. Catheter-related complications

No significant differences were found between the groups regarding mechanical complications, with 13 episodes reported in the taurolidine group and 14 in the saline group. The types and incidence rates are detailed in Table 2. CVC removals due to mechanical complications were also comparable between the groups (Table 2).

A total of 15 local infections were recorded, with 4 infections in the taurolidine group and 11 in the saline group. This resulted in incidence rates of 0.23 and 0.59 per 1000 CVC days, respectively. No significant differences were found in either local infections or CVC removals due to local infections between the two groups.

One patient in the taurolidine group developed catheter-related thrombosis, partially involving the left subclavian and axillary veins. The catheter was removed, and a new one was inserted on the contralateral side of the thorax. The patient was treated with anticoagulants.

3.4. CVC removals

3.4.1. Overall CVC removals

A total of 50 CVCs were removed due to catheter-related complications, including 14 in the taurolidine group and 36 in the saline group. This corresponded to incidence rates of 0.79 and 1.93 per 1,000 CVC days, respectively ($p = 0.006$).

3.4.2. CVC removals due to CRBSIs

CVC removals due to CRBSI were significantly lower in the taurolidine group (2 removals) compared to the saline group (23 removals), resulting in incidence rates of 0.11 and 1.23 per 1000 CVC days, respectively ($p = 0.002$). The HR for CVC removal due to CRBSI was 0.09 (95% CI; 0.02–0.43), indicating a 91% reduction in CVC removal rate with taurolidine use compared to saline (p-exact = 0.002). No CVCs were removed using the guidewire replacement (GWR) method [41].

3.5. Microorganisms causing CRBSIs

Among the 33 CRBSIs, 18 were monobacterial, 6 polybacterial, 5 fungal, and 4 combined bacterial and fungal infections. In the taurolidine group, all 6 CRBSIs were monobacterial, with 4 (67%) caused by coagulase-negative staphylococci and 2 (33%) caused by gram-negative bacteria, specifically *Klebsiella pneumoniae* and *Klebsiella oxytoca*.

In the saline group, 27 CRBSIs were observed, of which 12 (44%) were monobacterial, with 3 (25%) caused by coagulase-negative staphylococci and 9 (75%) by gram-negative bacteria (3 caused by *Klebsiella pneumoniae*, 3 by *Escherichia coli*, and the rest caused by miscellaneous gram-negative bacteria). Additionally, 6 (22%) were polybacterial, 5 (19%) were fungal (all *Candida* species), and 4 (15%) were combined bacterial and fungal infections (Figs. 1 and 2). Detailed microbiological data are presented in Supplementary Tables 2 and 3.

Table 1
Baseline characteristics of study participants.

	1.35% taurolidine	0.9 %saline	Total	p-value[e]
Number of patients, *n*	31	30	61	
Sex, *Female/Male*	19/12	17/13	36/25	0.92 [f]
Age at enrollment, *median years [IQR]*	64.5 [52.7, 72.9]	63.1 [53.7, 75.7]	63.3 [52.6, 75.6]	0.93 [g]
BMI, *mean (SD)*	23.7 (4.6)	23.4 (4.4)	23.6 (4.5)	0.76 [h]
Underlying disease, *n (%)*				0.23 [f]
IBD	15 (48.4)	9 (30.0)	24 (39.3)	
Complications of surgery	9 (29.0)	7 (23.3)	16 (26.2)	
Mesenteric ischemia	2 (6.5)	3 (10.0)	5 (8.2)	
Cancer	4 (12.9)	5 (16.7)	9 (14.8)	
Other	1 (3.2)	6 (20.0)	7 (11.5)	
Mechanism of Intestinal Failure, *n (%)*				0.19 [f]
SBS	23 (74.2)	16 (53.3)	39 (63.9)	
Intestinal dysmotility	2 (6.5)	5 (16.7)	7 (11.5)	
Mechanical obstruction	1 (3.2)	1 (3.3)	2 (3.3)	
Mucosal disease	2 (6.5)	3 (10.0)	5 (8.2)	
Intestinal fistulae	2 (6.5)	0 (0.0)	2 (3.3)	
Combined	1 (3.2)	5 (16.7)	6 (9.8)	
Stoma, *n (%)*				1.00 [f]
No	6 (19.4)	6 (20.0)	12 (19.7)	
Yes	25 (80.6)	24 (80.0)	49 (80.3)	
Medication, *n (%)*				
Anticoagulants [a]	9 (29.0)	9 (30.0)	18 (29.5)	1.00 [f]
Opioids [b]	19 (61.3)	18 (60.0)	37 (60.7)	1.00 [f]
Immunosuppressants [c]	3 (9.7)	3 (10.0)	6 (9.8)	1.00 [f]
Prophylactic antibiotics [d]	1 (3.2)	1 (3.3)	2 (3.3)	1.00 [f]
CRBSI incidence per 1,000 CVC days	1.2	1.7	1.3	0.27 [i]
CVC days before enrollment, *total days (years)*	86,038 (235.6)	85,839 (235.0)	171,877 (470.6)	
CVC days per patient, *median days [IQR]*	2344 [1800–3333]	1912 [1508–3437]	2277 [1513–3349]	0.70 [g]
CVC age at baseline, *median days [IQR]*	420 [202–799]	364 [128–672]	364 [166–742]	0.53 [g]
Number of CRBSIs in pre-existing CVC, *n*	6	10	16	
CRBSI incidence in pre-existing CVC per 1000 CVC days	0.3	0.6	0.4	0.16 [i]
HPS infusions per week, *median [min–max]*	7 [2, 21]	7 [3, 14]	7 [2,21]	0.73 [g]
HPS components, *n (%)*				1.00 [f]
Nutrition	27 (87.1)	26 (86.7)	53 (86.9)	
Fluids only	4 (12.9)	4 (13.3)	8 (13.1)	
HPS administration, *n (%)*				0.23 [f]
Patient	26 (83.9)	19 (63.3)	45 (73.8)	
Relative	0 (0.0)	2 (6.7)	2 (3.3)	
Healthcare nurse	3 (9.7)	6 (20.0)	9 (14.8)	
Combination	2 (6.5)	3 (10.0)	5 (8.2)	
CVC placement, *n (%)*				0.50 [f]
Right subclavian vein	8 (25.8)	4 (13.3)	12 (19.7)	
Left subclavian vein	3 (9.7)	5 (16.7)	8 (13.1)	
Right internal jugular vein	16 (51.6)	14 (46.7)	30 (49.2)	
Left internal jugular vein	4 (12.9)	6 (20.0)	10 (16.4)	
Right femoral vein	0 (0.0)	1 (3.3)	1 (1.6)	

Abbreviations: CRBSI, Catheter-related Bloodstream Infection; CVC, Central venous catheter; HPS, Home Parenteral Support; IBD, Inflammatory Bowel Disease; IQR, Interquartile range; SBS, Short Bowel Syndrome; SD, Standard Deviation.
[a] Anticoagulants include all antithrombotic drugs, including acetylsalicylic acid, warfarin, and clopidogrel.
[b] Opiates include all drugs containing opium or its derivatives, such as codeine, fentanyl, tramadol, oxycodone, morphine, tapentadol, methadone, and ketobemidone.
[c] Immunosuppressants include drugs that suppress or reduce immune system activity, such as tacrolimus, vedolizumab, methotrexate, and prednisolone.
[d] Prophylactic antibiotics were administered periodically by one patient, who self-administered cefuroxime for recurrent advanced urinary tract infections, while another patient alternated between pivmecillinam and trimethoprim every three month for recurrent urinary tract infections.
[e] P-values were calculated to test the null hypothesis (no difference between groups), with a two-sided p-value of < 0.05 considered statistically significant.
[f] Determined by Chi-square test (categorical data).
[g] Determined by Wilcoxon's rank-sum test (continuous and not normally distributed data).
[h] Determined by two-sample t-test (continuous and normally distributed data).
[i] Determined by Poisson model, Robust 97.5% CI, cluster patient ID to adjust for the correlation between CRBSIs in one patient.

3.6. Adverse events and mortality

Mild adverse events related to catheter locking were reported by seven patients (11.5%). The most common adverse event was an unpleasant or metallic taste, experienced by three patients, two of whom were in the taurolidine group.

Three patients withdrew consent due to adverse events. In the taurolidine group, one patient experienced flushing during catheter lock instillation after 20 months of treatment; symptoms resolved upon discontinuation. In the saline group, two patients withdrew—one citing headache and joint pain, and the other reported nausea (Table 3).

During the study, two deaths occurred, both in the taurolidine group. Neither death was related to CRBSIs or taurolidine treatment. One patient died from disseminated cancer, while the other, from age-related decline and multiple comorbidities while receiving palliative care.

4. Discussion

Our study demonstrates that a 1.35% taurolidine-containing catheter lock solution significantly reduces the rate of *recurrent* CRBSIs by 68% in adult patients with CIF, when adjusted for baseline CRBSI incidence. To the best of our knowledge, this is the

Table 2
Results on *recurrent* Catheter-Related Bloodstream Infections (CRBSIs), Central Venous Catheter (CVC) removals, and other catheter-related complications.

	1.35% taurolidine	0.9% saline	Total	IRR or HR or HR-adjusted	p-value[g]
Number of patients	31	30	61		
CVC days	17,750	18,613	36,363		
CRBSI					
Episodes, *n*	6	27	33		
Incidence per 1000 CVC days [a]	0.34	1.46	0.91		
IRR, *[97.5 % CI]*				0.23 [0.09–0.61]	0.003 [c]
HR, *[95 % CI]*				0.23 [0.09–0.62]	0.009 [d]
HR adjusted [b], *[95 % CI]*				0.32 [0.14–0.72]	0.009 [e]
CVC removals due to CRBSI					
Episodes, *n*	2	23	25		
Incidence per 1000 CVC days [a]	0.11	1.23	0.68		
IRR, *[97.5 % CI]*				0.09 [0.02–0.42]	0.002 [c]
HR, *[95 % CI]*				0.09 [0.02–0.43]	0.002 [d]
Local infections					
Episodes, *n*	4	11	15		
Incidence per 1000 CVC days [a]	0.23	0.59	0.41		
IRR *[97.5 % CI]*				0.38 [0.12–1.22]	0.103 [c]
HR *[95 % CI]*				0.38 [0.11–1.26]	0.113 [d]
CVC removals due to local infections, *n*	4	8	12		
Mechanical complications					
Episodes, *n*	13	14	27		
Incidence per 1000 CVC days [a]	0.73	0.74	0.73		1.00 [f]
CVC occlusion	4	1	5		
CVC displacement	2	5	7		
CVC defect	7	8	15		
CVC removals due to mechanical complications, *n*	5	6	11		
Catheter-related venous thrombosis					
Episodes, *n*	1	0	1		–
Incidence per 1000 CVC days [a]	0.06	0.00	0.03		–
CVC removals due to catheter-related venous thrombosis, *n*	1	0	1		
CVC removals due to any reason					
Episodes [h], *n*	14	36	50		
Incidence per 1000 CVC days [a]	0.79	1.93	1.40		
IRR *[97.5 % CI]*				0.40 [0.21–0.74]	0.006 [c]

Abbreviations: CI, Confidence Interval; CRBSI, Catheter-related blood stream infection; CVC, Central venous catheter; HR, Hazard ratio; IRR, Incidence rate ratio.
[a] CVC days; Days at risk of CRBSI; days with a tunneled CVC and no use of IV antibiotics as defined in the methods section.
[b] HR adjusted for prior CRBSI incidence rate.
[c] Poisson model, Robust 97.5% CI, Cluster patient ID to adjust for the correlation between CRBSIs in one patient.
[d] Hazard ratio calculated by the Andersen-Gill model, and exact p-value calculated by permutation test to eliminate small sample issues.
[e] Hazard ratio calculated by the Anderson-Gill model adjusted for CRBSI incidence rate prior to enrollment in the study, and exact p-value calculated by permutation test to eliminate small sample issues.
[f] Determined by Wilcoxon's rank-sum test (continuous and not normally distributed data).
[g] P-values were calculated to test the null hypothesis (no difference between groups), with a two-sided p-value of < 0.05 considered statistically significant.
[h] Two CVCs in the taurolidine group were removed due to suspected CRBSI, but subsequent investigation revealed that the source of infection was unrelated to the CVC.

first RCT in this field, to accurately reflect the clinical challenges faced by CIF patients with a history of CRBSIs, who therefore are at elevated risk of *recurrent* infections.

The prevention of CRBSIs is crucial for patients with CIF, whose survival depends on maintaining a reliable central venous access. CRBSIs pose a significant clinical burden, often necessitating recurrent hospital admissions, prolonged intravenous antimicrobial therapy, and CVC replacements. Even a single episode can result in severe complications such as septic shock, metastatic infections, loss of vascular access, and potentially death. CIF patients face a persistent risk of CRBSIs which can substantially impact their spontaneity and overall quality of life.

While strict adherence to aseptic CVC handling remains the primary strategy for CRBSI prevention, catheter locking has emerged as an important adjunctive measure. Prior studies have consistently demonstrated the effectiveness of taurolidine in reducing CRBSI rate across various patient populations [25,33,42–44]. Our findings further support its clinical value, with a favorable NNT of 892 treatment days to prevent one CRBSI. Given taurolidine's advantageous safety profile - degrading into taurine, carbon dioxide, and water [45] – its declining costs in many countries, and the lack of evidence for microbial resistance [22,46], we recommend taurolidine locking as a standard practice for secondary CRBSI prevention in adult CIF patients relying on HPS. This recommendation is consistent with ESPEN guidelines [35], which advocate for taurolidine locking as an additional preventive measure.

All participants were enrolled with an existing CVC, likely already harboring intraluminal biofilms [16]. In a randomized trial involving pediatric cancer patients, Handrup et al. [25] compared a taurolidine-citrate-heparin lock to a heparin lock in 48 long-term CVCs, assessing biofilm formation using electron microscopy. Biofilm was detected in 23 of 26 CVCs in the taurolidine group and 21 of 22 CVCs in the heparin group, with no significant difference between the groups. Despite this, the CRBSI incidence was significantly lower in the taurolidine group (0.1 and 0.9 CRBSIs per 1,000 CVC days, $p = 0.03$). These findings suggest that the clinical benefit of taurolidine may not lie in eliminating established biofilms but could involve other mechanisms. Although in vitro studies have demonstrated that taurolidine reduce biofilm formation, these models typically involve young, mono-species biofilms that may not fully replicate the complexity of in vivo conditions [10,47–49]. Therefore, the exact mechanism by which taurolidine prevents CRBSIs in long-term CVCs warrants further investigation. Our findings, specifically the observed microbial patterns, provide additional context for

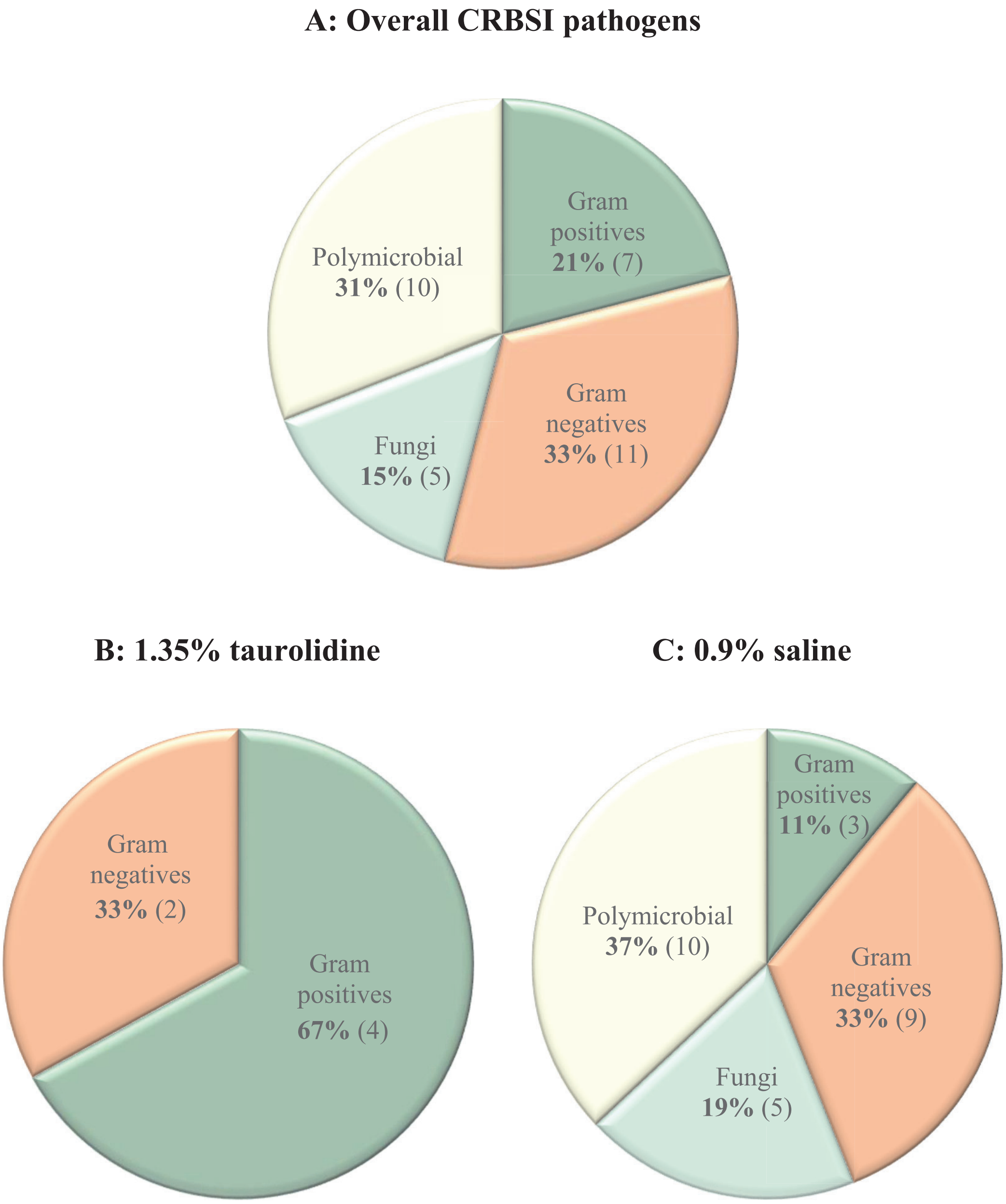

Fig. 1. Distribution of pathogens causing catheter-related bloodstream infections (CRBSIs) in patients with chronic intestinal failure (CIF). The data are presented as percentages, calculated from the absolute numbers of pathogens, with the absolute counts shown in parentheses.
Abbreviations: CIF, Chronic Intestinal Failure; CRBSI, Catheter-related bloodstream infections; CVC, central venous catheter; HPS, Home Parenteral Support.
A: Overall distribution of pathogens causing CRBSIs in patients with CIF.
B: Distribution of pathogens in the 1.35% taurolidine group.
C: Distribution of pathogens in the 0.9% saline group.

this observation. All six CRBSIs in the taurolidine group were monobacterial and primarily caused by coagulase-negative staphylococci. Notably, no polymicrobial or fungal infections were observed in this group. In contrast, the saline group exhibited more complex microbial patterns, with polymicrobial CRBSIs occurring nearly as often as monobacterial ones, and 19% of infections being fungal. These infection types are particularly problematic, as they are associated with a higher risk of a severe disease course and secondary complications, including osteomyelitis, endocarditis, and ophthalmitis, especially when the CVC is not removed [37,50,51]. Standard clinical practice is to remove the CVC in cases of fungal infection. Moreover, microorganisms within polymicrobial biofilms may develop and share survival strategies, such as enhanced antimicrobial resistance, thereby complicating treatment [52] and increasing the likelihood of CVC removal. Consistent with this, our study demonstrated a significant 91% reduction in CRBSI-related CVC removals in the taurolidine group. This likely reflects the lower incidence of complex, high-risk infections in this group, suggesting that taurolidine may help prevent these infections. However, the precise mechanisms remain unclear, as we did not perform biofilm analyses on the removed CVCs. This limits our ability to directly assess taurolidine's effect on biofilm morphology or microbial colonization.

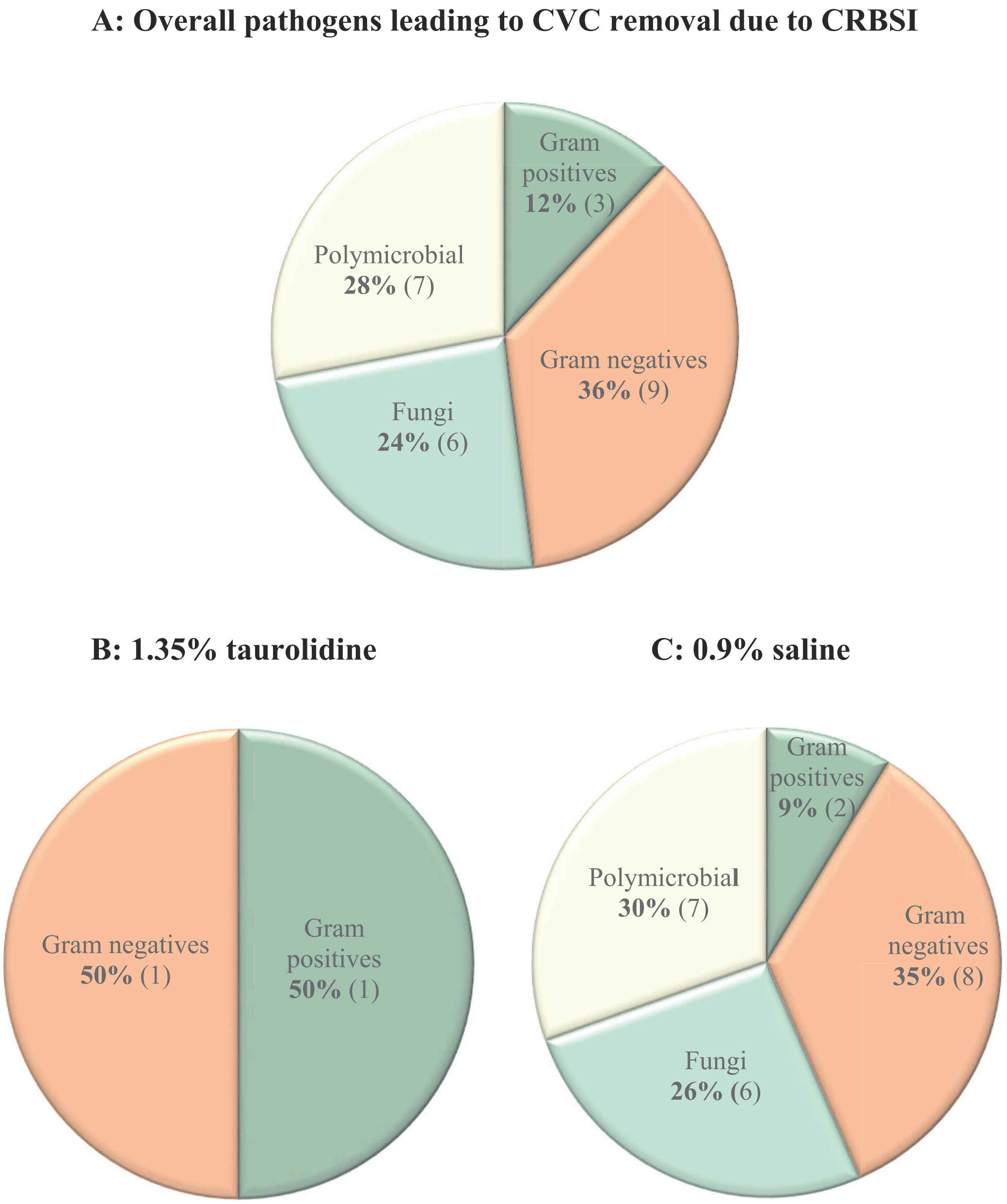

Fig. 2. Distribution of pathogens leading to central venous catheter (CVC) removal due to catheter-related bloodstream infections (CRBSIs) in patients with chronic intestinal failure (CIF). The data are presented as percentages, calculated from the absolute numbers of pathogens, with the absolute counts shown in parentheses.
Abbreviations: CIF, Chronic Intestinal Failure; CRBSI, Catheter-related bloodstream infections; CVC, central venous catheter; HPS, Home Parenteral Support.
A: Overall distribution of pathogens causing CVC removal due to CRBSI in patients with CIF.
B: Distribution of pathogens in the 1.35% taurolidine group. C: Distribution of pathogens in the 0.9% saline group.

The composition of taurolidine-based lock solutions varies across studies, particularly with respect to taurolidine concentration and the addition of anticoagulants. In our study, we used a formulation containing 1.35% taurolidine, 4% citrate, and 100 IU/ml heparin, reflecting standard clinical practice at the time of study design. An in vitro study by Olthof et al. [53] demonstrated that various taurolidine-containing lock solutions exhibited strong microbiocidal activity against fungal, Gram-negative, and Gram-positive pathogens. While higher taurolidine concentration provided slightly greater inhibition of microbial growth, the clinical relevance of this difference remains unclear. Notably, the presence of citrate and/or heparin did not diminish taurolidine's antimicrobial efficacy. Direct clinical comparisons of taurolidine formulations are limited, and no consensus exists on the optimal composition. Head-to-head clinical trials are needed to determine the most effective and feasible formulation for routine use.

Previous studies in CIF patients receiving HPS have often faced methodological limitations, including retrospective designs, absence of control groups, open-label protocols, and small sample sizes, as highlighted by recent meta-analyses and systematic reviews [27,54–56]. The rarity of CIF further complicates patient recruitment, making well-powered RCTs difficult to conduct [2]. A 2022 meta-analysis [54] identified only five prospective RCTs involving patients with IF receiving HPS, three of which focused on

Table 3
Adverse events and deaths during the study.

	1.35% taurolidine	0.9% saline	Total	p-value [a]
Adverse events				
Patients with adverse events, *n (%)*	4 (12.9)	3 (10.0)	7 (11.5)	
Unpleasant/metallic taste	2	1	3	
Nausea	0	1[c]	1	
Flushing	1[c]	0	1	
Headache and sore joints	0	1[c]	1	
Urinary urgency	1	0	1	
Deaths				
Number of deaths, *n*	2	0	2	
Disseminated cancer	1	0	1	
Age-related decline and multiple comorbidities	1	0	1	
Admissions				
Admission days, *n*	363	1008	1371	
Admission days per patient, m*edian [IQR]*	3 [1–7]	3 [1–12]	3 [1–9]	0.25[b]
Antibiotic treatment				
IV antibiotic treatment, *total days*	151	736	887	
IV antibiotic treatment, *median days per patient, [IQR]*	2 [0–7]	8.5 [0–13]	5 [0–10]	<0.001[b]

Abbreviations: HPS, Home Parenteral Support; IQR, Inter Quartile Range.
[a] P-values were calculated to test the null hypothesis (no difference between groups), with a two-sided p-value of <0.05 considered statistically significant.
[b] Determined by Wilcoxon's rank-sum test (continuous not normally distributed data).
[c] Patients who withdrew informed consent due to adverse events.

adults [33,42,57]. These studies primarily examined the time to first CRBSI, overlooking the fact that many CIF patients experience recurrent CRBSIs. Since prior infections can increase the risk of subsequent episodes, time-to-first event analyses may limit the ability to capture the full burden of disease and underestimate the treatment effect over time.

To address these limitations, we designed this study with a recurrent event design. By focusing on *recurrent* CRBSIs rather than only the first episode, the study captured a greater number of events, thereby enhancing statistical power and yelding valuable insights for this small patient population. This approach also enabled the calculation of the NNT, providing clinicians with practical guidance on the intervention's clinical impact. We applied minimal exclusion criteria, enrolling a diverse population of CIF patients while maintaining their daily routines except for the introduction of locking procedures. By combining the recurrent event design with the inclusion of a heterogeneous group of CIF patients, the study closely mirrors clinical reality, thereby enhancing its real-world relevance. Adopting a similar design in future studies may provide a more comprehensive understanding of treatment effects in clinical practice, extending beyond a sole focus on the time to first CRBSI. Despite the two-year follow-up in this study, evidence on the long-term efficacy of taurolidine remains limited.

The study has certain limitations. Recruitment challenges during the COVID-19 pandemic necessitated an extension of the treatment period from 18 to 24 months. No significant difference in time to first CRBSI was observed between groups, likely due to limited statistical power resulting from the relatively small sample size and the low number of events captured by this endpoint. While underpowered for this specific outcome, the study was adequately powered to detect differences in overall CRBSI incidence, as it accounted for all *recurrent* events. This approach enhanced statistical power and provided a more sensitive and clinically relevant assessment of taurolidine's effect, which is particularly important in CIF patients, who face an ongoing risk of recurrent infections, each contributing to the cumulative clinical burden.

The saline group showed a higher proportion of polymicrobial and fungal CRBSIs than is typically reported in the literature [32,42]. This may reflect random variation due to the low number of events or clustering of complex infections in a small number of patients. Selection bias is also possible, as patients with a history of prior infections may have been more motivated to participate in this prevention trial. Additionally, in the absence of standardized definitions in the HPS literature, ultra-high-risk patients (defined by a prior CRBSI incidence rate of > 4 per 1000 CVC days) were classified based on expert opinion. To address this limitation and reduce potential bias, we employed stratified randomization based on prior CRBSI incidence, to ensure a balanced distribution of these patients across the treatment groups. However, the benefit of catheter lock solutions for ultra-high-risk patients remains uncertain and requires further investigation.

Identifying which patients are most likely to develop CRBSIs remains a clinical challenge, and there is ongoing debate about whether taurolidine containing catheter locks should be reserved for high-risk patients or considered for broader use. Regardless of risk category, each preventable episode of CRBSI is of high value to the patient. Given taurolidine's declining costs in many countries and low incidence of adverse events, investigating its potential for primary prevention is important. While this study focused on secondary prevention, a cost-effectiveness analysis could further support its broader adoption for primary prevention in clinical practice. Future studies should also investigate taurolidine's impact on CRBSI severity, microbial patterns, and the virulence of causative microorganisms, as these factors influence the risk of CVC removal and clinical outcomes.

5. Conclusion

In conclusion, this study demonstrates that a 1.35% taurolidine-containing catheter lock solution significantly reduces the rate of *recurrent* CRBSIs in adult CIF patients compared to 0.9% saline. Importantly, the intervention also reduces the rate of CRBSI-related CVC removals without increasing the incidence of other catheter-related complications or adverse events. By adopting a recurrent event design, this study offers a clinically relevant reflection of the challenges faced by CIF patients with a history of CRBSI. These findings strongly support the implementation of 1.35% taurolidine as a safe and effective standard practice for the secondary prevention of *recurrent* CRBSIs in patients with CIF.

Author contributions

Camilla T. Nerstrøm: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing –

Original Draft, Writing – Review & Editing, Visualization, Project administration.

Thomas Scheike: Methodology, Formal Analysis, Writing – review & Editing, Supervision.

Claus E. Moser: Validation, Writing – Review & Editing, Supervision.

Siri Tribler: Conceptualization, Methodology, Validation, Writing – Review & Editing, Supervision.

Palle B. Jeppesen: Conceptualization, Methodology, Validation, Investigation, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Data availability statement

Raw patient data is not available to protect patient confidentiality. Protocol and Analytical code will be made available upon request.

Disclaimers

The Department of Digestive Diseases, Transplantation and General Surgery, Section for Intestinal Failure at Copenhagen University Hospital, Rigshospitalet, Denmark is responsible for all analyses, interpretations, and conclusions. The funder was not involved in the study design, data collection, data analysis, manuscript preparation, or the decision to publish. The authors declare no conflicts of interest related to this study.

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Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.05.020.

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