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ORIGINAL ARTICLE

Longitudinal evolution of catheter-related bloodstream infections, kidney function and liver status in a nationwide adult intestinal failure cohort

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ABSTRACT

Objectives: The development of intestinal failure-related complications in Finnish adults is unknown. This study aimed to investigate the incidence of catheter-related bloodstream infections (CRBSI), and the longitudinal changes in biochemical liver and kidney tests in a nationwide cohort.

Materials and methods: The search for Finnish adults with intestinal failure (IF) utilized a survey to Finnish health-care providers ($n = 111$) with the potential to provide long-term parenteral support (PS) for adult IF. Our nationwide, cross-sectional cohort included all IF patients aged $\geq$ 18 years who had received PS for $\geq$ 120 d in 2017. Data regarding CRBSI and biochemical liver and kidney tests were collected from patient records at the start of PS up to the latest available measurement in 2017.

Results: In the nationwide cohort of 52 patients, the CRBSI incidence was 1.35/1000 catheter days. Seventy-three percent of CRBSI in a long-term catheter led to catheter replacement. During a median PS duration of 27.5 (interquartile range [IQR] 11.3–57.3) months, a statistically significant median change occurred in estimated glomerular filtration rate (eGFR; −8.5 ml/min/1.73 m^2, IQR −30–7, $p = .005$) and alkaline phosphatase (ALP; 26 U/l, IQR −11–95, $p = .019$). In a multiple regression model for eGFR at data collection, baseline eGFR and age were strong explanatory variables.

Conclusions: Incidence of CRBSI, but not treatment strategies, in this nationwide adult IF population correspond well to those reported from specialized centers. Decreased kidney function and abnormal liver test results are frequent findings, and even more so over time, emphasizing the importance of regular monitoring.

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Introduction

Long-term dependency on parenteral support (PS) to maintain health defines intestinal failure (IF) [1]. Both IF and long-term PS are associated with significant complications, such as catheter-related bloodstream infection (CRBSI), IF-associated liver disease (IFALD) and impaired kidney function [2]. Mortality directly related to complications of long-term PS is today rare [3], but complications and their treatment constitute a substantial proportion of costs related to home parenteral support (HPS) [4] and impair patients' quality of life [5]. Moreover, complication rate acts as a marker of safety and quality of care for HPS patients [6].

Comparison of IF-related complication rates reported in the literature is challenging because the rates vary greatly. This wide range may, in part, pertain to variation in the applied diagnostic methods and definitions [7,8]. To illustrate, a recent review and meta-analysis on CRBSI stratified the included studies by the definition of infectious catheter complication and reported a random-effects summary rate per 1000 catheter days of 0.85 (95% confidence interval [CI] 0.27–2.64) for CRBSI, and 1.65 (95% CI 1.09–2.48) for central line-associated bloodstream infections, the latter of which has less strict criteria [9].

Widely used methods for assessment of organ function might be inaccurate in IF patients, as is the case for estimated glomerular filtration rate (eGFR) in assessing kidney function [10], and methods considered gold standards may lack IF-specific reference values and classifications, e.g., liver histology for IFALD detection [11]. Furthermore, current knowledge regarding risk factors of IF-related complications is conflicting, as in CRBSI [9], or limited, as in kidney failure [12].

Taken together, many aspects of IF-related complications require further investigation. The aim of our study was to investigate the incidence of CRBSI and the longitudinal changes in biochemical kidney and liver tests, and factors affecting them in a register-based retrospective nationwide cohort of adults with IF.

Methods

The search for adult IF patients in September 2017 utilized a survey submitted to all Finnish units with the potential of

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providing long-term PS, as previously described [13]. Patient inclusion criteria were age $\geq$ 18 years, PS duration $\geq$ 120 d, IF as the indication for PS, and the availability of patient records. We defined and classified IF according to the European Society for Clinical Nutrition and Metabolism recommendations [1,14]. Clinical data were manually collected from hospital patient records from the start of PS (baseline) up to the latest available measurement in 2017 (data collection). If a patient weaned off PS during 2017, the data were collected from the last available measurement when the patient still received the treatment.

The strict definition of CRBSI was the growth of an identical organism from at least one peripheral blood culture and from a culture of the catheter tip on removal in a patient with clinical symptoms of sepsis. We also collected the data when clinicians had considered the bloodstream infection to be catheter-related, even though the definitive diagnosis had not been set as per the Infectious Diseases Society of America 2009 recommendations [15]. The overall CRBSI rate was calculated by dividing the number of CRBSI in the whole patient cohort by the combined 1000 catheter days in the whole cohort. Plasma alanine aminotransferase (ALT, U/l) and alkaline phosphatase (ALP, U/l) served as markers for liver status and creatinine (μmol/l) and eGFR (ml/min/1.73 m^2; estimated with CKD-EPI equation) [16] as markers for kidney function.

Statistical analyses

Descriptive statistics are expressed as frequencies (%) or median and interquartile range (IQR), as appropriate. Statistical analyses between related samples were carried out with Wilcoxon signed-rank test, t-test or McNemar's test. If a statistically significant change had occurred, multiple regression analysis was run for normally distributed variables to study factors explaining the variation in the measurements at data collection. For non-normally distributed data, we used Mann–Whitney U-test, Kruskal–Wallis H-test and generalized linear model with gamma distribution. The software for statistical analysis was IBM SPSS statistics version 27 (IBM Corp., Armonk, NY). We set the statistical significance level to 5%.

Ethics statement

The study was approved by the Helsinki University Hospital Medical Research Ethics Committee (HUS/751/2017), the Finnish Institute for Health and Welfare (THL/1305/5.05.00/2017), and, when required, also by local authorities to collect data from patient records. This register-based study required no patient consent.

Results

Patient characteristics

Of the 111 contacted Finnish healthcare units, 105 responded, and majority of them (72%) had not treated adult patients with long-term PS during the preceding year. The remaining 29 units reported a total of 74 patients on long-term PS. Twenty-two patients were excluded, mainly due to multiple reporting. Most (69%) of the 52 identified patients were women, and short bowel syndrome (SBS) was the most frequent (73%) mechanism of IF (Table 1). Ten patients (19%) weaned off PS during 2017. The flow of the study and the characteristics of this patient cohort are described in detail elsewhere [13].

Table 1. Patient characteristics at data collection.

	n (%)
Sex	
Female	36 (69)
Age, years	62 (45–72)
BMI, kg/m^2	21.8 (19.0–24.8)[a]
Mechanism of IF	
SBS	38 (73)
Dysmotility	6 (11)
Other	8 (16)
Length of small bowel in SBS patients, cm	100 (70–150)[b]
Clinical classification of IF, ml/d	
FE 1, $\leq$1000	6 (11)
FE 3, 2001–3000	2 (4)
PN 1, $\leq$1000	19 (37)
PN 2, 1001–2000	15 (29)
PN 3, 2001–3000	4 (8)
PN 4, >3000	6 (11)
PS duration, months	27.5 (11.3–57.3)
PS infusions per week	7 (3.5–7)
PS volume per week, liters	7.3 (4.4–14)
PS energy per week, 1000 kcal	6.1 (3.9–9.8)[c]
PS energy, kcal/d	864 (550–1400)[c]
PS lipids, g/d	24.4 (12.6–42.9)[c]
Biochemical liver tests	
ALP, U/l	125 (90–206)[a]
ALT, U/l	34 (20–60)[a]

ALP: alkaline phosphatase; ALT: alanine aminotransferase; BMI: body mass index; FE: fluids and electrolytes; IF: intestinal failure; PN: parenteral nutrition; PS: parenteral support; SBS: short bowel syndrome
Data are frequencies (%) or median (interquartile range).
[a]Data available for 51/52 patients.
[b]Data available for 34/38 patients.
[c]Data available for 43/44 patients.

Catheter-related blood-stream infections

Of the 52 IF patients, 31 experienced 107 CRBSI events during 78,973 catheter days, for an overall CRBSI rate of 1.35 per 1000 catheter days. In 37 events (35%), the CRBSI diagnosis was confirmed using cultures from both peripheral blood and the tip of the removed catheter. Of the remaining 70 events, in five cases blood samples were taken from both a peripheral vein and the catheter, and in all these five, both samples were positive. Diagnosis was based on positive peripheral blood cultures in 49 events, on clinical symptoms alone in 12 events, and data regarding blood cultures was missing in four events.

Fifteen percent of CRBSI occurred in a non-tunneled central venous catheter (CVC), and 85% in a long-term CVC, of which 69% were in a tunneled catheter, 2% in a peripherally inserted central catheter and 29% in an implanted port. Seventy-three percent of CRBSI in a long-term catheter led to catheter replacement, while 27% were treated with antibiotics alone (Table 2). In five cases, the same causative microorganism (coagulase-negative *Staphylococcus*) reoccurred

within 30 d after antimicrobial therapy and resulted in catheter replacement.

Kidney function

The latest kidney function tests were taken after a median of 2.0 (IQR 0.3–4.0) PS years. Plasma creatinine presented a median increase of 7.0 μmol/l (IQR −11.0–37.3, $p = .011$), whereas in eGFR, a median decrease of −8.5 ml/min/1.73 m^2 (IQR −30–7, $p = .005$), occurred (Table 3). At the baseline, 19% of patients had eGFR < 60 ml/min/1.73 m^2, and the respective proportion at data collection was 35% ($p = .039$).

In a multiple regression model, age, body mass index (BMI), and baseline eGFR were all explanatory variables of eGFR at data collection (Table 4). When adjusted for these three factors, none of the variables concerning IF or PS, including the incidence or number of CRBSIs, explained eGFR at data collection (data not shown). Exclusion of BMI from the model had only a minor effect on the estimates for patient age and baseline eGFR.

Biochemical liver tests

The latest liver tests were obtained after a median of 2.0 (IQR 1.0–4.0) PS years. The median change in ALT was −1.0 U/l (IQR −30–25, $p = .948$), while ALP presented a statistically significant median increase of 26.0 U/l (IQR −11–95, $p = .019$; Table 3), At data collection, 10 patients (19%), and at both time points three patients had both ALP and ALT 1.5 times above the reference range.

Median ALP at data collection was statistically significantly higher in patients who received ≥ 5 weekly PS infusions ($n = 18$; 152 U/l, IQR 97–283) than in those who received < 5 PS infusions per week ($n = 33$; 92 U/l, IQR 86–123, $\chi^2(1) = 9.04$, $p = .003$). To account for baseline ALP, an additional generalized linear model with gamma distribution was run (Table 5). In this model, baseline ALP was not a statistically significant explanatory variable of ALP at data collection, but the statistical significance of the number of weekly PS infusions remained. None of the other tested variables were associated with ALP at data collection (data not shown).

Imaging tests of the liver

According to the hospital patient records, 30 IF patients had undergone an abdominal ultrasound at some point during their PS treatment and 22 had not. Most patients (81%) had undergone some other kind of abdominal imaging test, e.g., computed tomography or magnetic resonance imaging, but usually these tests were conducted for reasons other than hepatobiliary imaging specifically for IFALD detection. Liver steatosis (in ten patients) and gallstones (in seven patients) were the most frequently observed abnormalities in liver imaging tests. Liver biopsy had been conducted in seven patients during the time they were receiving PS.

A subgroup of patients ($n = 12$) monitored in the gastroenterology clinic of Helsinki University Hospital had undergone more detailed imaging tests of the liver. Abdominal ultrasound revealed liver steatosis in eight patients, and gallstones in one patient. Transient elastography (TE; Fibroscan®; Echosens, Paris, France) suggested advanced fibrosis or cirrhosis (F3–F4) in five patients. Liver fat content (LFC) according to magnetic resonance spectroscopy (MRS) was increased (≥5.56%) in three patients. Liver biopsy was clinically indicated in three patients. Advanced fibrosis (Metavir

Table 2. Treatment of catheter-related bloodstream infections ($N = 91$) in long-term catheters and identified pathogens.

	Treatment	
Organism	Catheter removal *n* (%)	Antibiotics alone *n* (%)
Coagulase-negative *Staphylococci*	23 (35)	19 (76)
Candida species	8 (12)	–
Klebsiella pneumoniae	7 (11)	1 (4)
Staphylococcus aureus	4 (6)	1 (4)
Multiple	8 (12)	2 (8)
Other	9 (13)	1 (4)
Data unavailable	7 (11)	1 (4)

Table 4. Multiple regression model for estimated glomerular filtration rate at data collection.

Explanatory variable	Adjusted β (95% CI)[a]	*p* Value
Age at data collection	−0.81 (−1.26 to −0.36)	<.001
Baseline eGFR	3.60 (2.78 − 4.04)	<.001
BMI at data collection	1.78 (0.20 − 3.36)	.028

B: regression coefficient; BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate
[a]Adjusted for other variables included in the model.

Table 5. Gamma generalized linear model for alkaline phosphatase at data collection.

Explanatory variable	Coefficient (95% CI)	Wald χ^2	*p* Value
Baseline ALP	0.001 (−0.001 − 0.002)	0.71	.400
PS infusions/week	0.17 (0.09 − 0.26)	15.22	<.001

ALP: alkaline phosphatase; CI: confidence interval; PS: parenteral support

Table 3. Biochemical kidney and liver tests at the start of parenteral support (baseline) and at data collection.

	Baseline *n* (%)	Data collection *n* (%)	*p* Value
Creatinine, median (IQR), μmol/l[a]	73.0 (57.5–94.8)	80.0 (62.5–112)	.011
eGFR, median (IQR), ml/min/1.73 m^2[2a]	91.0 (64.5–103)	78.0 (47.5–104)	.005
≥90	26 (54)	18 (38)	–
60–89	13 (27)	13 (27)	–
<60	9 (19)	17 (35)	–
ALT, median (IQR), U/l[b]	35.0 (19.0–63.0)	34.0 (20.0–61.0)	.948
ALP, median (IQR), U/l[b]	95.0 (66.0–137)	127 (90.0–223)	.019

ALP: alkaline phosphatase; ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate; IQR: interquartile range
[a]Data available at both time points for 48/52 patients.
[b]Data available at both time points for 47/52 patients.

classification F3 or F4) was present in two patients, and of these two, one had also moderate steatohepatitis. The third patient was diagnosed with mild steatohepatitis. Both patients with histologically confirmed advanced fibrosis had a TE result exceeding 10.3 kPa, suggestive of cirrhosis. The patient with moderate steatohepatitis had, according to MRS, an abnormal LFC, while LFC was normal in the patient with mild steatohepatitis.

Discussion

These longitudinal observations in a nationwide cohort of adult IF patients indicated a decrease in kidney function and an increase in ALP over time, even during a relatively short median follow-up of two years. The rate of CRBSI in this patient cohort was comparable to those reported from dedicated centers [17–19], but a substantially high proportion of infections led to catheter replacement.

Less than 40% of the detected CRBSI episodes in our cohort fulfilled the definitive CRBSI diagnostic criteria. Our reported CRBSI rate, thus, represents a more clinically based CRBSI incidence. Accordingly, our rate is closer to the CRBSI incidence of 1.87 per 1000 catheter days reported in a Danish study employing a similar CRBSI definition and reporting a combined CRBSI rate for both non-tunneled CVC and long-term catheters [19] than the very low rate of 0.38 CRBSI per 1000 catheter days in a British study applying the strict microbiological diagnostic criteria for infections in tunneled catheters [20]. When CRBSI diagnostics utilizes peripheral blood samples only or relies solely on clinical and biochemical signs of infection, the confirmation of the catheter as the primary source of the infection is impossible. The result of such practice can be inappropriate therapy, including unnecessary catheter removal.

The proportion of removed long-term catheters due to CRBSI in our study was, indeed, as high as 73%. Along with the aforementioned diagnostic methods, one explanation for this rate might be the frequent use of implanted ports. First, this practice may be associated with a higher CRBSI risk than the use of tunneled catheters [17,21]. Second, catheter salvage in implanted ports can be more difficult than in tunneled catheters [22]. Preservation of long-term venous access in PS-dependent IF patients is essential, and therefore, current recommendations on CRBSI treatment support catheter-salvaging strategies whenever safe and clinically reasonable [2]. Such strategies can result in an overall catheter salvage rate of up to 73% [20]. We did not gather data on whether catheter replacement took place due to septic shock or otherwise complicated infection, both of which warrant an acute catheter removal; nevertheless, it is unlikely that a large proportion of identified replacements would have occurred under such severe conditions. To sum up, our results reveal the need to promote both diagnostic methods and catheter-salvaging treatment strategies for CRBSI encountered in Finnish IF patients.

Our results indicated a deterioration of kidney function in adult IF patients over time, the most important explanatory factors being age and baseline kidney function. These findings are in agreement with a recent Italian study reporting a decline in kidney function in 72 adult IF patients during a 30-month follow-up, and the deterioration depended on kidney function at the start of HPS, age, and urologic disease [23]. Findings from retrospective cohorts of both pediatric IF patients and adult SBS patients suggest impaired kidney function is prevalent even after weaning off HPS [24,25]. This accumulating evidence supports the recommendation that monitoring kidney function in IF patients is essential and known modifiable risk factors for kidney failure require attention [2], because even though IF in a patient might be reversible the impairment in kidney function can persist.

In line with our results, two historical cohorts of adults with long-term PS have demonstrated that derangement in biochemical liver tests is common, and the most frequent abnormality is elevated ALP [26,27]. Furthermore, we found an increase of ALP over time, an observation similar to that in a study of 107 IF patients with a median of 40 HPS months [26]. We acknowledge that assessment of liver status with biochemical tests alone is insufficient, because their correlation with the histologic severity of liver injury is poor [28]. ALT and ALP were, however, the only tests available at both time points in most patients in our cohort. Liver tests, such as GGT and total bilirubin, were performed on only a few patients, and imaging tests offered limited data regarding liver status. Taken together, our results suggest a lack of systematic evaluation and follow-up of liver status in Finnish adult IF patients.

The retrospective nature of our nationwide cohort set a limitation on data collection; we had to rely on data available from the patient records, and these data proved to be insufficient in part, especially regarding liver tests. Nevertheless, we consider our results reflect the clinical reality of long-term PS in Finnish adult patients. Our cohort was heterogeneous, mixing patients with chronic and acute IF and including both benign and malignant underlying diseases. The small size of our sample can be criticized, but we here describe a nationally representative cohort of patients with a rare disease as opposed to more frequently reported single-center cohorts.

In adult IF patients, deterioration in kidney function and noninvasive test results suggestive of abnormal liver status are frequently observed, and even more so over time. Despite current comprehensive guidelines [2], a need for a consensus on optimal, yet clinically feasible, methods for evaluation, diagnosing and monitoring of IF-related complications exists. Such best practices then need to be implemented on a national level to ensure good quality of care for IF patients. Currently, a systematic, evidence-based approach for detecting and treating IF-related complications is lacking in Finland.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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