Optimising care for chronic intestinal failure patients

Julia W. Korzilius

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Radboud Dissertation Series

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Radboud Dissertations Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Julia W. Korzilius & Proefschrift AIO | Guntra Laivacuma
Printing: DPN Rikken/Pumbo

ISBN: 9789465150086
DOI: 10.54195/9789465150086
Free download at: https://doi.org/10.54195/9789465150086

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PRESS

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Proefschrift ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

maandag 12 mei 2025
om 16.30 uur precies

door

Julia Wilhelmina Korzilius
geboren op 1 september 1996
te Nijmegen

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Chapter 1

General introduction

Intestinal failure

Intestinal failure (IF) is defined as a reduction of gut function that results in the inability to sufficiently absorb macronutrients, water or electrolytes, such that intravenous supplementation is required to maintain health and/or growth.[1] IF can be classified into three functional categories based on the onset, metabolic characteristics, and expected duration of the condition (Table 1).[1] IF can be further categorised in five major pathophysiological conditions that can result from various gastrointestinal or systemic diseases.[2] The primary mechanisms of IF and examples of underlying diseases are shown in Table 2. This thesis will concentrate solely on type III, i.e., chronic intestinal failure (CIF).

Table 1. Functional classification of intestinal failure.[1]

Type	Duration	Characteristics
I	Days to weeks	Acute condition: short-term and usually self-limiting
II	Weeks to months	Prolonged acute condition: metabolically unstable patients require complex multidisciplinary care
III	Months to years	Chronic condition: metabolically stable patients require long-term home parenteral nutrition

Chronic intestinal failure

CIF, a rare condition affecting approximately 400 patients in the Netherlands, is characterised by the persistence of IF over months or years in a metabolically stable patient that can be managed outside the hospital setting.[1] The primary and life-saving therapy for CIF patients is the administration of total parenteral (intravenous) nutrition (TPN). TPN comprises an artificial nutrition formulation that contains all essential micro- and macronutrients, which is tailored to meet the patient's needs and is administered through a central venous access device (CVAD). For long-term use, a subcutaneously tunnelled catheter, an implantable subcutaneous port system, or an arteriovenous fistula may be used. Due to the chronic nature of this condition, TPN administration needs to be performed in the home setting, a strategy that is coined as home parenteral nutrition (HPN). HPN encompasses a complex and time-consuming treatment that can cause serious harm if not correctly prescribed, prepared or administered. In addition, HPN-related (life-threatening) complications may occur. Therefore, these patients need to be managed in expert centres by a multidisciplinary nutrition support team. This team includes medical specialists with a background in gastroenterology, nutrition, and surgery, and specialised nurses, dietitians, and pharmacists. Psychologists and social

workers ideally are included as well, given the repercussions of IF and its treatment on the patient's personal, occupational, and family life. Radboud university medical center is one of two tertiary referral centres for CIF support in the Netherlands and aims to further improve patient care for this condition through research.

Knowledge gaps

Chapter 2: Body composition of chronic intestinal failure patients

So far, TPN adjustments have been primarily based on basic yet imprecise parameters such as body weight and overall clinical judgement. While these methods have long been the only means available, they obviously lacked the precision that is required for optimal patient care, for instance, because disease-related alterations in body composition are not sufficiently taken into account. Recently, however, there has been a significant shift towards the use of more sophisticated techniques, which for CIF patients now include a detailed nutritional assessment that comprises dietary assessment, physical examination, anthropometric measurements, diagnostic tests, laboratory tests, and body composition measurements.[3]

Body composition is most commonly assessed by means of bioelectrical impedance analysis (BIA) in clinical practice and, as such, also plays a crucial role in understanding the nutritional status of CIF patients.[4] BIA is a method in which body impedance is assessed, and fat mass (FM) and fat-free mass (FFM) are calculated therefrom using a population-specific equation.[5] From 2019 on, we have assessed body composition using BIA in the routine care of our CIF patients to guide our TPN support. With the research presented in this thesis, we aim to provide a comprehensive overview of the body composition of our CIF cohort and to evaluate whether certain groups (aetiologies of CIF) have a more (un)favourable body composition.

Key research question

- What is the actual body composition of our adult CIF cohort?

Chapter 3: Fasting bioelectrical impedance analysis

To further optimise the care for our CIF patients, we aim to make the nutritional assessment process as practical and evidence based as possible. Current guidelines, without supporting evidence, recommend that BIA measurements should be performed after a minimum of eight hours of fasting.[6] However, this poses practical problems in clinical practice and is even undesirable in already malnourished

patients. We, therefore, might improve patient care by providing evidence that fasting can be safely omitted when performing BIA in these patients.

Key research question

- What is the effect of breakfast on FFM estimation as assessed by BIA?

Chapter 4: Parenteral nutrition infusion and bioelectrical impedance analysis

BIA has been used in our routine care of CIF patients since 2019. As this technology is relatively new to our practice, we still need to expand our understanding of its application and implications. Several aspects have remained unexplored so far, including the impact of parenteral nutrition (PN) infusions on FFM assessments as evaluated by BIA.

Key research question

- What is the effect of TPN infusion on FFM estimation as assessed by BIA?

Chapter 5: Taurolidine-related adverse events

HPN is a complex and high-risk treatment that empowers patients to regain their lives after developing a catastrophic condition (IF) by managing their CVADs and infusion pumps at home. Despite these obvious benefits, HPN patients face frequent hospitalisations, mainly due to catheter-related bloodstream infections (CRBSIs). To prevent this potentially life-threatening problem, strict adherence to antiseptic protocols when managing CVADs is critical.[7] Other preventive strategies include the use of antimicrobial catheter lock solutions (CLSs) that are instilled into the CVAD in between infusions.[1] Taurolidine is a CLS with a broad spectrum of activity against bacterial and fungal pathogens.[8-10] Clinical studies, also from our centre, have shown that taurolidine prevents CRBSIs in CIF patients.[11-13] While taurolidine has been used for many years with over one million infusions in patients from our centre alone, and is generally considered safe, there is limited understanding of how patient-reported adverse events (AEs) correlate with catheter dysfunction rather than actual taurolidine-related problems such as intolerance or allergy. Therefore, there is a need for more information on taurolidine-related AEs and their implications. By identifying and effectively managing these AEs, we will improve patient safety and optimise the long-term management of central venous access, ultimately improving patient outcomes in this challenging clinical setting.

Key research questions

- What is the incidence of taurolidine-related AEs among CIF patients?
- Which taurolidine-related AEs are seen in CIF patients?
- What are the causes of taurolidine-related AEs?
- How to deal with taurolidine-related AEs in clinical practice?

Chapter 6: Enteral absorption of antimicrobial agents in short bowel syndrome patients

Short bowel syndrome (SBS), one of the five pathophysiological causes of CIF, is usually caused by (partial) removal of the small intestine and is defined as having a functional small bowel length of less than 200 cm (Table 2).[1] Approximately 70% of all hospital admissions in SBS patients are due to CRBSIs, requiring prolonged intravenous antimicrobial treatment.[14] In many other clinical settings, it is recommended to switch to oral antimicrobials after recovery or for mild infections whenever feasible, as this shortens hospital stays, reduces costs and lowers the risk of complications from intravenous access.[15] However, this therapeutic strategy of switching from intravenous to oral antimicrobials is not universally applicable in individuals with SBS, given their diminished absorptive gut capacity. Despite this issue, successful treatment with oral antimicrobials has been reported in incidental cases.[16-19] The study presented in this thesis addresses this gap by evaluating the enteral absorption of commonly prescribed antimicrobials in a larger group of SBS patients with varying degrees of IF. The results might bolster non-intravenous treatment strategies by demonstrating that effective oral administration is possible, with the potential advantages on hospital resources mentioned before. In addition, this study sets the stage for further research on the absorption of other drugs in the setting of SBS.

Key research question

- What is the bioavailability of orally administered antimicrobial agents in SBS patients?

Chapter 7: Superior vena cava syndrome in chronic intestinal failure patients

Superior vena cava syndrome (SVCS) is a complication that occurs when the superior vena cava is (partially) occluded, usually as a result of catheter-related venous thrombosis in HPN patients.[20] SVCS results in serious complaints associated with venous congestion of the upper body and head. Besides, the threat posed by the loss of options to obtain central venous access for CVAD insertion due to SVCS jeopardises both the well-being of the patient and the sustainability of HPN

as a therapeutic modality. Despite its devastating consequences, the diagnosis of SVCS is often missed in its early stages, and recent studies in HPN patients are lacking. By highlighting the incidence and clinical characteristics of SVCS in CIF patients, healthcare providers can better anticipate and proactively manage this potentially life-threatening complication. These results will guide clinicians in the early detection, timely intervention, and effective management of SVCS, ultimately improving the safety and sustainability of long-term HPN therapy.

Key research questions

- What is the incidence of SVCS among CIF patients?
- What are the most common SVCS-related symptoms among CIF patients?
- What is the location of the CVAD tip after insertion and at the time of SVCS diagnosis?

Outline of this thesis

The work presented in this thesis aims to optimise the care for CIF patients. Table 3 summarises the main research questions, study designs and outcome measures per chapter. **Chapter 2** describes the body composition of our CIF patient cohort. **Chapters 3 and 4** describe the effect of a breakfast meal and TPN infusion, respectively, on FFM estimation as assessed by BIA. **Chapter 5** reports how many CIF patients experience taurolidine-related AEs and the presumed causes. We provide an algorithm on how to deal with these taurolidine-related AEs in clinical practice. **Chapter 6** explores the bioavailability of orally administered antimicrobial agents commonly used in the treatment of SBS patients to guide clinical decision-making when faced with infections. **Chapter 7** reports on the incidence and outcomes of SVCS in CIF patients. Finally, **Chapter 8** summarises and discusses the main findings of this thesis, followed by conclusions and implications for further research.

Table 2. Pathophysiological classification of intestinal failure and examples of underlying diseases.[2]

Condition	Primary mechanism of intestinal failure	Examples of underlying diseases
Short bowel	Reduced absorptive mucosal surface	Extensive surgical resection (e.g., mesenteric ischemia, Crohn's disease, radiation enteritis, surgical complications) or congenital (e.g., gastroschisis, intestinal atresia)
Intestinal fistula	Bypass of large areas of absorptive mucosal surface	Inflammatory (e.g., Crohn's disease, diverticular disease), neoplastic (e.g., small bowel malignancy, coloncancer), iatrogenic (surgery, percutaneous drainage), infectious disease (tuberculosis, actinomycosis), trauma, or foreign body.
Intestinal dysmotility	Restricted oral/enteral nutrition or total fasting from intolerance due to feeding-related exacerbation of digestive symptoms or episodes of non-mechanical intestinal obstruction	Primary CIPO (no underlying disorder) or secondary CIPO (due to underlying disorder, e.g., primary systemic sclerosis, systemic lupus erythematosus)
Mechanical obstruction	Incomplete or total fasting (bowel rest)	Obturation (e.g., gallstones, polypoid tumours), intrinsic bowel lesions (e.g., neoplastic, inflammatory bowel disease), or extrinsic lesions (e.g., abdominal adhesions, hernias, volvulus)
Extensive small bowel mucosal disease	Inefficient absorptive and/ or nutrient-losing mucosal surface	E.g., microvillous inclusion disease, tufting enteropathy, celiac disease, autoimmune enteropathy

Abbreviations: CIPO, chronic intestinal pseudo-obstruction.

Table 3. Main research questions, study design, and outcomes addressed in this thesis.

Chapter	Research question(s)	Study design	Measurements/outcomes
2	What is the actual body composition of our adult CIF patient cohort?	Retrospective descriptive cohort study	Body composition, including body mass index, fat-free mass index, and fat percentage
3	What is the effect of breakfast on FFM estimation as assessed by BIA?	Prospective cohort study	Changes in fat-free mass before and after breakfast
4	What is the effect of TPN infusion on FFM estimation as assessed by BIA?	Explorative cohort study	Changes in fat-free mass before and after TPN infusion
5	What is the incidence of taurolidine-related AEs among CIF patients? Which taurolidine-related AEs are seen in CIF patients? What are the causes of taurolidine-related AEs? How to deal with taurolidine-related AEs in clinical practice?	Retrospective descriptive cohort study	Incidence of taurolidine-related AEs Cause of the taurolidine-related AEs Algorithm on how to manage taurolidine-related AEs in clinical practice
6	What is the bioavailability of orally administered antimicrobial agents in SBS patients?	Explorative cohort study	Oral bioavailability of clindamycin, ciprofloxacin, flucloxacillin and fluconazole
7	What is the incidence of SVCS among CIF patients? What are the most common SVCS-related symptoms among CIF patients? What is the location of the CVAD tip after insertion and at the time of SVCS diagnosis?	Retrospective descriptive cohort study	Incidence of SVCS Symptoms of SVCS CVAD tip location after insertion and at time of SVCS diagnosis

Abbreviations: AE, adverse event; BIA, bioelectrical impedance analysis; CIF, chronic intestinal failure; CVAD, central venous access device; FFM, fat-free mass; TPN, total parenteral nutrition; SBS, short bowel syndrome; SVCS, superior vena cava syndrome.

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Chapter 2

Body composition of adults with chronic intestinal failure receiving home parenteral nutrition: A descriptive cohort study

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Journal of Parenteral and Enteral Nutrition, June 2024

Abstract

Background

Chronic intestinal failure (CIF) refers to the long-lasting reduction of gut function below the minimum necessary to absorb macronutrients, water, and/or electrolytes. Patients with CIF likely develop various forms of malnutrition and dehydration, yet studies that focus primarily on body composition are lacking. Therefore, this study aimed to evaluate the body composition of adult patients with CIF.

Methods

This retrospective descriptive cohort study was performed at Radboud university medical center, a tertiary referral centre for CIF treatment in the form of home parenteral nutrition. We collected available bioelectrical impedance analysis (BIA) data from routine care between 2019 and 2023. The primary outcome was body composition, which was evaluated by assessing body mass index (BMI), fat-free mass index (FFMI), and fat percentage (fat%).

Results

Overall, 147 adult patients with CIF were included with a median (IQR) age of 58 (25–68) years; 69% were female. The mean (SD) BMI was 22.1 (4.3) kg/m^2, FFMI was 14.2 (1.9) kg/m^2 in females and 17.0 (2.0) kg/m^2 in males, and fat% was 33.7% (6.8%) in females and 24.6% (6.4%) in males. Sixty-three percent had an FFMI below references, and 48% had a high fat%.

Conclusion

This study found that most adult patients with CIF have an unfavourable body composition characterised by a high fat% and low FFMI despite having a normal mean BMI. These results highlight the necessity for in-depth nutritional assessment, including BIA measurement. Moreover, future studies should focus on exercise interventions to increase FFMI and improve body composition and function.

Introduction

Body composition, the proportion of fat, lean tissue, and bone in the human body, is a pivotal indicator of overall health and nutrition status.[1] Understanding and assessing body composition is essential to comprehensive patient care, particularly with the emergence of the consensus malnutrition framework, which highlights the loss of muscle mass as a key characteristic of malnutrition.[2] This loss of muscle mass is also central to conditions like sarcopenia and cachexia, underscoring the need for accurate assessment methods.[3] From a therapeutic perspective, understanding lean tissue is crucial for appropriately calculating protein requirements.[4]

Moreover, monitoring body composition is paramount for individuals with chronic intestinal failure (CIF). CIF is defined as the persistent reduction of the gut function below the minimum necessary for the absorption of macronutrients, water, and/or electrolytes, such that intravenous supplementation is required to maintain health and/or growth.[5] Patients with CIF usually require life-long treatment by means of home parenteral nutrition (HPN) and/or fluids. In this intricate clinical scenario, alterations in body composition can offer valuable insights into the effectiveness of HPN and the overall health trajectory of these patients. Therefore, and because of the heterogeneity in this patient group, individual adjustment of the nutrition therapy based on nutrition assessment, including body composition measurements, is recommended by the European Society for Clinical Nutrition and Metabolism guideline on HPN.[6]

The two-compartment model is the most used method for analysing body composition, which identifies a patient's fat mass (FM) and fat-free mass (FFM). FFM refers to any component with the exclusion of FM, for example, body water, organs, skeletal muscle mass, and bone minerals. In clinical practice, body composition assessment most frequently relies on bioelectrical impedance analysis (BIA) because of portability, ease of use, safety, non-invasiveness, and relatively low cost compared with other methods (dual-energy x-ray absorptiometry and computed tomography).[7] BIA is a double indirect method in which body impedance is measured, and FM and FFM are subsequently calculated using a population-specific equation.[8] Single-frequency (SF)-BIA involves administering a weak alternating electrical current at 50 kHz through surface electrodes attached to the body.[7] This current assesses the conductive and nonconductive components of body tissues and fluids. Water- and electrolyte-rich tissues like blood and muscle conduct the current well, whereas fat, bone, and air-filled spaces impede it. By detecting the voltage decrease of the current as it traverses the body, BIA devices record impedance data, providing insights into body composition.

In the literature, only one study by Køhler et al. shows the body composition results of a Danish metabolically stable patient group with CIF who are receiving long-term HPN. These authors reported a low mean FFM index (FFMI; 14.8 kg/m^2).[9] However, more knowledge about body composition in adult patients with CIF is required to optimise the nutrition and physical care for these patients. As of 2019, we include the measurement of body composition using SF-BIA in the routine care of patients with CIF to characterise the effects of our nutrition support. We hereby present our data to underpin our hypothesis that, despite our efforts, most patients have a suboptimal body composition characterised by a high fat percentage (fat%).

Methods

Study design and patients

We performed a retrospective descriptive cohort study at Radboud university medical center (Radboudumc), a tertiary CIF referral centre. Patients ≥18 years old who met the criteria for CIF, received HPN, and were measured using SF-BIA in routine care between January 2019 and August 2023 were included.[5] Patients were excluded if no informed consent was obtained or the hydration status was considered abnormal.

Outcomes

The primary outcome was body composition, which was evaluated by assessing body mass index (BMI), FFMI, and fat%. The secondary outcomes included the following:

- The comparison of body composition outcomes in patients with short bowel syndrome (SBS) vs those with intestinal dysmotility (ID).
- The comparison of body composition outcomes in patients with malnutrition vs those without malnutrition.
- The comparison of body composition outcomes in short-term HPN users (<2 years) vs long-term HPN users (≥2 years).

Body composition

Body composition measurements were performed in routine care according to the standard operating procedure using the SF-BIA Bodystat 500 (Bodystat).[10] FM and FFM were subsequently calculated using the Kyle equation.[8] Bioelectrical impedance vector analysis (BIVA) plots were used to verify the assumption of normal hydration status.[11,12] BodygramPlus software (version 1.2.1) was used to create BIVA plots; hydration status was considered abnormal when a vector point

was above 75% tolerance ellipse, and those measurements were excluded from the analysis. Body composition outcomes were computed based on the first BIA measurement performed according to the standard operating procedure. Body composition outcomes BMI, FFMI, and fat% were calculated and categorised using the following reference values:

- BMI (kg/m^2) was calculated as body weight (kg) divided by the square of height (meters squared) and subsequently categorised into underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥30 kg/m^2).[13]
- FFMI (kg/m^2) was calculated as FFM (kg) divided by the square of height (meters squared) and categorised as low for women if the FFMI was <15 kg/m^2 and low for men if the FFMI was <17 kg/m^2.[14]
- Fat% was calculated as the ratio of FM (kg) to total body weight (kg) multiplied by 100%. Patients were categorised based on their fat%, considering age and sex, into the following groups: low fat%, normal fat%, high fat%, and very high fat%.[15,16]

Secondary outcomes

Secondary outcomes comprised the following. Comparisons were made regarding body composition outcomes between patients diagnosed with SBS and those with ID. The cohort was categorised into patients with SBS and patients with ID according to the classification of intestinal failure in adults.[17] SBS is defined as having a (functional) small bowel length <200 cm. ID refers to disorders affecting the propulsion of gut contents in the absence of fixed occluding lesions.

Comparisons were made regarding the body composition outcomes of patients with and without malnutrition. The presence of malnutrition was determined using the Global Leadership Initiative on Malnutrition (GLIM) criteria.[2] The GLIM criteria comprise five elements, three phenotypic and two etiologic criteria. The phenotypic criteria include: (1) weight loss, >5% within the past 6 months or >10% beyond 6 months; (2) low BMI, <20 kg/m^2 if <70 years or <22 kg/m^2 if >70 years; and (3) reduced muscle mass, with an FFMI threshold <17 kg/m^2 in males and <15 kg/m^2 in females. The etiologic criteria include (1) reduced food intake, >1 week ≤50% of energy requirements met by the combination of oral nutrition and HPN or HPN alone and (2) inflammation, indicated with elevated C-reactive protein (≥10 mg/L) and/or hypoalbuminemia (≤35 g/L). Malnutrition was diagnosed when at least one phenotypic and etiologic criteria was present. Comparisons were made regarding body composition outcomes of short-term HPN users and long-term HPN users.

The cohort was categorised into short-term HPN users (<2 years) and long-term HPN users (≥2 years). Short-term HPN users were defined as those who received HPN for a period ranging from 0 to 24 months, whereas long-term HPN users were categorised as individuals with a cumulative HPN duration ≥24 months.

Data collection

The following data were collected from the electronic health records: sex, age (years), body weight (kg), body height (m), the HPN start date, the underlying cause of CIF,[17] the date of measuring body composition, resistance (ohms), reactance (ohms), the date of GLIM measurement, the percentage of weight loss in 6–12 months, the percentage energy intake vs requirement (calculated by the HPN dietitian),[18] C-reactive protein (mg/L), and the plasma albumin level (g/L).

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or, if not normally distributed, as median with interquartile range (IQR). Categorical variables were described as proportion. The primary outcome was calculated using descriptive statistical methods. The independent t-test was used to compare continuous body composition outcomes between patients with SBS and ID, malnutrition, and no malnutrition, and short-term HPN users and long-term HPN users. The chi-square test was used to compare categorical body composition outcomes between patients with SBS and ID, malnutrition, and no malnutrition, and short-term HPN users and long-term HPN users. Risk factor analyses for the primary outcome (BMI, FFMI, and fat%) were performed using a univariate general linear model. The factors were age at body composition measurement, sex, HPN duration (<2 years and ≥2 years), presence of malnutrition (yes and no), and cause of CIF (SBS, ID, and other). The final multivariate analyses included factors with a p-value ≤0.20 in the univariate analysis. One at a time, nonsignificant variables were removed from the multivariate model until all variables were statistically significant ($p<0.05$). Missing data were excluded from the analysis, and for the GLIM criteria, these were denoted as a score of 'no' for the corresponding criteria. Two-sided p-values of <0.05 were considered significant. The software package IBM SPSS Statistics 27 was used for statistical analysis.

Ethical approval

This study underwent assessment by the research ethics committee of Radboudumc, Nijmegen, the Netherlands (reference number 2023-16161), which determined its exemption from the Medical Research Involving Human Subject Act. The study was

reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

Results

Patient characteristics

Between January 2019 and August 2023, 308 patients with CIF were under treatment at Radboudumc; 147 were included in this study (Figure 1). Patient characteristics are presented in Table 1. The median age was 58 years (range 18–83 years), and 69% were female. The median HPN duration was 3 years (range 0–29 years).

Body composition

Body composition outcomes of all patients are shown in Table 2 (column 2) and Figure 2. The mean BMI was 22.1 kg/m^2, 63% of patients had an FFMI below reference, and 48% had a high or very high fat%. A total of 10% (15/147) of the CIF population had a body composition with BMI, FFMI, and fat% within the reference values (Figure 2).

Secondary outcomes

The body composition outcomes of patients with SBS and ID, of patients with malnutrition and without, and of short-term HPN users and long-term HPN users are shown in Table 2 (columns 3–8). Patients with ID had a significantly larger proportion of patients with a low FFMI than patients with SBS (Table S1). Patients with malnutrition had a significantly lower BMI, FFM, and FFMI than those without malnutrition (Table S2). Patients with malnutrition had a significantly lower BMI category and proportion of patients with a low FFMI than those without malnutrition (Table S2). Short-term HPN users had a significantly larger proportion of patients with malnutrition than long-term HPN users (Table S3).

The results of the univariate and multivariate general linear model analysis for BMI, FFMI, and fat% are shown in Table 3. Multivariate analysis showed that age (0.052 [0.010–0.094]) positively affects BMI, and malnutrition (−2.619 [−4.008 to −1.230]) negatively affects BMI. Multivariate analysis showed that age (0.020 [0.002–0.039]) positively affects FFMI, and female sex (−2.668 [−3.293 to −2.042]) and malnutrition (−1.456 [−2.069 to −0.842]) negatively affect FFMI. Multivariate analysis showed that female sex (9.038 [6.683–11.392]) positively affects fat%.

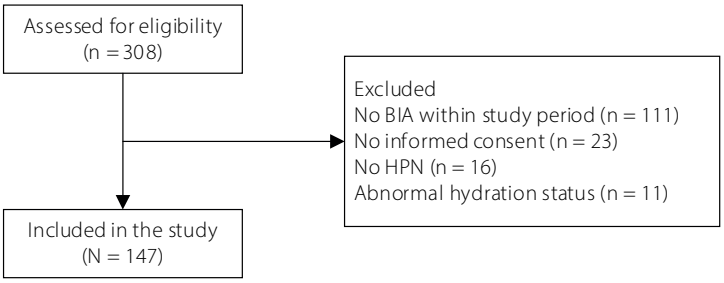

Figure 1. Participant screening and enrolment.

Abbreviations: BIA, bioelectrical impedance analysis; HPN, home parenteral nutrition.

Table 1. Characteristics of patients with CIF.

Patient characteristics	***N* = 147**
Female, n (%)	102 (69)
Age, median (IQR), years	58 (25–68)
Weight, median (IQR), kg	61 (54–74)
Height, mean (SD), m	1.70 (0.1)
HPN duration, median (IQR), years	3 (1–6)
Cause of CIF, n (%)	
Intestinal dysmotility	67 (46)
Short bowel syndrome	54 (37)
Extensive small bowel mucosal disease	4 (3)
Mechanical obstruction	3 (2)
Intestinal fistula	3 (2)
Other	16 (11)

Abbreviations: CIF, chronic intestinal failure; HPN, home parenteral nutrition; IQR, interquartile range; SD, standard deviation.

Table 2. Body composition outcomes of all patients with CIF (column 2) and secondary outcomes (columns 3-8).

Participant characteristics	All CIF patients *N* = 147, ♀ = 102	SBS *n* = 54, ♀ = 32	ID *n* = 67, ♀ = 51	Malnutrition *n* = 50, ♀ = 37	No malnutrition *n* = 97, ♀ = 65	HPN <2 years *n* = 60, ♀ = 41	HPN ≥2 years *n* = 87, ♀ = 61
BMI, mean (SD), kg/m²	22.1 (4.3)	22.9 (4.0)	21.6 (4.8)	20.2 (3.5)	23.1 (4.3)	21.8 (4.2)	22.3 (4.3)
BMI category, n (%)							
Underweight	28 (19)	5 (9)	16 (23.9)	18 (36)	10 (10)	12 (20)	16 (18)
Normal weight	89 (61)	37 (69)	38 (57)	28 (56)	61 (63)	37 (62)	52 (60)
Overweight	23 (16)	8 (15)	11 (16)	4 (8)	19 (20)	7 (12)	16 (18)
Obesity	7 (5)	4 (7)	2 (3)	0 (0)	7 (7)	4 (7)	3 (3)
FFM, mean (SD), kg	44.2 (9.3)	46.2 (9.6)	43.0 (8.9)	41.0 (7.5)	45.8 (9.7)	43.3 (9.3)	44.8 (9.2)
Low FFMI, n (%)	93 (63)	27 (50)	46 (69)	46 (92)	47 (49)	43 (72)	50 (58)
FFMI ♀, mean (SD), kg/m²	14.2 (1.9)	14.7 (1.9)	14.0 (2.0)	13.5 (1.4)	14.6 (2.0)	13.9 (1.7)	14.4 (2.0)
FFMI ♂, mean (SD), kg/m²	17.0 (2.0)	17.3 (2.0)	16.6 (1.5)	15.2 (1.5)	17.8 (1.6)	16.9 (2.3)	17.2 (1.8)
Fat% ♀, mean (SD), %	33.7 (6.8)	34.4 (6.0)	33.5 (7.1)	32.1 (7.8)	34.5 (6.0)	34.6 (6.8)	33.0 (6.7)
Fat% ♂, mean (SD), %	24.6 (6.4)	24.9 (6.9)	24.5 (6.0)	23.7 (5.4)	25.0 (6.8)	22.6 (7.5)	26.1 (5.1)
Fat% category, n (%)							
Low	8 (5)	2 (4)	4 (6)	5 (10)	3 (3)	4 (7)	4 (5)
Normal	68 (46)	26 (48)	33 (49)	24 (48)	44 (45)	23 (38)	45 (52)
High	46 (31)	18 (33)	17 (25)	12 (24)	34 (35)	19 (32)	27 (31)
Very high	25 (17)	8 (15)	13 (19)	9 (18)	16 (17)	14 (23)	11 (13)

Abbreviations: BMI, body mass index; CIF, chronic intestinal failure; FFM, fat-free mass; FFMI, fat-free mass index; fat%, fat percentage; HPN, home parenteral nutrition; ID, intestinal dysmotility; SBS, short bowel syndrome; SD, standard deviation.

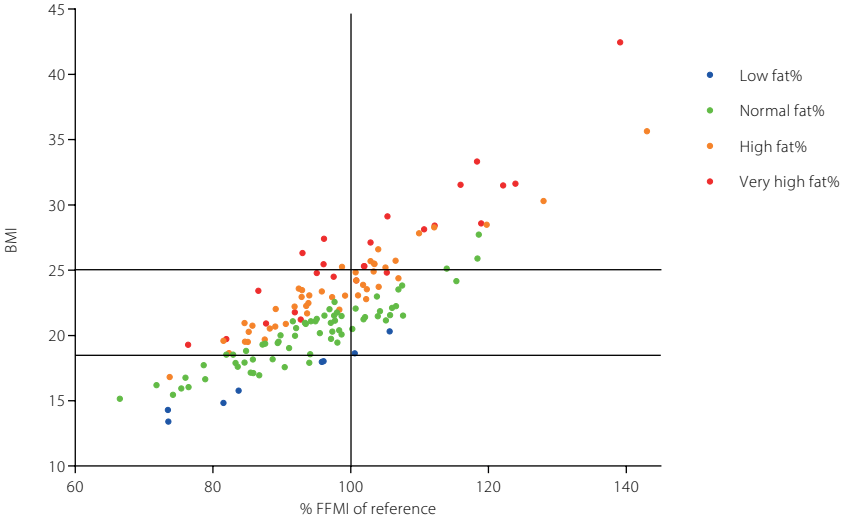

Figure 2. BMI kg/m^2 versus FFMI (percentage of reference: 15 for females and 17 for males was considered 100%) of patients with chronic intestinal failure.[14] Data points are shown in the category of fat%.[16]

Abbreviations: BMI, body mass index; fat%, fat percentage; FFMI, fat-free mass index.

Discussion

This study investigated the body composition of a large cohort of patients with CIF. Although their mean BMI appeared normal, half of this group had a high fat%, and two-thirds had a low FFMI, underscoring the relevance of a detailed nutrition assessment, including BIA measurement. Moreover, 90% of the CIF population had an unfavourable body composition outside the reference (Figure 2).

The disadvantageous body composition of our cohort is in line with outcomes reported by Køhler et al., who also found a normal mean BMI (20.0 kg/m^2), low FFMI (14.8 kg/m^2), and 64% FFMI below reference.[9] Two other studies evaluated the prevalence of sarcopenia in patients with CIF.[20,21] Sarcopenia is a progressive skeletal muscle disorder associated with impaired clinical outcomes, for example, lower quality of life and higher morbidity and mortality.[3] According to the European consensus, sarcopenia is diagnosed by the presence of low muscle quantity or quality.[3,22] Skallerup et al.[21] reported a sarcopenia prevalence of 73%, slightly higher than the result presented by Graungaard et al. (59%).[20] During the study period, muscle function was not yet routinely measured; therefore, sarcopenia could not

Table 3. Univariate and multivariate general model analysis to analyse possible risk factors for body mass index, fat-free mass, and fat percentage.

Variable	Univariate model		Multivariate model	
	Beta coefficient (95% CI)	**p-value**	**Beta coefficient (95% CI)**	**p-value[a]**
Body mass index				
Age	0.065 (0.021, 0.108)	0.004	0.052 (0.010, 0.094)	0.015
Sex (female)	-1.024 (-2.529, 0.481)	0.181		
HPN duration (<2 years)	-0.523 (-1.940, 0.894)	0.467		
Malnutrition (yes)	-2.893 (-4.287, -1.499)	<0.001	-2.619 (-4.008, -1.230)	<0.001
Cause of CIF		0.192		
SBS	1.417 (-0.587, 3.421)	0.164		
ID	0.129 (-1.810, 2.069)	0.895		
Other	Reference			
Fat-free mass index				
Age	0.035 (0.011, 0.058)	0.004	0.020 (0.002, 0.039)	0.033
Sex (female)	-2.838 (-3.518, -2.158)	<0.001	-2.668 (-3.293, -2.042)	<0.001
HPN duration (<2 years)	-0.349 (-1.120, 0.422)	0.372		
Malnutrition (yes)	-1.749 (-2.498, -1.000)	<0.001	-1.456 (-2.069, -0.842)	<0.001
Cause of CIF		0.020		
SBS	1.038 (-0.036, 2.112)	0.058		
ID	-0.085 (-1.124, 0.954)	0.872		
Other	Reference			
Fat percentage				
Age	0.045 (-0.037, 0.126)	0.282		
Sex (female)	9.038 (6.683, 11.392)	<0.001	9.038 (6.683, 11.392)	<0.001
HPN duration (<2 years)	-0.197 (-2.807, 2.412)	0.881		
Malnutrition (yes)	-1.400 (-4.097, 1.298)	0.307		
Cause of CIF		0.833		
SBS	-0.139 (-3.860, 3.581)	0.941		
ID	0.691 (-2.910, 4.292)	0.705		
Other	Reference			

Possible risk factors were analysed with a multivariate general linear model.

[a] $p \leq 0.05$ is significant in the multivariate model.

Abbreviations: CI, confidence interval; CIF, chronic intestinal failure; HPN, home parenteral nutrition; ID, intestinal dysmotility; SBS, short bowel syndrome.

be assessed. However, based on the high prevalence in both other studies and its associated risks, we urge screening for sarcopenia as part of the in-depth nutrition assessment in patients with CIF.

As hypothesised, we found that despite their intravenous nutrition support and apparently normal BMI, most patients have a suboptimal body composition characterised by a high fat% and low FFMI. High fat% is relevant because this is linked to numerous adverse conditions, including type 2 diabetes mellitus, cardiovascular disease, certain types of cancer, and increased mortality.[23–26] At the same time, a low FFMI is relevant because of the association with impaired physical functioning, type 2 diabetes mellitus, and increased mortality.[9,27,28] The combination of low FFMI and high fat% is even worse. Those are two of three criteria needed to diagnose sarcopenic obesity, leading to cumulative health-related risks.[29]

CIF can arise from various conditions, and the nature of these underlying diseases can directly impact body composition. For example, the persistent inflammatory state in patients with inflammatory bowel diseases can contribute to metabolic alterations and disruptions in nutrient absorption, ultimately affecting body composition.[30] In addition, we suppose that in line with previous reports in the CIF setting, most patients receiving treatment at our centre have a suboptimal body composition because of insufficient exercise.[20,31] However, we could not demonstrate this assumption because our centre has only recently implemented accelerometry measurements. Besides adequate nutrition support, which the PN formulation can provide, improving body composition requires exercise. Our findings call for an interventional investigation, prompting a prospective study to optimise body composition through a comprehensive approach integrating physical activity and determining the ideal macronutrient composition in exclusive PN.

In practice and inherent to the underlying condition, HPN and oral nutrition intake seem to be better tolerated by patients with SBS than by those with ID. Therefore, it seems reasonable to hypothesise that patients with SBS have a favourable body composition compared with patients with ID. Our study confirms this hypothesis because we found a higher proportion of patients with low FFMI in patients with ID compared with patients with SBS (Table S1). No differences were found in other outcomes. However, the heterogeneity within both patient groups emphasises the necessity for personalised treatment strategies, as recommended in the European Society for Clinical Nutrition and Metabolism guideline.[6]

As expected, we found lower BMI, FFM, and FFMI in those patients with malnutrition compared with well-nourished individuals (Table S2). Moreover, patients with malnutrition had a lower BMI category and a higher proportion of patients with a low FFMI than those without (Table S2). This difference was expected because malnutrition can be defined as ''a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased FFM).''[32] Therefore, measuring malnutrition in patients with CIF and adjusting nutrition strategies accordingly remains important.

The frequency and volume of the PN formulation fluctuate the most within the first two years after commencing HPN. Moreover, patients are more clinically and metabolically stable after this period, during which intestinal adaption takes place.[5] Therefore, we hypothesised that long-term HPN users have a better body composition than short-term HPN users. However, our study did not detect such differences in the body composition outcomes of short-term HPN users and long-term HPN users, although all body composition outcomes trend worse in the former group. One possible explanation is the lack of a baseline BIA measurement before starting HPN because most patients receiving treatment at our centre had already started HPN in a peripheral centre. Only 11 patients had a BIA measurement within the first month after starting HPN, emphasising the need for a baseline BIA measurement for monitoring purposes. We found more malnourished patients in the short-term HPN group than in the long-term HPN group (Table S3). This finding highlights the effectiveness of HPN as a treatment.

This study has limitations, including the retrospective aspect of this study. Moreover, we used BIA to assess body composition. The validity of BIA in clinical populations remains a topic of ongoing investigation and debate, as highlighted by a systematic review conducted by the American Society for Parenteral and Enteral Nutrition.[33] Although 23 BIA studies were identified, the evidence supporting BIA's validity in specific patient populations remains limited in scope. Challenges, such as the proprietary nature of manufacturer-specific BIA regression models, further complicate acquiring reliable body composition data. Although BIA has known limitations and may not offer the same level of precision as dual-energy x-ray absorptiometry, it remains one of the most widely used methods. If standardised to minimise the influence of various factors, using SF-BIA in this stable outpatient population with CIF is feasible.

Regarding the GLIM criteria, we had some missing data on inflammation, and we did not score reduced food intake for >2 weeks. Therefore, we may have underestimated

the proportion of patients with malnutrition. In this study, we could not include the accelerometry data and muscle function, which would have made our data more robust. On the other hand, we collected body composition data from a substantial group of patients with CIF who were receiving HPN. In addition, the measurements were standardised, and we used BIVA plots to check for normal hydration status, which contributed to the study data's reliability.

Conclusion

Our study highlights the high frequency of unfavourable body composition (i.e., high fat% and low FFMI) while having a normal BMI in patients receiving HPN through in-depth nutrition assessment using BIA, thus indicating that expanded assessment should be the standard of care.

Acknowledgements

We thank Melina van Rossum for data collection, Judith Beurskens and Hester Wierda for performing BIA measurements, and Reinier Akkermans for helping with the statistical analysis.

Financial disclosures

None

Conflict of interest

None

Conference presentation

Poster tour presentation ESPEN September 2023

Supplementary data

Supplementary files are available at:
https://aspenjournals.onlinelibrary.wiley.com/doi/10.1002/jpen.2658

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Chapter 3

Having breakfast has no clinically relevant effect on bioelectrical impedance measurements in healthy adults

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Nutrition Journal, October 2023

Abstract

Background

Bioelectrical impedance analysis (BIA) is commonly used to evaluate body composition as part of nutritional assessment. Current guidelines recommend performing BIA measurements in a fasting state of at least 2 hours in a clinical setting and 8 hours in a research setting. However, since asking patients with malnutrition or sarcopenia to fast is not desirable and literature to support the strategy in the guidelines is lacking, this study aimed to assess the impact of breakfast on BIA measurements.

Methods

We performed an explorative, prospective study in healthy volunteers aged between 18 and 70 years, with a normal fluid balance and a body mass index between 18.5 and 30 kg/m^2. BIA measurements were performed according to the standard operating procedure in the fasting state, and 1, 2, 3, and 4 hours after ingesting a standardised breakfast meal of about 400 kcal with a 150 ml drink, using the hand-to-food single-frequency BIA (Bodystat 500). The Kyle formula was used to calculate the primary outcome, i.e., fat-free mass (FFM, kg). A linear mixed model was used to compare baseline values with other time points. A difference of 1 kg in FFM was considered clinically relevant.

Results

Thirty-nine (85% female) volunteers were included, with a median age of 28 years (IQR 24–38). In 90% of the participants, having breakfast had no clinically relevant impact on the estimated FFM. For the group, the most pronounced mean difference, a statistically but not clinically significant higher value of 0.2 kg (0.4%), was observed after 3 hours of fasting compared to baseline. No statistically significant differences were found at the other time points.

Conclusion

Eating affects single-frequency BIA measurements, but differences in FFM remain below clinical relevance for most participants when using a standardised breakfast. Thus, the current study suggests performing a BIA measurement in a fasting state is not required.

Introduction

Several methods are available to estimate body composition, including dual-energy X-ray absorptiometry (DXA), computed tomography (CT), air displacement plethysmography (ADP), and bioelectrical impedance analysis (BIA). BIA is a non-invasive and relatively cheap method that can easily be applied in clinical settings due to portability of the required device.[1, 2] BIA measures resistance and reactance; these variables are used in a formula to estimate a person's fat-free mass (FFM) and fat mass (FM).[3] The principle of BIA is based on the difference in resistance between tissues; fat and bone yield higher resistance, while water-containing tissues like blood and muscle have a higher conductivity.[2]

Although BIA is not the most reliable method to measure body composition when compared to DXA, CT, or ADP, it is the easiest to apply in a clinical setting. Standardising the different factors that influence the measurement is key to improve precision, e.g., placing of electrodes, body position, and electrolyte abnormalities can influence the measurement.[4] Hence, a Standard Operating Procedure (SOP) is used for standardisation.[5] The SOP and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that the measurement should be performed after a fasting period of at least 8 hours in a research setting and 2 hours in clinical settings.[5, 6] BIA is frequently applied in patients with malnutrition or sarcopenia; however, measuring in a fasted state is undesirable in this situation.[7, 8]

The recommendation of fasting before BIA measurements in the ESPEN guideline (2004) is based on three studies.[6] Deurenberg et al. (1988) evaluated the effect of a liquid-formula meal on BIA and reported a mean impedance decrease of 13–17 ohms, representing a 3.3% change.[9] Additionally, Fogelholm et al. (1993) found an increase of 0.6% in resistance 1-hour post-meal, followed by a significant decrease of about 5 and 4 ohms at 2.5 and 4 hours post-meal, respectively.[10] Kushner et al. (1996) concluded that, depending on the experimental condition, impedance might decrease 4–15 ohms over 2–4 hours after a meal.[11] Another study, not mentioned in the guideline by Gallagher et al. (1988), concluded that fasting is necessary due to a decrease in impedance after consumption of a breakfast meal.[12] Thus, the evidence for 8 hours of fasting mentioned explicitly in the guideline is scarce. Moreover, all studies use impedance or resistance as the primary outcome, which is not directly clinically relevant.

Given the limited literature on the necessity and timing of fasting when performing BIA measurements and the urge to prevent fasting in patients with

malnutrition or sarcopenia, we aimed to assess whether fasting leads to clinically relevant differences in FFM estimation when performing single-frequency (SF) BIA measurements.

Methods

Study design and participants

This exploratory, observational, multi-centre non-inferiority study in healthy participants was conducted from September to December 2022. The study was designed to determine the necessity and timing of fasting before a BIA measurement. Participants were recruited through advertisement and word of mouth within the Gastroenterology and Hepatology – Dietetics department at Radboud university medical center (Radboudumc) and the Department of Dietetics at HAN University of Applied Sciences. People were eligible to participate if they were aged between 18 and 70, with a body mass index (BMI) of 18.5–30 kg/m^2. Due to possible interference with the BIA measurement, people were excluded if they were breastfeeding or pregnant, had a pacemaker or defibrillator, used medication influencing fluid balance, had an abnormal fluid balance, or suffered from burn wounds or decubitus. All subjects provided their written informed consent before participation.

Study procedures

During the study, participants underwent BIA measurements at five different time points. The initial measurement (t0) was performed after an overnight fast of at least 8 hours and after determining the participant's height (InLabS50, InBody, Seoul, South Korea). Before each measurement, participants were questioned about their adherence to the study protocol. After this, the participant received their chosen standardised breakfast. This was either full-fat yoghurt (200 g) with granola (50 g) and raisins (15 g) (388 kcal) or two slices of brown bread (70 g) with 30 + matured cheese (63 g) and margarine (10 g) (400 kcal). Remaining measurements were performed 1, 2, 3 and 4 hours after breakfast (t1, t2, t3 and t4, respectively). Participants drank coffee, tea, or water during breakfast and after t2 (150 ml). During the remaining part of the study, participants could not eat or drink anything. Figure 1 shows an overview of the study timeline.

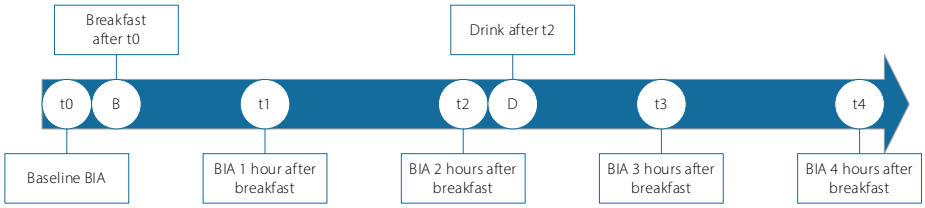

Figure 1. Study timeline.
Abbreviations: BIA, bioelectrical impedance analysis; t, timepoint.

Bioelectrical impedance analysis measurement and calculations

BIA measurements were conducted following the SOP for SF-BIA using a hand-to-foot Bodystat 500 (Bodystat, UK).[5] Before each BIA measurement, participants were asked to urinate, after which their weight (kg) was measured with one layer of clothing and without shoes on a seca 877 scale. A correction of 1 kg for clothes was applied. At each time point, the participant was measured three times consecutively to determine the variation within time points. We used the mean of the three measurements to calculate the additional variables. FFM and FM were calculated using the Kyle formula.[3] Afterwards, both FFM and FM were divided by squared height to obtain the index (kg/m^2): FFM index (FFMI) and FM index (FMI).

Outcomes

Primary outcome was the difference in FFM between the baseline (t0) and the other time points (t1, t2, t3 and t4). Secondary outcomes were the differences between baseline (t0) and the other time points (t1, t2, t3, t4) for FM, FFMI, FMI, weight, impedance, reactance, resistance, and phase angle. A difference of ≥1 kg in FFM and FM was considered clinically relevant, as determined by BIA experts of the Dutch BIA workgroup Nutritional Assessment Platform.[3,4]

Statistical methods

No sample size calculation was performed because we were not so interested in detecting (minor) mean group differences but rather sought to focus on the individual effects of having breakfast as well as the proportion of individuals with acceptable differences in that regard in the setting of a pilot study. According to the literature, including thirty participants was sufficient to perform a pilot study.[13] Continuous variables were presented as mean with standard deviation (SD) or median and interquartile range (IQR) in case of not-normal distribution. Binary variables were described as percentages.

For primary and secondary outcomes, linear mixed models were applied to test whether baseline measurements differed from the other time points. Participant ID was the random variable, and time point was the fixed variable, with t0 as a reference. Sidak adjustment was applied to correct for multiple testing. The residuals were checked for normality with histograms. Bland–Altman plots were generated, showing the mean difference and limits of agreement (LOA).

Furthermore, independent t-testing was performed to determine whether there was a difference between the types of breakfast regarding the change in FFM estimation. The coefficient of variation (CV, %) for FFM was calculated within and between time points. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA).

Ethical approval

This study was reviewed by the research ethics committee of Radboudumc in Nijmegen, the Netherlands (reference number 2022–15782). The committee declared this study was not subject to the Medical Research Involving Human Subject Act. Reporting was according to STROBE guidelines.[14]

Results

Demographics

In total, 39 adults between 19 and 66 years participated. Most participants had a healthy BMI ranging from 18.7 to 29.7 kg/m^2. Baseline characteristics of the participants are presented in Table 1. Thirty-one participants chose the yoghurt breakfast (80%), while eight chose the bread breakfast (21%).

Fat-free mass

No statistically significant difference was found 1 and 2 hours after breakfast compared to baseline (Table 2). FFM estimation increased by 0.4% (0.2 kg) after 3 hours (Figure 2C). The mean FFM estimation returned to baseline values after 4 hours (Table 2). For all four time points, the difference between fasted and non-fasted FFM measurements was not clinically relevant, with a difference of <1 kg of FFM in 90% of participants. The CV was 4.7 times higher between time points (CV = 0.42%) than the average CV of the three measurements within one time point (CV = 0.09%).

Secondary outcomes

Average FM estimates decreased significantly by 0.9% at 3 and 4 hours after breakfast, resulting in a 0.2 kg reduction (Table 2, Figure S1). No differences were found between breakfast meals for either outcome.

Table 1. Baseline characteristics of participants.

Participant characteristics	***N* = 39**
Female, n (%)	33 (85)
Age, median (IQR), years	28 (24–38)
Weight, mean (SD), kg	67 (9.6)
Height, mean (SD), m	1.74 (0.07)
BMI, median (IQR), kg/m^2	21.9 (20.1–24.1)

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 2. Means (SD) of all outcomes at baseline (t0) and 1 to 4 hours after breakfast ingestion (t1-4).

Outcome	**Baseline (t0)**	**t1**	**t2**	**t3**	**t4**
Weight, mean (SD), kg	67.3 (9.6)	**67.5 (9.6)***	67.3 (9.6)	67.3 (9.6)	**67.1 (9.6)***
FFM, mean (SD), kg	46.2 (6.2)	46.3 (6.3)	46.3 (6.3)	**46.4 (6.2)***	46.2 (6.2)
FM, mean (SD), kg	21.1 (5.7)	21.2 (5.7)	21.0 (5.7)	**20.9 (5.7)***	**20.9 (5.7)***
FFMI, mean (SD), kg/m^2	15.23 (1.45)	15.26 (1.46)	15.27 (1.43)	**15.29 (1.43)***	15.24 (1.44)
FMI, mean (SD), kg/m^2	6.98 (1.89)	7.01 (1.90)	6.96 (1.93)	6.93 (1.92)	**6.92 (1.90)***
Impedance, mean (SD), Ω	617 (61)	615 (62)	613 (60)	**611 (59)***	614 (59)
Reactance, mean (SD), Ω	63.3 (6.8)	63.2 (6.6)	63.1 (6.9)	62.9 (6.8)	63.1 (6.5)
Resistance, mean (SD), Ω	614 (61)	612 (62)	610 (60)	**608 (59)***	611 (59)
Phase angle, mean (SD), ^{o}	5.9 (0.5)	5.9 (0.5)	5.9 (0.5)	5.9 (0.5)	(0.5)

*p<0.05 in bold, compared to t0.
Abbreviations: SD, standard deviation; FFM, fat-free mass; FM, fat mass; FFMI, fat-free mass index; FMI, fat mass index; t, timepoint; Ω, ohm; °, degrees.

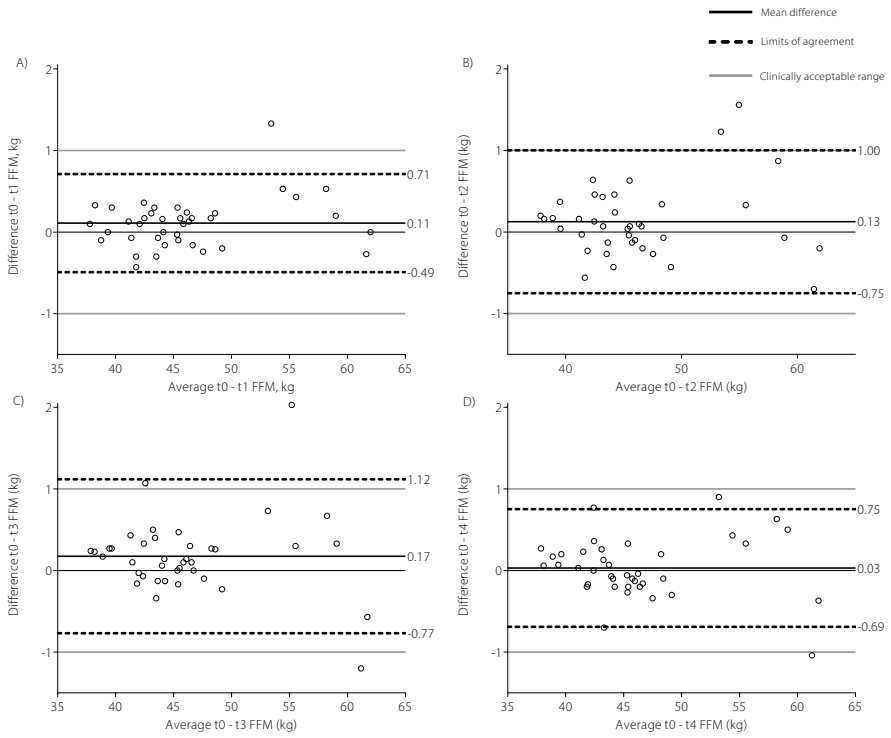

Figure 2. Bland-Altman plots showing the difference in fat-free mass between the baseline measurements (t0) and t1 (A), t2 (B), t3 (C), and t4 (D). Lines represent the mean difference, the limits of agreement, and clinically acceptable range.

Abbreviations: FFM, fat-free mass.

Discussion

This study explored the effect of breakfast on FFM estimation and found no clinically relevant difference between fasted and non-fasted measurements. In 90% of participants, FFM estimates changed less than 1 kg compared to their fasting value. In four participants, the difference exceeded the pre-set limit of 1 kg, of whom two admitted to having breached the research protocol. The most pronounced mean difference in FFM was found after 3 hours; this was statistically significant but not clinically relevant, remaining well below 1 kg difference. We hypothesised that this difference after 3 hours was due to the uptake of the breakfast at this time. In the first 2 hours after breakfast, most of the food remains in the stomach, which would not affect impedance outcomes.[15] However, body weight increased due to

the breakfast mass, influencing the calculation since weight is a variable in the Kyle formula.[3]

The results of our study are consistent with the findings of Hollander-Kraaijeveld et al. (2020, n = 84) in cystic fibrosis patients. These authors found a mean decrease of 0.2 kg in FFM after eating a non-standardised meal, with a difference of <1 kg of FM and FFM in 86% of the patients.[16] Although the trends compared to our study are in different directions in these (metabolically) substantially differing subject populations, the average change was minor and not clinically relevant. Furthermore, both studies found opposing individual responses, with participants increasing or decreasing FFM estimation after eating.

Androutsos et al. (2015, n = 55) studied the effect of a high-fat meal or high-carbohydrate meal on impedance and FM estimation.[17] These authors reported that average FM increased most after 2 hours, increasing 0.8 kg with a median difference of 4.8%. While the present study found a decrease in FM estimation, both studies have found non-clinically relevant changes (Table 2).

Our results are consistent with the three studies mentioned in the ESPEN guideline.[9–11] These all found differences in resistance and impedance outcomes before and after eating. However, none of these differences appeared clinically relevant, i.e., leading to treatment changes. In hindsight, in our opinion, we never had robust evidence to let our patients fast. Thus, all studies in the literature report similar results, while concluding on statistically significant differences in BIA outcomes but without clinically relevant differences between fasted and non-fasted BIA measurements.

In our study, a difference of ≥1 kg in FFM was considered clinically relevant, whereas Hollander-Kraaijeveld et al. used ≥1.5 kg as a clinically relevant difference. If we also defined 1.5 kg as a clinically relevant difference, we would only have one outlier left, which empowers the argument of measuring in a non-fasting state.

According to the literature, there is a within-day variability of 1–2% of resistance when performing an SF-BIA measurement and a weekly intra-person variability of 2–3.5%.[3] Comparing these values with the CV of 0.42% in FFM between time points found in this study, the variation due to having breakfast is below the within-day and the weekly variability. This finding further supports our opinion that measuring in a fasted state is unnecessary.

Weight increased on average by 0.2 kg 1 hour after breakfast and decreased by 0.2 kg after 4 hours (Table 2). This increase was due to the weight of the breakfast, while the decrease can be explained by losing water due to urinating before each measurement. There was no statistically significant change in reactance, while resistance and impedance decreased by 6 ohms after 3 hours (Table 2). This indicates that this change caused the increased FFM estimation at t3 rather than weight since the average weight was similar at baseline and at this time point.

This study has limitations, including the homogeneity of our study population, mostly compromising of females aged 24–38 with a healthy BMI. This homogeneity reduces the external validity of this study, but there is no evidence to suggest that there would be other findings in other types of populations. Furthermore, participants could choose between two breakfast meals. Differences in composition between the meals could have affected the BIA measurements differently, although we found no difference between breakfast groups regarding all outcomes. Hollander-Kraaijeveld et al. also did not find clinically relevant differences, and their participants had no limitations regarding nutritional intake.[16] Finally, we cannot be completely certain whether all subjects correctly reported their adherence to the study protocol.

Concerning the strengths, the research was standardised, following the SOP. Moreover, all measurements were performed by the same researcher, and on each study day, the SF-BIA was calibrated using the same device throughout the study.

Conclusion

In conclusion, these results indicate important implications for BIA measurements since, depending on the study protocol, it is feasible to include non-fasted subjects without negatively impacting study quality. Based on all the currently available literature and our data, we advise removing the advice on fasting from the current guideline. This facilitates body composition measurements in more patients, thereby enabling personalised patient care. Future studies should combine all these data to provide evidence as to whether the implemented nutritional treatment leads to improved patient outcomes, especially in the vulnerable population of patients suffering from malnutrition or sarcopenia.

Acknowledgements

We want to thank all the participants for participating in this study, the BIA experts of the Dutch BIA workgroup for contributing to establishing a clinically relevant difference in FFM and Reinier Akkermans for helping with the statistical analysis.

Financial disclosures

None

Conflict of interest

None

Conference presentation

Poster presentation ESPEN September 2023

Supplementary data

Supplementary files are available at:
https://nutritionj.biomedcentral.com/articles/10.1186/s12937-023-00882-5

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Chapter 4

Parenteral nutrition and bioelectrical impedance analysis estimated fat-free mass in adult patients with chronic intestinal failure: A descriptive cohort study

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Journal of Parenteral and Enteral Nutrition, January 2025

Abstract

Background

In patients with chronic intestinal failure (CIF), the content and type of parenteral nutrition (PN) are individually determined based on various factors, including body composition. In clinical practice, bioelectrical impedance analysis (BIA) is used to assess body composition using standardized protocols. However, these protocols lack specific recommendations for patients receiving PN. Therefore, this study described the effect of PN infusion on fat-free mass (FFM) as evaluated by single-frequency BIA.

Methods

We performed a descriptive cohort study using BIA to assess adult patients with CIF receiving PN. Measurements were performed at baseline (before PN infusion) and 0, 1, 2, and 4 hours after (usually) 18-hour PN infusion using hand-to-foot single-frequency BIA (Bodystat 500). The primary outcome of FFM was calculated using the Kyle equation. A linear mixed model was used to compare baseline values with other time points. A difference of >1 kg in FFM compared with baseline was considered clinically relevant.

Results

Twenty patients (70% female) with a mean age of 58 (SD, 14) years and a median body mass index of 22.3 (IQR, 21.2–24.8) kg/m^2 were included in the analysis. No significant change in FFM after PN infusion was observed, and 90% (69/77 measurements) of all FFM outcomes after PN infusion remained within the ≤1-kg clinically relevant range.

Conclusion

This study found that PN infusion does not affect FFM estimation as assessed by hand-to-foot single-frequency BIA.

Introduction

In patients with chronic intestinal failure (CIF), decreased gut function leads to insufficient absorption of macronutrients, water, and/or electrolytes, necessitating intravenous supplementation of these components to maintain their health and growth.[1,2] The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline on parenteral nutrition recommends measuring body composition in patients with CIF at every scheduled visit because they have an increased risk of unfavourable changes in body composition.[3] Bioelectrical impedance analysis (BIA) is a widely used bedside method to assess body composition, mainly because of its portability, ease of use, safety, non-invasiveness, and relatively low costs compared with other methods.[4,5] Various types of BIA are available, of which single-frequency BIA (SF-BIA) is most often used. Fat-free mass (FFM) can be calculated from the resistance and reactance of body tissues to a single alternating current (50 kHz) using a population-specific prediction equation containing different patient characteristics, such as age, sex, height, and weight.[6] As SF-BIA is a double-indirect method in which many different variables influence the outcome, using a standardized protocol is very important to obtain reliable results.[7] Currently, however, these protocols have no recommendations for patients receiving parenteral nutrition (PN) because the effect of PN infusion on FFM as assessed by BIA is unclear.

Although data on the effect of PN infusion on FFM are lacking, there has been one investigation into the effect of oral fluid intake on estimation of FFM. This study in 140 healthy participants found that 500 ml of water administered every 15 min led to an underestimation of FFM values.[8] Other studies have focused on the effect of intravenous fluids on resistance rather than the effect on FFM. A review has summarized how hyperhydration and rehydration can influence resistance,[9] with intravenous saline infusions decreasing resistance[10–12] and intravenous mannitol increasing resistance.[11] Similarly, in patients undergoing haemodialysis, changes in electrolyte levels have been shown to influence resistance, which could be incorrectly interpreted as changes in body water.[13] Other studies have also found that the ionic content of intravenous fluids (e.g., saline or dextrose) affects BIA outcomes for a varying period after supplementation.[14,15] Despite these findings, the specific effects of PN infusion on FFM, as measured by BIA, remain underexplored. This is a critical knowledge gap because understanding if and how PN influences estimation of FFM is important for optimizing body composition management in these patients. Therefore, the primary aim of this study was to address this gap and describe the effect of PN infusion on FFM evaluated by SF-BIA in patients with CIF.[16]

Methods

Study design and participants

This descriptive cohort study was conducted from December 2021 to June 2024. Patients were eligible to participate if they were aged ≥18 years, diagnosed with CIF, receiving PN, and hospitalized at Radboud university medical center (Radboudumc) in Nijmegen, the Netherlands. Patients were excluded if they were pregnant or breastfeeding, had a temperature ≥38°C, or had a clinical suspicion of infection or sepsis. All participants provided their written informed consent before the study.

Study procedures

Participants underwent SF-BIA measurements during the study at five different time points (t0, t1, t2, t3, and t4) over 2 days. The first measurement (t0) was performed just before the start of the PN infusion, and the second measurement (t1) was performed at the end of a usually 18-h nonstop overnight PN infusion. The remaining measurements were performed 1, 2, and 4 hours after PN infusion (t2, t3, and t4, respectively). Figure 1 shows an overview of the study timeline.

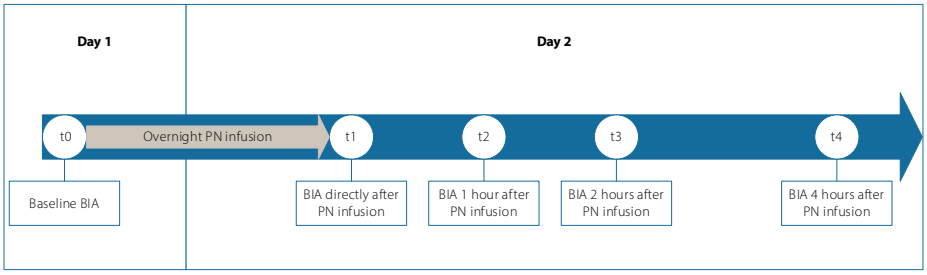

Figure 1. Study timeline.

Abbreviations: BIA, bioelectrical impedance analysis; PN, parenteral nutrition; t, timepoint.

Bioelectrical impedance analysis and calculations

Following a standard operating procedure developed by the Dutch Nutritional Assessment Platform (https://nutritionalassessment.nl), based on recent and recommended international BIA guidelines,[4,6] SF-BIA measurements were performed using a hand-to- foot Bodystat 500 (Bodystat).[17] Participants were not allowed to exercise and were required to fast for at least 4 hours prior to the measurements. Before each BIA measurement, participants were asked to urinate and were weighed with clothing and without shoes on a seca 956 chair scale (seca). A correction of 1 kg for clothes was applied. FFM was calculated using the Kyle equation.[6] Fat-free mass index (FFMI) was determined by dividing FFM by the

square of height. Fat mass (FM) was determined by subtracting FFM from total body weight and was subsequently used to calculate fat percentage by dividing FM by total body weight multiplied by 100%. BodygramPlus software (version 1.2.1; AKERN) was used to create bioelectrical impedance vector analysis (BIVA) plots to determine hydration status at each measurement. Hydration status was considered abnormal when a vector point was above the 75% tolerance ellipse.[7,18]

Outcomes

The primary outcome of this study was the difference in FFM between the baseline (t0) measurement before PN infusion and the other time points after PN infusion (t1-t4). Secondary outcomes were the differences between baseline (t0) and the other time points (t1-t4) for weight, resistance, reactance, impedance, phase angle, FM, FFMI, and fat percentage.

Clinically acceptable variation in fat-free mass

To interpret raw BIA values in clinical practice, these must be translated into clinically interpretable variables, like FFM. In this study, the equation by Kyle et al. was used to calculate FFM because no population-specific equation is available for patients with CIF. The Kyle equation has been validated against dual-energy x-ray absorptiometry, with a standard error of the estimate of 1.8 kg.[6] A change of >1 kg in FFM compared with baseline (t0) was considered clinically relevant, in accordance with Dutch BIA experts from the Nutritional Assessment Platform.

Coefficient of variation resistance

The coefficient of variation, a measure that represents the ratio of the SD to the mean, is used to assess the relative variability of data. We report the coefficient of variation of resistance for assessing acceptable variation before and after PN infusion, as no information regarding FFM is available in the literature. Daily reported mean coefficient of variation for resistance ranges from 1% to 2%, whereas weekly intraindividual variation ranges from 2.0% to 3.5%.[6,19–21] In the current study, SF-BIA measurements were performed over 2 days. Therefore, a coefficient of variation between 2% and 3.5% in this study corresponds with the expected normal variation in daily resistance measurements. A coefficient of variation above 3.5% may indicate the influence of PN infusion.

Statistical methods

No power calculation was performed because this is an exploratory study with five repeated BIA measurements per patient. A sample size of 20 participants was expected to be sufficient to describe the difference in FFM before and after PN

infusion and to describe whether this exceeds the predefined clinically acceptable range of 1 kg. Continuous variables were presented as mean with SD or median with IQR in case of not-normal distribution. Binary variables were expressed in numbers and percentages. Linear mixed-model analysis was performed to determine the difference in FFM and secondary outcomes between baseline and other time points. Participant ID was used as a random factor, and time point was used as a fixed factor, with t0 as a reference. Sidak adjustments were applied to correct for multiple testing. Estimated marginal means with 95% CIs were reported to interpret the fixed effects at each time point. A P value of 3 SD from the average SD (FFM) of the study population.[22] All analyses were performed using IBM SPSS Statistics for Windows, version 29 (IBM).

Ethical approval

The research ethics committee of Radboudumc, Nijmegen, the Netherlands (reference number 2021-13266) reviewed this study and declared it not subject to the Medical Research Involving Human Subject Act.

Results

Demographics

Twenty-one adult patients with CIF, aged between 23 and 81 years, were included in this study. One patient was excluded from the analysis because of a large difference in FFM between baseline and other time points, with an SD of 3.6 higher than the average SD. Three patients had one missing value: these were discharged earlier (n = 1) or in PN training (n = 2). Body mass index ranged from 16.5 to 37.4 kg/m^2. Table 1 shows the baseline characteristics of the 20 patients included in the final analysis. Information on PN infusion per patient (including type, volume, osmolarity, energy, infusion time, and amount of protein, glucose, and fat) is shown in Table S1.

Fat-free mass

For FFM, no significant difference between baseline and other time points was found (Table 2). The mean differences (95% CI) in FFM compared with baseline were as follows: at t1 0.14 kg (-0.13 – 0.41); at t2 0.21 kg (-0.07 – 0.48); at t3 -0.01 kg (-0.28 – 0.26); and t4 -0.01 kg (-0.29 – 0.26). In Figure 2, the change of FFM over time is presented per patient. From the total number of measurements after PN infusion, 90% (69/77) differed by ≤1 kg compared with the baseline. Considering intra-individual differences in FFM per patient, no trend or pattern was observed.

Secondary outcomes

The mean coefficient of variation for resistance was 2.18% (SD, 1.04%; Table S2). Significant differences compared with baseline were found for weight at t1–t3, reactance at t1, and phase angle at t1 (Table 2). No significant differences were found for the remaining secondary outcomes compared with the baseline (Table 2).

Hydration status

Figure S1 presents BIVA plots per patient. According to the BIVA plots, three patients had an abnormal hydration status, which remained constant throughout all measurements. All remaining patients had an overall normal hydration status.

Table 1. Characteristics of participants with chronic intestinal failure.

Patient characteristics	***n = 20***
Female sex, n (%)	14 (70)
Age, mean (SD), years	58 (14)
Weight, mean (SD), kg	66.8 (16.4)
Height, mean (SD), m	169 (16)
BMI, median (IQR), kg/m^2	22.3 (21.2 – 24.8)
Cause of CIF, n (%)	
Intestinal dysmotility	7 (35)
Short bowel syndrome	5 (25)
Mechanical obstruction	4 (20)
Other	3 (15)
Extensive small bowel mucosal disease	1 (5)

Abbreviations: BMI, body mass index; CIF, chronic intestinal failure; IQR, interquartile range; n, number; SD, standard deviation.

Table 2. Estimated marginal means and 95% CI of FFM, weight, resistance, reactance, impedance, phase angle, FM, FFMI, and fat percentage per time point assessed using single-frequency bioelectrical impedance analysis.

Outcome	Baseline (t0)	t1	t2	t3	t4
FFM, EMM (95% CI), kg	44.8 (40.1 – 49.5)	44.9 (40.2 – 49.6)	45.0 (40.3 – 49.7)	44.8 (40.0 – 49.5)	44.8 (40.0 – 49.5)
Weight, EMM (95% CI), kg	66.8 (59.1 – 74.4)	**67.1 (59.4 – 74.8)***	**67.1 (59.4 – 74.7)***	**67.1 (59.4 – 74.7)***	67.0 (59.3 – 74.7)
Resistance, EMM (95% CI), Ω	579 (542 – 617)	582 (545 – 620)	576 (538 – 613)	585 (547 – 622)	586 (549 – 624)
Reactance, EMM (95% CI), Ω	45.6 (40.8 – 50.3)	**47.6 (42.9 – 52.4)***	45.6 (40.9 – 50.4)	46.5 (41.7 – 51.2)	47.3 (42.6 – 52.1)
Impedance, EMM (95% CI), Ω	576 (536 – 617)	584 (544 – 625)	577 (536 – 618)	587 (546 – 627)	607 (566 – 648)
Phase angle, EMM (95% CI), °	4.5 (4.1 – 5.0)	**4.7 (4.3 – 5.2)***	4.6 (4.1 – 5.0)	4.6 (4.1 – 5.0)	4.7 (4.2 – 5.1)
FM, EMM (95% CI), kg	22.0 (17.4 – 26.6)	22.2 (17.6 – 26.8)	22.1 (17.5 – 26.7)	22.3 (17.7 – 26.9)	22.3 (17.6 – 26.9)
FFMI, EMM (95% CI), kg/m^2	15.5 (14.4 – 16.7)	15.6 (14.5 – 16.7)	15.6 (14.5 – 16.8)	15.5 (14.4 – 16.7)	15.5 (14.4 – 16.7)
Fat, EMM (95% CI), %	32.2 (28.1 – 36.3)	32.3 (28.2 – 36.4)	32.1 (28.0 – 36.3)	32.5 (28.4 – 36.6)	32.4 (28.3 – 36.6)

* Statistical significance compared with baseline (t0).
Abbreviations: CI, confidence interval; EEM, estimated marginal means; FFM, fat-free mass; FM, fat mass; FFMI, fat-free mass index; FMI, t, timepoint Ω, ohm; °, degrees.

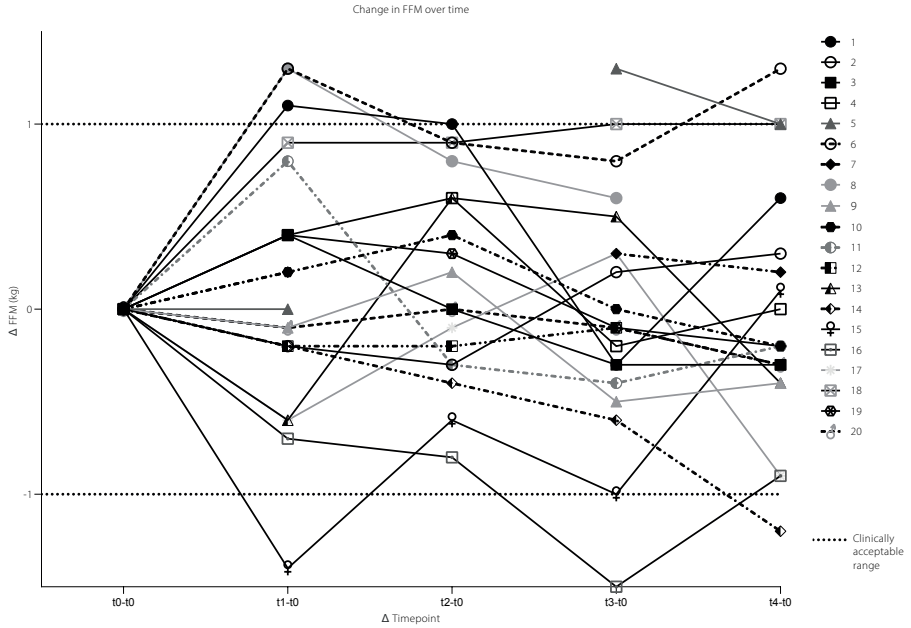

Figure 2. Absolute differences (kg) in FFM measurements over time compared with baseline (t0) per patient. Clinically relevant range indicated with dotted line on y-axis.

Abbreviation: FFM, fat-free mass.

Discussion

To the best of our knowledge, this is the first study that explored the effect of PN infusion in patients with CIF on FFM estimation as assessed by hand-to-foot SF-BIA at different time points within 4 hours after PN infusion. No significant change in mean FFM was observed at any time point compared with the baseline. These results indicate that PN infusion does not significantly affect FFM outcomes within the first 4 hours after PN infusion. This is the first study that explored the effect of PN infusion on FFM, which precludes comparisons with other studies. In theory, hyperhydration is expected to decrease resistance compared with normal hydration because increased fluid volume provides more conductive pathways for the current.[9] Previous studies have found contradictory results of the effect of intravenous infusion on BIA, depending on the ionic content. Decreased resistance was found after intravenous saline infusions, whereas increased resistance was found after hypertonic intravenous infusions.[9,10,12,14,15] In this study, patients received PN with an average infusion time of 18 hours. This makes it difficult to compare with studies in which, for example, intravenous saline was administered

over 1 hour. The prolonged infusion time in this study may have contributed to the fact that no significant differences were detected, as it allows the PN solution to be gradually absorbed into the tissues. Regarding the secondary outcomes, we found a few results worth discussing. First, we observed a coefficient of variation of 2.18% for resistance, which is comparable to the range (2%–3.5%) reported in the ESPEN bioelectrical impedance analysis guideline.[6] This result indicates that PN infusion falls within the expected normal variation in daily resistance measurements. Second, a significant increase in weight was found at t1–t3, compared with baseline (Table 2). However, this 0.3-kg change in weight is not clinically relevant. Moreover, this weight change can be expected following PN infusion, as the high ionic content infused in the body causes fluid retention and subsequent weight gain. Although weight affects FFM in the equation, this did not significantly change the actual FFM outcome. Third, a significant increase at t1 for phase angle and reactance was observed compared with baseline. The phase angle reflects the interaction between resistance and reactance.[4] The greater the number of cell membranes and cell integrity, the greater the reactance and, therefore, the phase angle.[23] Recovery of the body due to sleep may contribute to the increased phase angle and reactance at t1 (first bioelectrical impedance analysis measurement in the morning). Moreover, the mean phase angle of this study is low, which is expected in a diseased state.[4,18] This study had limitations that need to be acknowledged. First, in this study, we used hand-to-foot SF-BIA, which relies on population-specific predictive equations. No specific equation is available for patients with CIF, so we used an equation developed for healthy individuals. This equation includes multiple variables. Potentially small changes in FFM caused by PN might be masked by the greater influence of these additional variables (age, sex, height, and weight). To address this, we presented both raw data and derived outcomes such as FFM. Additionally, SF-BIA is a double-indirect method, requiring careful standardization to obtain reliable data. We implemented standardization procedures to mitigate this limitation. Hand-to-foot SF-BIA primarily measures impedance in the limbs, which represent a small proportion of total body water, and therefore, the impact of PN–induced fluid shifts may have been minimal in these regions. This may explain the limited effects observed. Although segmental BIA, which is more sensitive to detect fluid shifts, is now more commonly used, it was not available at our centre for research purposes at the time of our study. Future research should incorporate this technique to enhance the robustness of our findings. Second, the absence of a control group (i.e., patients not receiving PN) is a limitation, and its presence would have allowed us to better assess whether the observed variations reflect natural fluctuations in BIA over time. Although we acknowledge that such fluctuations could be a factor, we do not anticipate that the lack of a control group significantly impacted our findings, as no substantial differences were observed in our

data. Third, the sample size was limited. However, the 95% CI ranges at its maximum from −0.29 to 0.48 kg, which falls well within the predefined clinically acceptable range. Increasing the number of study participants would enhance the precision and accuracy of the estimated marginal means and narrow the CI. However, because our results already fall within the clinically acceptable range, it was deemed unnecessary to include additional patients. Fourth, while the recruitment of patients was cumbersome, the need to fast was also a limiting factor in several patients. Therefore, after a study concluded that a fasting state is not required when performing BIA measurements, our patients were allowed to consume food in amounts lower than 200 kcal before the BIA measurement.[16] Apart from this minor protocol deviation, we were able to follow the standard operating procedure and protocol for the rest of the study. Fifth, three patients had an abnormal hydration status according to bioelectrical impedance vector analysis plots. This is a contraindication for SF-BIA, as the measurement assumes normal hydration.[7,18] These patients had vectors of all measurements below the short major axis, interpreted as fluid overload. However, all vector points were placed closely together. For this study, in which individual differences in FFM compared with baseline were determined, we argued that a constant error in resistance and reactance due to fluid overload is not expected to significantly alter the results per patient. Sixth, we limited SF-BIA measurements to the first 4 hours after PN infusion. However, we have no reason to expect a significant change in the last 2 hours before returning to baseline, as the FFM values of t3 and t4 are already, on average, similar to baseline. Moreover, previous studies limited their measurements to even shorter time frames. The results from this study have relevant implications for practice and research. Current BIA guidelines do not provide specific recommendations regarding the timing of measurements in patients receiving PN, despite the frequent use of BIA in the CIF population, for whom body composition assessment is recommended at all scheduled visits.[1] The suggested flexibility in measurement timing allows healthcare professionals to conduct BIA without coordinating with specific infusion schedules, thereby increasing the convenience and efficiency of patient monitoring. For researchers, these results validate the use of BIA as a robust tool for assessing body composition in studies with patients receiving PN, ensuring more consistent and comparable data collection across studies.

Conclusion

This study indicates that PN infusion does not significantly affect FFM estimation as assessed by hand-to-foot SF-BIA in patients with CIF.

Acknowledgements

We thank Radboudumc CIF team for helping with the recruitment, the patients who participated, the nursing staff who cared for them, and Reinier Akkermans for helping with the statistical analysis.

Financial disclosures

None

Conflict of interest

None

Conference presentation

Poster presentation ESPEN September 2024

Supplementary data

Supplementary files are available at:
https://aspenjournals.onlinelibrary.wiley.com/doi/10.1002/jpen.2723

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5

Chapter 5

Taurolidine-related adverse events in patients on home parenteral nutrition frequently indicate catheter-related problems

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Clinical Nutrition, October 2022

Abstract

Background

A catheter-related bloodstream infection (CRBSI) is a serious complication of home parenteral nutrition (HPN) treatment. Despite taurolidine's frequent use as catheter lock solution (CLS) to prevent CRBSIs and its presumed favourable safety profile, data on taurolidine-related adverse events (AEs) and the clinical implications thereof remain merely anecdotal. The aim of this study was to explore taurolidine-related AEs in our large cohort of HPN patients and to develop an algorithm on how to deal with these AEs in clinical practice.

Methods

This retrospective cohort study comprised all adult HPN patients who used taurolidine as a CLS between 2006 and 2021 at our national HPN referral centre. The primary outcome was to identify taurolidine-related AEs. Secondary outcomes were median time to a taurolidine-related AEs and development of a clinical algorithm. A taurolidine-related AE was defined as an event that occurred directly after instillation of taurolidine in the CVAD or at start of fluid/PN infusion.

Results

In total, 470 patients used taurolidine during 700.232 catheter days. In 89 (19%) patients, 103 mild- to severe AEs related to taurolidine were observed. Six patients developed an allergic reaction. Reported AEs compromised vascular access device-related problems (group A) or taurolidine-related problems (group B) in 53 (51%) and 50 (49%) patients, respectively. In groups A and B, 51 (85%) and 21 (18%) patients presented with taurolidine infusion-related pain. Upon rechallenge, 45 (85%) and 16 (32%) patients, respectively, successfully resumed taurolidine locking without residual symptoms.

Conclusion

In this study, use of taurolidine as CLS was generally safe. Most reported AEs were vascular access device-related, and the majority of symptoms concerned pain. Upon rechallenge, a substantial number of patients, especially those in whom pain was the main symptom, could resume CLS locking after addressing the underlying catheter-related problem. Based on these results, we present a clinical algorithm for patients with possible taurolidine-related symptoms.

Introduction

Chronic intestinal failure (CIF) patients require long-term parenteral (intravenous) nutrition (PN) and/or fluid supplementation to maintain health and/or growth because of severe gut dysfunction.[1] Home parenteral nutrition (HPN) is a complex and time-consuming treatment that focuses on training patients to self-manage their central venous access device (CVAD) and infusion pump at home.[2] Unfortunately, HPN patients are frequently admitted to the hospital because of potentially life-threatening catheter-related bloodstream infections (CRBSIs). Thus, preventing CRBSIs by maintaining adequate and safe venous access remains key to both patient and technique survival. The most crucial strategy to prevent CRBSIs is strict adherence to antiseptic protocols when managing CVADs.[3] An additional preventive technique is the use of antimicrobial catheter lock solutions (CLSs), such as taurolidine.[1]

Taurolidine, a derivative of the amino acid taurine, was first synthesised in the 1970s and used initially as a local treatment for bacterial peritonitis.[4,5] This agent prevents microbial adhesion to catheter surfaces and biofilm formation by engaging an irreversible reaction of its metabolites with bacterial cell components.[6-8] Because of this mode of action, which fundamentally differs from antibiotics, taurolidine displays a very broad spectrum of activity against bacterial as well as fungal pathogens.[9-11]

In line with these notions, clinical studies found taurolidine to be highly effective in preventing CRBSIs when compared to other CLSs.[12-14] From 2006 on, HPN patients in our own tertiary CIF referral centre started using 2% taurolidine as CLS, initially in the context of an open-label randomised trial.[15] Based on the favourable results of this study, in 2008, all of our patients were switched to taurolidine. This has remained our preferred CLS ever since, resulting in CRBSI rates as low as 0.6 events per 1000 catheter days.[14] Over these years, we have obtained a solid body of experience comprising more than 600.000 taurolidine locks.

The reason for the present study is that despite its efficacy in preventing CRBSIs, and while the use of taurolidine locks has generally been found to be safe, there is still limited information on (suspected) taurolidine-related adverse events (AEs) and the implications thereof. To our knowledge, studies are lacking in CIF patients that focused primarily on taurolidine-related AEs. In addition, we wanted to confirm our impression that in a substantial number of cases, patient-reported 'side effects' in fact indicate catheter dysfunction, rather than taurolidine-related problems per

se (intolerance, allergy, anaphylaxis). Hence, the aim of this study was to evaluate taurolidine-related AEs in our HPN patient cohort who used taurolidine as CLS and provide an algorithm on taurolidine use for clinical practice.

Methods

Study design and patient selection

This retrospective cohort study was conducted at Radboud university medical center, a tertiary referral centre for CIF. Patients were selected from the Nijmegen IF Registry, a web-based Castor EDC database.[16] Patients aged ≥18 years were included if they met the criteria for CIF, received HPN for a minimum of three months, and used taurolidine as CLS between January 2006 and December 2021.[1]

Data collection

Patient characteristics (sex, age, and underlying disease leading to CIF), CVAD characteristics (type, site of vein insertion, date of insertion, and removal), and HPN characteristics (type of infusion, number of infusions per week, CLS) were collected from the Nijmegen IF registry. For this study we conducted a search in the medical records of all patients, and we added data on taurolidine-related AEs to the Nijmegen IF registry.

Taurolidine management

After each PN or fluid infusion, the CVAD is rinsed with 20 ml 0.9% saline. Subsequently, 5 ml 2% taurolidine (Taurosept, Geistlich Pharma AG Wolhusen, Switzerland) is instilled in the CVAD and remains until the next PN or fluid infusion, when the taurolidine lock is slowly flushed into the patient. Hence, the dwell time of taurolidine differs per patient and depends on the number of infusions per week but usually ranges from 8 hours (daily PN) to 72 hours (PN twice weekly).

When patients experience a taurolidine-related AE, our strategy is to switch to another taurolidine-containing solution (1.35% taurolidine with 4% citrate; TauroLock, TauroPharm GmbH Waldbüttelbrunn, Germany) or 0.9% saline, depending on the severity of the AE. A rechallenge with 2% taurolidine is conducted if considered safe by a treating physician. In case of doubt, this procedure is performed at the clinical ward.

Outcomes and definitions

The primary outcome was taurolidine-related AEs in patients with CIF receiving HPN. Secondary outcomes were to identify the cause of the AEs, the median time to a taurolidine-related AE, present the number and location of rechallenges with taurolidine, and provide an algorithm on how to deal with taurolidine-related AEs in clinical practice. A taurolidine-related AE was defined as an event that occurred directly after instillation of taurolidine in the CVAD or at start of fluid/PN infusion. Patients were categorised into two groups: group A (vascular access device-related problems) included patients who experienced an AE during a vascular access device-related problem, and group B (taurolidine-related problems) consisted of patients with most likely taurolidine-related AEs.

Taurolidine-related adverse events

Taurolidine-related symptoms were independently assessed by two investigators (JK and VG) according to the common terminology criteria for AEs (CTCAE version 5.0).[17] A third investigator made a final judgement in the absence of consensus (GW). The CTCAE classifies the severity of symptoms into grades from 1 to 5, with a clinical description per grade. In general, grade 1 is mild (asymptomatic or mild symptoms), grade 2 is moderate (minimal, local, or non-invasive intervention indicated), grade 3 is severe (medically significant, but not immediately life-threatening), grade 4 is life-threatening, and grade 5 is a death related to an AE. A list of the used CTCAE terms can be found in Table S1.

Statistical methods

Baseline characteristics, primary and secondary outcomes were summarised using descriptive statistics (frequencies, percentages, mean, median, and interquartile range (IQR). Continuous variables were presented as means with standard deviations (SD) or medians and IQR if not normally distributed. Missing data were separately noted in the baseline Table. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp. Armonk, NY, USA).

Ethical approval

This study was approved by the research ethics committee of Radboudumc in Nijmegen, the Netherlands (reference number 2020-6524) and was reported according to the STROBE guidelines.[18]

Results

Demographics

Between 2006 and 2021, a total of 518 patients were under treatment in Radboud university medical center, of whom 470 used taurolidine during 700.232 catheter days. Baseline characteristics of both patients and CVADs are presented in Table 1.

Taurolidine-related adverse events

In total, 175 symptoms were reported, resulting in 103 taurolidine-related AEs in 89 (19%) patients (Figure 1). A patient could experience multiple symptoms during one AE. The AE rate was 0.15 per 1000 catheter days. Symptoms ranged from mild to severe, and mostly were pain-related. No life-threatening AEs occurred. Six patients developed an allergic reaction, all grade 3 reactions. The cause of AEs was considered in 53 (51%) vascular access device-related (group A), while 50 (49%) were taurolidine-related (group B, Figure 1).

Vascular access device-related problems (group A)

In total, 53 AEs in 43 patients were considered vascular access device-related problems. The various symptoms and their severity are shown in Figure 1. Fifty-one (85%) patients presented with taurolidine infusion-related pain (Figure 2). Reasons for the symptoms were 23 thromboses (43%), 14 CVAD malpositions (26%), 7 CRBSIs or local infections (13%), 3 CVAD malfunctions (6%), and 6 unknown (11%). The patients with an unknown cause had no abnormalities on imaging. However, the CVAD was removed because of persistent pain. After treatment or CVAD removal, 45 (85%) patients restarted with taurolidine without recurring AEs (Figure 1). Thirty-four rechallenges were performed at the clinical ward (not because of severe symptoms but because patients were already admitted), other 11 rechallenges were performed at home due to mild symptoms. Eight patients received no rechallenge with taurolidine since one patient restarted HPN using an arteriovenous fistula (shunt), four patients stopped HPN, two patients did not agree to a rechallenge, and one patient died due to a non-HPN related problem.

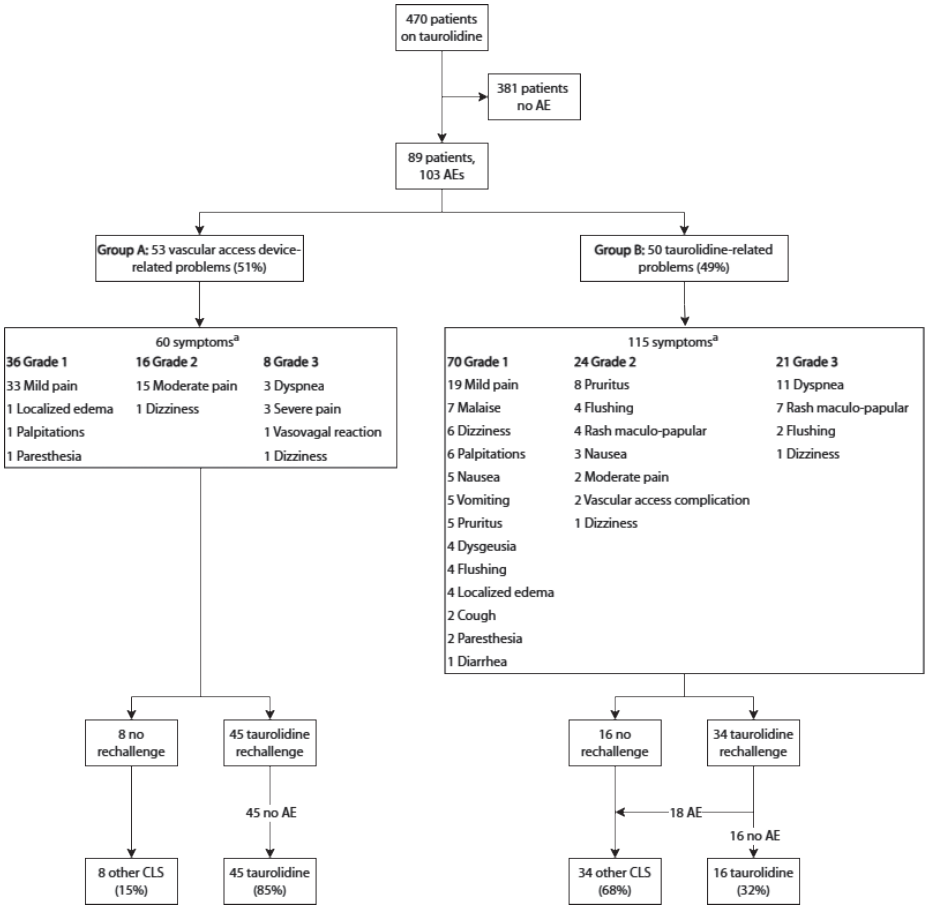

Figure 1. Flowchart of patient-reported symptoms when using 2% taurolidine, categorised into two groups according to their underlying cause and subsequent rechallenges with taurolidine.

[a] Patients may have experienced multiple symptoms during one AE. In total, six patients developed an allergic reaction. Grade 1: mild (asymptomatic or mild symptoms), grade 2: moderate (minimal, local, or non-invasive intervention indicated), and grade 3: severe (medically significant, not immediately life-threatening).

Abbreviations: AE, adverse event; CLS, catheter lock solution.

Table 1. Baseline characteristics of both patients and central vascular access devices.

Patient characteristics	***n* = 470**
Female, n (%)	316 (67)
Age, median (IQR), years	63 (51–72)
Cause of intestinal failure, *n* (%)	
Short bowel syndrome	191 (41)
Gastrointestinal motility disorder	167 (36)
Extensive small bowel mucosal disease	23 (5)
Intestinal fistula	29 (6)
Mechanical obstruction	18 (4)
Other	42 (9)
CVAD characteristics	***n* = 1.482**
Type of CVAD, n (%)	
Tunnelled catheter	1.030 (70)
Subcutaneous port system	267 (18)
Nontunneled catheter	62 (4)
Peripherally inserted central catheter	116 (8)
Other or unknown	7 (0)
Site of vein insertion, n (%)	
Left	550 (37)
Right	877 (59)
Other	2 (0)
Unknown	53 (4)
Type of vein insertion, n (%)	
Jugular vein	847 (57)
Subclavian vein	287 (19)
Femoral vein	141 (10)
Other	21 (1)
Unknown	186 (13)
Type of infusion, n (%)	
Nutrition	610 (41)
Fluids	160 (11)
Nutrition and fluids	710 (48)
Other or unknown	2 (0)
Infusion, number per week (%)	
1	2 (0)
2	32 (2)
3	73 (5)
4	83 (6)
5	84 (6)
6	78 (5)
7	1130 (76)

Abbreviations: CVAD, central venous access device; IQR, interquartile range.

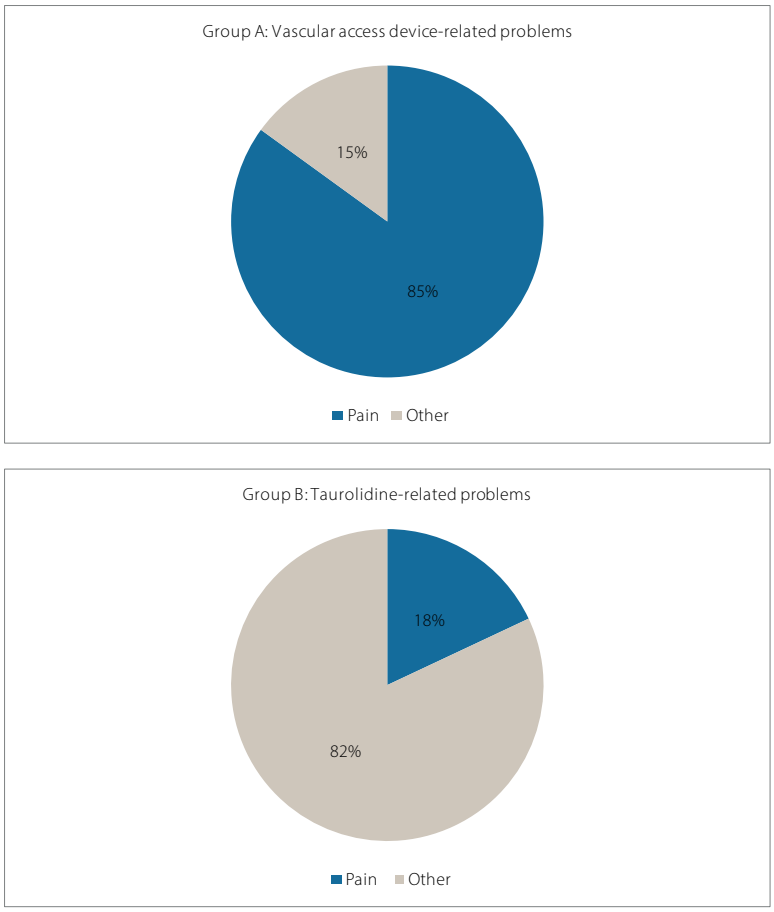

Figure 2. Proportion of taurolidine infusion-related pain versus 'other' symptoms.

Taurolidine-related problems (group B)

In this group, 115 symptoms were reported, resulting in 50 taurolidine-related AEs in 50 patients. The various symptoms and their severity are shown in Figure 1. Twenty-one (18%) patients presented with taurolidine infusion-related pain (Figure 2). Sixteen patients received no rechallenge because in 10 patients the attending physician decided that a rechallenge was not appropriate due to the severity of symptoms, two patients restarted HPN via an arteriovenous fistula, two patients did not agree to a rechallenge, one patient stopped HPN, and one patient was lost to follow up as care was transferred to another hospital. The other 34 patients received a rechallenge with a taurolidine containing CLS. Twenty-nine rechallenges were performed at home due to mild symptoms, the other five were performed at the clinical ward (due to severe symptoms or because these patients had already

been admitted). Eighteen patients experienced symptoms again and subsequently switched to 0.9% saline as CLS. Sixteen patients experienced no or mild symptoms. Hence, two continued with taurolock and fourteen with taurosept as CLS (Figure 1). Four patients immediately experienced symptoms after taurolidine instillation. The median time to an AE in this group was 701 days (IQR 264–1936).

Notably, eight patients (16%) experienced a total of 12 mild symptoms due to extra-protocol use of taurolidine. This mostly concerned: a double dosage injection (1 patient) or a too rapid infusion (seven patients). After receiving protocol guidance on how to use taurolidine correctly, all eight (100%) patients restarted without developing new AEs.

Clinical algorithm on taurolidine-related adverse events

Based on our experience and the data gathered in this study, we propose a clinical algorithm for patients who develop symptoms following taurolidine use (Figure 3). In case of symptoms, patients are requested to replace taurolidine with 0.9% saline locking for one week. Depending on the severity of the AE, a rechallenge should be performed either at home or in a controlled hospital setting. The attending physician should always determine whether a rechallenge is justified in case of a severe AE (e.g., anaphylactic reaction). Before rechallenge, protocol guidance on how to use taurolidine correctly should be provided, for example, by extra slowly instilling taurolidine in the CVAD and by flushing taurolidine at least every week. The patient may continue taurolidine treatment in case of no recurrence of symptoms after the rechallenge. Diagnostics to rule out vascular access problems should be performed whenever the patient experiences recurrent symptoms during this rechallenge. Diagnostics usually concern careful inspection of the catheter (exit site) for catheter damage. In addition, fluoroscopy may be performed to detect catheter malpositioning or occlusion. The latter mostly occurs in the form of thrombosis or a fibrin sheath that surrounds the catheter tip and reverses blood flow. In case of a vascular access problem, a rechallenge can be performed after treatment of the underlying problem. The latter mostly implies the use of a fibrinolytic agent to remove a clot or fibrin sheath, but in case of dislocation, catheter removal is required. If diagnostic imaging shows no abnormalities or in case of recurrent symptoms, consider switching to another CLS.

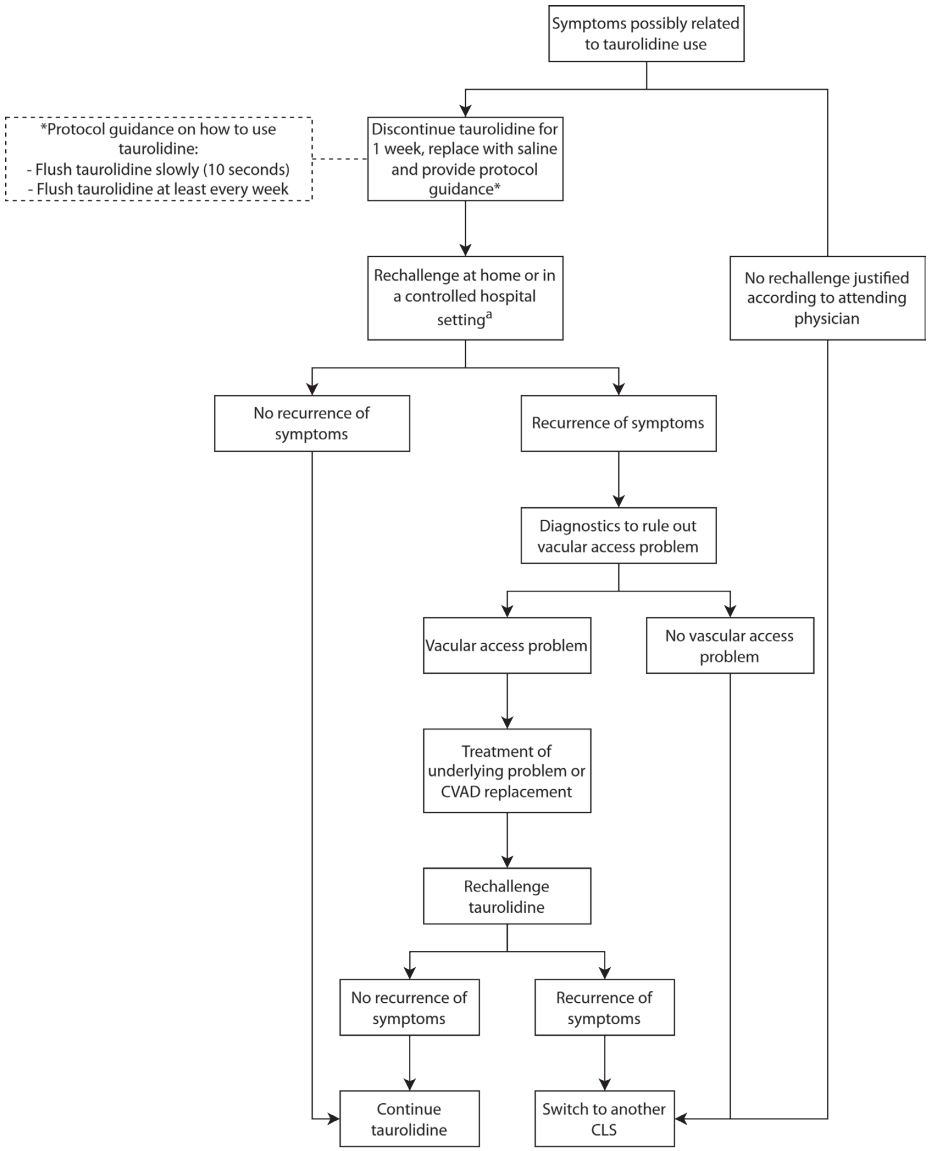

Figure 3. Algorithm on taurolidine-related adverse events in clinical practice.

[a] Left to the discretion of the treating physician.

Abbreviations: CLS, catheter lock solution.

Discussion

While taurolidine-containing formulations are becoming increasingly popular as CLS to prevent CRBSIs, data on safety and related AEs are lacking. This study describes the largest body of such data in a single centre HPN cohort available to date and provides an algorithm on how to address possibly taurolidine-related problems. Based on an observation period that spans sixteen years, we demonstrate that taurolidine is generally safe but that in case of lock-related symptoms, suspicion should be raised concerning CVAD dysfunction, especially occlusion or dislocation. More specifically, vascular access-related problems caused 51% of all AEs, 85% of which presented with pain, and almost all resolved by treating the underlying CVAD-related problem.

To date, nine smaller studies on adult HPN patients reported on taurolidine-related AEs. Five (total of 65 patients) found no AEs,[15,19-22] while four studies (450 patients) observed 45 patients (10%) with drug-related AEs,[12-14,23] mainly pain, taste changes, dyspnea and nausea, vomiting or anorexia. These symptoms corroborate the findings of our study and those reported in oncology and dialysis patients.[24,25]

CLSs may be used in two ways, i.e., as a lock solution that is flushed into the patient upon the next PN administration or as a lock that is withdrawn to avoid contact with the systemic circulation. Taurolidine is registered as a medical device, which would preclude intravenous use, however, we choose to flush this lock for several reasons. First, aspiration is not always possible due to obstruction of the catheter tip opening at the level of the vessel wall following suction. Second, since the catheter volume is about 1.5 ml, and assuming that around 5 ml is instilled as a lock, this implies that with each locking of the CVAD, approximately 3.5 ml is flushed into the systemic circulation anyway. Third, by omitting aspiration of taurolidine, we seek to prevent blood from entering the catheter since the latter promotes intraluminal biofilm formation.[26] While the half-life of taurolidine is short, with rapid breakdown into its natural downstream metabolites (i.e., taurine, carbon dioxide, and water[27-29]), concerning toxicity, it has to be realised that intravenous infusions have been reported of up to 20 g/day in the context of treatment of oncological conditions (1000 ml of 2% taurolidine), with an acceptable safety profile.[30-32] Nevertheless, the fact that we flush taurolidine into our patients may have influenced the number and severity of the AEs.

We categorised our cohort into two groups based on the cause of the AE, i.e., vascular access device-related problems (group A) or taurolidine-related problems (group B). In group A, 85% of the patients presented with taurolidine infusion-

related pain compared to 18% in group B (Figure 2). Infusion-related pain is most probably due to congestion and backflow of blood. Moreover, it is known that taurolidine, similar to propofol, reversibly activates the irritant receptor transient receptor potential ankyrin 1 (TRPA1) in calcitonin gene-related peptide (CGRP)-expressing, thus nociceptive, neurons.[33] Transient pain induction and irritation due to neuropeptide release are probably consequences of these properties. A key finding of the present study is that a major subset of patients with vascular access-related problems presents with taurolidine infusion-related pain, which in fact indicates device malfunctioning. Hence, we recommend performing diagnostic imaging, including fluoroscopy or ultrasonography, to rule out vascular problems if the taurolidine-related AE continues after rechallenge. In addition to the previous paragraph, flushing taurolidine into the patient reveals vascular access device-related problems, allowing us to detect and treat this problem earlier.

In the taurolidine-related AE group, a broad range of symptoms was observed. It is essential to realise that besides taurolidine, these CLSs also contain other components such as stabilising agents and sometimes anticoagulants (citrate, heparin, urokinase). It is considered unlikely that the reported AEs were caused by taurolidine itself because, as mentioned before, it is rapidly metabolised into bodily taurine, carbon dioxide, and water. Polyvinylpyrrolidone (povidone, PVP), a synthetic hydrophilic polymer used as a stabilator in taurolidine, could possibly cause AEs since allergy to povidone has been reported in increasing frequency.[34,35] In the taurolidine-related AE group, two patients had a vascular access complication according to the CTCAE classification while using taurolidine. Both patients had a subcutaneous port system and used suppletion of magnesium chloride, which we think may have clogged due to precipitation of magnesium and taurolidine. The median time to an AE in this group was 701 days, which shows that taurolidine-related AEs can occur even after prolonged taurolidine use. Eight patients in this group experienced symptoms when infusion of taurolidine was performed too fast or when a double dosage (10 ml 0.2 g taurolidine) was applied. Concerning the latter, this issue remains uncertain; in a study on 18 healthy men where 5 g of taurolidine were administered by intravenous infusion, all subjects noted discomfort at the infusion site, however, no serious AEs were observed.[27] These notions show that it is crucial to check for protocolar use of taurolidine in case patients present with a suspected taurolidine-related AE.

In our cohort, two patients experienced an AE when taurolidine had remained inside the CVAD for more than two weeks, whereas previously, they had no symptoms with daily flushing of their lock. This implies that alterations in the

composition of the CLS may play a role, for instance, due to precipitation after a prolonged instillation period.

An extensive protocol on how to use taurolidine as CLS was lacking in the literature. Based on our experience, we proposed a clinical algorithm to prevent the discontinuation of taurolidine as a tool to prevent CRBSIs (Figure 3). Since 51% of the possibly taurolidine-related AEs were caused by vascular device-related problems, and 85% of patients restarted taurolidine without any issues in this group, diagnostic imaging is a cornerstone in our algorithm. In addition, given the experienced problems after extra-protocol use of taurolidine and symptoms following the presence of taurolidine inside the CVAD for more than two weeks, we made recommendations for the use of taurolidine as CLS; it is important to flush taurolidine slowly (a minimum of 10 s), and we suggest that taurolidine may stay in the CVAD for a maximum of one week before flushing it.

This study has strengths and limitations. The retrospective nature is a limitation that precludes statements on causality. Underreporting of AEs may have played a role and retrospective assessment, especially grading, of AEs is suboptimal. On the other hand, we collected and analysed the most robust patient cohort from a single centre so far. Another strength is that we not only list these AEs but also point out a frequent underlying cause (catheter malfunction) that should urgently be addressed, and we provide an algorithm on taurolidine use for clinical practice (Figure 3).

Conclusion

In conclusion, our study shows that not only the use of taurolidine was found to be generally safe, but also it is essential to realise that many reported presumed taurolidine-related AEs signify catheter-related problems rather than an intolerance or allergy to taurolidine. After addressing these issues, based on its proven efficacy to prevent CRBSIs, a rechallenge should be strongly considered.

Financial disclosures
None

Conflict of interest
None

Conference presentation
Poster tour presentation ESPEN September 2022
Oral presentation WoCoVa October 2022

Supplementary data
Supplementary files are available at:
https://www.sciencedirect.com/science/article/pii/S0261561422002692

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Chapter 6

Oral antimicrobial agents in patients with short bowel syndrome: worth a try!

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Journal of Antimicrobial Chemotherapy, August 2023

Abstract

Background

The use of oral antimicrobial agents in patients with short bowel syndrome (SBS) is challenging due to the changes in gastrointestinal anatomy that may result in diminished absorption and altered drug bioavailability. Prospective studies evaluating bioavailability of antimicrobial agents after oral administration in SBS patients are lacking. The objective of this study was to determine the bioavailability of orally administered antimicrobial agents commonly used for treatment in SBS patients to guide clinical decision making when faced with infections.

Methods

We performed an explorative clinical study investigating the pharmacokinetics (PK) of clindamycin, ciprofloxacin, flucloxacillin and fluconazole in SBS patients with intestinal failure. Participants received a combination of two antimicrobial agents simultaneously. To determine the oral bioavailability, participants received a single oral and IV dose of both agents on two occasions, after which they underwent intensive PK sampling on six predefined time points up to 12 hours after administration. The primary outcome was the oral bioavailability of these antimicrobial agents. Secondary outcomes were intravenous PK characteristics following non-compartmental analysis.

Results

Eighteen SBS patients were included. The mean (SD) age was 59 (17) years and 61% of participants were female. The median observed (IQR) bioavailability of ciprofloxacin, clindamycin, flucloxacillin, and fluconazole were 36% (24–50), 93% (56–106), 50% (32–76), and 98% (61–107), respectively.

Conclusion

The bioavailability of selected antimicrobial agents in certain patients with SBS appeared to be better than expected, providing a feasible treatment option. Due to the large observed differences between patients, therapeutic drug monitoring should be part of the treatment to safeguard adequate exposure in all patients.

Introduction

Short bowel syndrome (SBS) is a rare condition usually caused by partial removal of the small intestine due to various underlying conditions and is defined as having a functional small bowel length shorter than 200 cm.[1] SBS leads to intestinal failure (IF) in case the remaining gut function is below the minimum to maintain or improve health without intravenous (IV) support of nutrients and/or fluids. IF patients require life-long home parenteral nutrition (HPN) support, which is administered via a central venous access device (CVAD), mostly a catheter. HPN is a complex, time-consuming treatment associated with life-threatening CVAD-related complications, mainly catheter-related bloodstream infections (CRBSIs). Nearly 70% of hospital admissions in HPN patients result from a CRBSI requiring prolonged IV antibiotic treatment.[2] In most clinical settings, once a patient is recovering, or when the infection is considered mild, it is advised to rapidly switch to oral antibiotics since this results in a reduced length of stay, lowers costs, and limits potential complications of IV access.[3] In addition, the 'IV-to-oral switch therapy' is a key quality-of-care indicator for evaluating appropriate antibiotic use.[4] However, this option of switching to oral therapy may not apply to SBS patients in whom changes in the anatomy of the gastrointestinal tract may result in significant loss of absorptive surfaces and presumed impaired drug uptake. Therefore, the American Gastroenterological Association advises prolonged IV therapy in SBS patients.[5] Besides bowel length, other factors influencing drug absorption and metabolism in patients with SBS comprise mucosal integrity, intestinal motility, site of drug absorption, drug formulation, presence of co-morbidities, pH of the gastric and intestinal lumen, and parenteral nutrition associated metabolic changes.[6–8] Following resection, the remaining intestinal tissue undergoes morphologic and functional changes to compensate for the lost function of the resected bowel over a prolonged period that may take months to years to complete. This process is known as intestinal adaptation and probably enhances drug absorption.[8] Despite the described changes in bowel function in SBS patients, successful treatment with orally administered antimicrobial agents has only been reported in selected, mostly paediatric cases.[9–13] The present investigation was fuelled by recent findings when we evaluated enteral absorption by measuring blood plasma concentrations of orally administered antibiotics in three SBS patients: two of these seemed to have more or less adequate enteral absorptive capacity.[14]

Unfortunately, well-designed studies evaluating bioavailability and other pharmacokinetic (PK) parameters of antimicrobial agents in SBS patients on HPN support are lacking.[7] Thus, based on both the available literature and the expected

process of intestinal adaptation following resection, we hypothesised that enteral absorption of antimicrobial agents may still be substantial in stable adult patients with SBS. To explore this, we included four frequently prescribed antimicrobial agents (clindamycin, ciprofloxacin, flucloxacillin and fluconazole) in our analysis.

Methods

Study design

This single-centre explorative study in SBS patients was conducted from July 2020 to January 2022 at Radboud university medical center (Radboudumc), Nijmegen, the Netherlands. The study was designed to determine the oral bioavailability of ciprofloxacin, clindamycin, flucloxacillin and fluconazole in patients with SBS. The trial (Dutch Trial Registry: NL7796) was approved by the review board of Radboudumc (reference number 2019-5561) and conducted according to the declaration of Helsinki. Written informed consent was obtained from all participants. The CONSORT guidelines were followed to report this study.[15]

Participants

Patients were eligible for inclusion if they were aged ≥18 years, received previous or current long-term HPN (>3 consecutive months) and in case they met the criteria for (functional) SBS.[16] The remaining bowel length was estimated from imaging studies or as reported in surgical records. Exclusion criteria were: signs of infection (e.g. chills, fever), active vomiting, worsening or new diarrhoea, a history of allergies or hypersensitivity to the study drugs, potential toxicity or interfering co-medication, making it impossible to include the patient in one of the two treatment groups, impaired renal function (creatinine clearance <30 ml/min/1.73 m^2), pregnancy and morbid obesity (BMI >35).

Study drugs and dosing

On two occasions, participants received a combination of two antimicrobial drugs administered successively as a single dose: orally and IV. Patients received either the combination of ciprofloxacin and clindamycin (CC group) or the combination of flucloxacillin and fluconazole (FF group). Group allocation (eight per group) depended on individual patient characteristics (e.g., known allergies, renal impairment, intolerances and interacting co-medication). When a patient could not receive the combination of CC or FF, another combination was considered.

Participants of the CC group received ciprofloxacin (750 mg) followed by clindamycin (600 mg) (tablet or suspension) on study day one and an IV dose of clindamycin 600 mg and ciprofloxacin 400 mg on study day two. FF-group participants received flucloxacillin (1000 mg) next to fluconazole (400 mg, tablet or suspension) on day one and an IV dose of flucloxacillin 1000 mg and fluconazole 400 mg on study day two. We gave the antimicrobial agents successively since administering two antimicrobial drugs together was not always compatible. A minimal washout period of 24 hours was chosen; for fluconazole, this was preferably at least 48 hours due to its long half-life.

Pharmacokinetic sampling

Blood samples were collected at baseline (before antimicrobial agent administration) and preferably at 1, 2, 4, 8 and 12 hours after administration of the study drugs to determine the blood concentration (µg/ml). The time of antimicrobial agent administration at the start (oral and IV) and end of infusion (IV only), and blood withdrawal procedures at various time points were documented.

A peripheral venous catheter for the purpose of drawing blood samples was placed. Blood samples of ciprofloxacin, clindamycin and flucloxacillin were collected in EDTA 3.0-ml tubes and blood samples for fluconazole analysis in Lithium Heparin 3.0-ml tubes. The blood samples were centrifuged at 1900g for 5 minutes and stored at −40°C until analysis.

Plasma concentrations of ciprofloxacin, clindamycin, fluconazole and flucloxacillin were assessed at the Department of Pharmacy of Radboudumc, Nijmegen, using a UPLC–MS (Waters Corporation, Milford, MA, USA) method that was fully validated according to EMA guidelines.[17] All analyses per group were analysed as a single batch on the same day to reduce measurement variation, i.e. all analyses were performed after the inclusion of all participants.

Biochemical analysis

The following blood parameters and plasma concentrations were analysed at Radboudumc clinical chemistry laboratory on the day of admission: albumin, glucose, haemoglobin, white blood cell count and differentiation, alanine aminotransaminase, total protein, creatinine and citrulline. Citrulline is a non-protein amino acid produced by the intestine and is a marker of the absorptive function of the small bowel.[18,19]

Data collection

The following data were collected: patient characteristics (sex, age, weight, height, underlying disease leading to SBS, estimated length of remaining small bowel after surgical intervention, sites of resection, year of last bowel resection and presence of gastroparesis), HPN characteristics (type of infusion and the number of infusions per week), stoma output, chronic kidney disease epidemiology collaboration estimated glomerular filtration rate (CKD-EPI eGFR) and any allergies or (serious) adverse events.

Pharmacokinetic analysis

PK parameters for ciprofloxacin, clindamycin, flucloxacillin and fluconazole were calculated by non-compartmental methods using WinNonLin software package (v.6.4; Pharsight, Mountain View, CA, USA) and the log-linear trapezoidal rule. On the basis of the individual plasma concentration–time data the following PK parameters were assessed: the AUC from zero to tau ($AUC_{0\text{-}tau}$ dose interval, 12 hours for ciprofloxacin, 8 hours for clindamycin, 6 hours for flucloxacillin and 24 hours for fluconazole), the maximum plasma concentration of the drug (C_{max}; in mg per litre), the time to reach C_{max} (T_{max}; in hours) and the average concentration (C_{avg}; in mg per litre). Bioavailability was determined by the ratio of AUC after oral and IV administration per patient, after correction for differences in dose ($AUC_{0\text{-}tau\ PO}/_{AUC0\text{-}tau\ IV}$). In the case of sampling anomalies (e.g., collecting a PK sample from an IV line used to deliver the drug dose), samples were excluded from the analysis. A minimum of three samples per patient in the terminal elimination phase was deemed acceptable to estimate the AUC correctly.

Safety

Vital signs (temperature, pulse saturation and blood pressure) were measured before and during the administration of the antimicrobial agents. (Serious) adverse events were recorded along with the degree of severity, timing, and onset.

Statistical analysis

Due to the explorative nature of this study and because the literature on enteral drug absorption in SBS is lacking, we have refrained from performing a formal power calculation. Baseline characteristics were summarised using descriptive statistical methods. Continuous variables were presented as means with standard deviations (SD) or, if not normally distributed, as medians and interquartile ranges (IQRs). Possible correlations between bioavailability and variables of interest were analysed in an exploratory analysis by making scatter plots of bioavailability versus variable. Variables analysed were remnant small bowel length, presence of

gastropareses, number of infusions per week, citrulline, presence of stoma and kidney function, and ingestion of oral antimicrobial agent in suspension or tablet, on the basis of a recent systematic review.[7] A Spearman's correlation test was performed if a monotonic relation between bioavailability and variable was found. All data analyses were performed using the software package GraphPad Prism, v.9, for Windows (GraphPad Software, San Diego, CA, USA) or IBM SPSS Statistics for Windows, v.27.0 (IBM Corp. Armonk, NY, USA). Statistical significance was defined as a p-value of <0.05 (two-tailed).

Results

Patient demographics and baseline characteristics

Between July 2020 and January 2022, 237 patients were treated in Radboudumc for the management of long-term HPN. Of these, 103 (43%) were diagnosed with SBS, of whom 79 patients were assessed as eligible by their treating physician. In total, 18 SBS patients were included in the study. A flowchart of the enrolment sequence is shown in Figure S1. The mean (SD) age of enrolled patients was 59 (17) years, and 61% of participants were female. Baseline characteristics of the participants are shown in Table 1 and Table S1. Both the CC and FF groups included eight participants. Due to allergies, group allocation was not possible in two participants; therefore, these individuals received a combination of fluconazole and clindamycin. Participant nine had a creatinine clearance >30 ml/min at screening; however, at the start of the study, the CKD-EPI eGFR had decreased to 28 ml/min.

Pharmacokinetics

A total of 432 samples were planned for calculating the PK, however, six were missing due to clerical errors. Thus, a total of 426 samples were used to calculate PK parameters. The median PK parameters of ciprofloxacin, clindamycin, flucloxacillin and fluconazole are described in Table 2. Boxplots of ciprofloxacin, clindamycin, flucloxacillin and fluconazole $AUC_{0\text{-}tau}$ are presented in Figure 1. A list of all PK parameters per participant can be found in Table S2. Fifteen samples were excluded after analysis due to sampling anomalies.

Correlation analysis

We analysed variables that might influence antimicrobial agent penetration in an exploratory analysis. We found a nonmonotonic association between bioavailability and all variables of interest. Therefore, we did not perform Spearman's correlation test. See Figure S2 for the scatter plots.

Safety

All antimicrobial agents were well tolerated, and none of the participants experienced adverse effects related to the drug administration. During the study, one female participant developed severe inguinal pain. The diagnosis was a psoas hematoma following a fall a few days before while having a dysregulated (high) anticoagulant (warfarin) level. This serious adverse event was classified as non-study related.

Table 1. Baseline characteristics of the participants included in the study.

Participant	Group	Age, years	Sex	Weight, kg	Height, m	CKD-EPI eGFR, ml/ min/ 1.73m²	Cause of intestinal failure	Remnant small bowel length, m	Stoma	Year since last bowel resection	Gastroparesis
1	CC	25	F	62	1.70	90	Necrotizing enterocolitis	1.7	No	2015	No
2	CC	48	F	87	1.65	70	Adhesions	>2	Ileostomy	2016	Yes
3	CF	52	F	46	1.73	81	Volvulus	>2	Ileostomy	2004	Yes
4	CC	41	M	65	1.72	90	Necrotizing enterocolitis	1	No	1982	No
5	CC	74	M	81	1.72	78	Adhesions	1.2	Ileostomy	2017	No
6	CC	76	M	87	1.72	34	Crohn's disease	>2	Ileostomy	2015	No
7	CC	76	M	74	1.62	59	Adhesions	2	Ileostomy	2012	No
8	FF	68	F	59	1.65	89	Crohn's disease	2	Ileostomy	2001	No
9	FF	65	F	59	1.78	28	Other	>2	Colostomy	1996	No
10	FF	61	F	83	1.68	90	Mesenteric ischemia	1.8	Jejunostomy	2020	No
11	CC	59	F	75	1.68	46	Crohn's disease	>2	Ileostomy	1992	No
12	FF	40	F	62	1.63	90	Cancer	0.05	No	2012	Yes
13	FF	69	M	84	1.93	67	Other	>2	No	NA	No
14	CF	31	F	55	1.66	90	Crohn's disease	1.4	Ileostomy	2010	No
15	FF	80	F	51	1.71	55	Cancer	1.4	Ileostomy	2016	No
16	FF	49	F	73	1.80	90	Ulcerative colitis	>2	Ileostomy	2010	Yes
17	FF	73	M	84	1.88	75	Mesenteric ischemia	0.07	No	2014	No
18	CC	73	M	84	1.81	71	Crohn's disease	1–1.5	Jejunostomy	2009	No

Abbreviations: CC, ciprofloxacin and clindamycin; CF, ciprofloxacin and fluconazole; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; F, female; FF, flucloxacillin and fluconazole; M, male; NA, not applicable.

Table 2. Median (IQR) pharmacokinetic parameters of ciprofloxacin, clindamycin, flucloxacillin and fluconazole.

	Ciprofloxacin† *n* = 8		Clindamycin *n* = 10		Flucloxacillin *n* = 8		Fluconazole *n* = 10	
Parameter	**IV**	**PO**	**IV**	**PO**	**IV**	**PO**	**IV**	**PO**
$AUC_{0\text{-}tau}$, mg x h/L	10.7 (10–13)	4.1 (2.4–5.2)	31.3 (26–41)	31.5 (14–41)	86.8 (69–221)	56.4 (25–75)	216 (151–244)	170 (142–221)
F, %	100	35.8 (24–50)	100	92.6 (56–106)	100	49.9 (32–76)	100	98.4 (61–107)
C_{max}, mg/L	2.1 (1.8–2.6)	0.5 (0.3–1.0)	7.0 (5.9–10)	5.3 (3.8–8.2)	40.1 (35–91)	17.5 (6.7–21)	12.5 (10–16)	9.4 (7.9–12)
C_{avg}, mg/L	0.9 (0.8–1.1)	0.6 (0.4–0.8)	3.9 (3.3–5.1)	3.9 (1.8–5.2)	14.5 (11.5–36.8)	9.4 (4.2–12.5)	9.0 (6.3–10.2)	6.7 (5.9–9.2)

† Ciprofloxacin oral dose is normalised to 400 mg to demonstrate oral bioavailability.

Abbreviations: $AUC_{0\text{-}tau}$, AUC from zero to tau (dose interval, 12 hours for ciprofloxacin, 8 hours for clindamycin, 6 hours for flucloxacillin and 24 hours for fluconazole); C_{avg}, average concentration; C_{max}, peak plasma concentration; F, bioavailability; IV, intravenous; PO, per os.

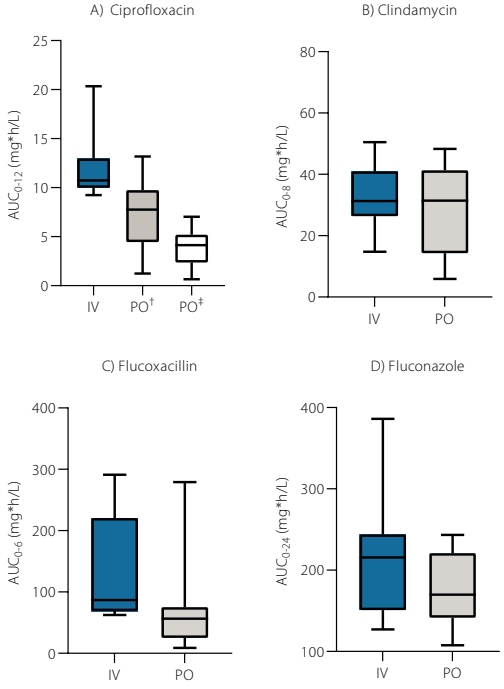

Figure 1. Boxplot of ciprofloxacin, clindamycin, flucloxacillin and fluconazole $AUC_{0\text{-}tau}$.

The bottom and top edges of the boxplots represent the 25th and 75th percentiles (the difference is IQR), the horizontal line is the median and the whiskers indicate the 5th and 95th percentiles.

† 750 mg, dose investigated; ‡ 400 mg, dose normalised to demonstrate oral bioavailability.

Abbreviations: $AUC_{0\text{-}tau}$, AUC from zero to tau (dose interval, 12 hours for ciprofloxacin, 8 hours for clindamycin, 6 hours for flucloxacillin and 24 hours for fluconazole).

Discussion

Although SBS patients suffering from IF frequently require treatment for (catheter-related) infections, only anecdotal information is available on the absorption of oral antimicrobial agents in this group. Since such data are key, and even more so in this heterogeneous group of patients, we report here on the PK of frequently used antimicrobial agents (ciprofloxacin, clindamycin, flucloxacillin and fluconazole) that were administered as a single oral and IV dose. Our findings indicate that enteral absorption of oral antimicrobial agents in patients with SBS may be better than expected and that individual profiling of enteral absorption may safeguard treatment with oral antimicrobial agents for less severe infections. Unfortunately, but not unexpectedly, it proved not possible to predict absorption using other easier-to-obtain patient characteristics, such as remnant (small) bowel length.

When looking at specific antibiotics in more detail, ciprofloxacin is commonly used to treat several bacterial infections, given its broad spectrum of action against especially Gram-negative bacteria. It is often administered orally in a dosage of 500–750 mg twice daily and is well absorbed from the gastrointestinal (GI) tract in healthy volunteers with a bioavailability of approximately 70%.[20,21] In comparison, we found a bioavailability of 36% (IQR 24–50) after correction for differences in dose (Table 2). To compensate for this loss in exposure, we advise prescribing ciprofloxacin in a higher dosage (750 mg BD) in SBS patients with normal kidney function.

Clindamycin is an antibiotic with a broad spectrum of activity against Staphylococcus spp., Streptococcus spp. and anaerobic bacteria. It is usually dosed at 600 mg three times daily. In the general population, it is rapidly and almost completely (bioavailability 90%) absorbed when administered orally.[22,23] The median bioavailability of 93% (IQR 56–106) that we report is comparable to that of healthy individuals (Table 2). Hence, oral clindamycin seems a reliable oral antibiotic option in most SBS patients.

Flucloxacillin is indicated primarily for treating various skin and soft tissue infections caused by Gram-positive bacteria, like Staphylococcus aureus. It is dosed three to four times daily and is absorbed for approximately 55% after oral administration on an empty stomach.[24,25] Flucloxacillin exhibits substantial interindividual variability in PK.[26] The median bioavailability of 50% (IQR 32–76) that we found corresponds with that in healthy individuals (Table 2).[24,25] However, also in line with the healthy population, a broad interindividual range between patients was observed; thus,

therapeutic drug monitoring (TDM) is advised as part of future oral treatment in SBS patients with mild infections and oral step down therapy for severe infections to safeguard adequate exposure at the individual level.

Fluconazole is an antifungal agent active against most Candida species and is typically dosed once daily due to its long plasma half-life. The drug is rapidly and almost completely absorbed from the GI tract; oral bioavailability exceeds 90% in healthy adults.[27,28] This matches our median bioavailability of 98 (IQR 61–107). Thus, fluconazole can be safely administered in most SBS patients.

It is unclear why ciprofloxacin displayed a diminished absorption and the other antimicrobial agents displayed bioavailability compared to the bioavailability described in the literature in the general population.

We analysed several variables that may influence antimicrobial agent absorption, including remnant small bowel length, presence of gastropareses, number of parenteral infusions per week, plasma citrulline concentration as a measure for functional enterocyte mass, presence of ostomies, ingestion of oral antimicrobial agent in suspension or tablet and kidney function. We could not demonstrate any clear correlation between oral bioavailability and these mentioned variables (Figure S1). This lacking correlation results from our modest sample size in combination with confounding factors and the heterogeneity of the SBS population in general.

This study comes with strengths and limitations. Due to its explorative nature, we only have a modest sample size. However, it should be realised here that our sample size matches that of studies in renal failure and liver failure patients.[29–31]

Also, the perfect timing of sample collection was hampered by the fact that infusion times varied per antimicrobial agent while collection time points were fixed for all drugs at baseline and 1, 2, 4, 8 and 12 hours after administration. We decided to take a sample 1 hour after the first antimicrobial agent infusion period, which may have been too late in some instances to pick up maximum plasma concentrations. Our primary outcome was not affected by this sampling design.

A few individual findings related to patient characteristics are worth mentioning. For instance, in one female participant, the oral bioavailability of ciprofloxacin was only 3%, which was not unexpected given that she underwent a major duodenal resection, which is the main absorption site for ciprofloxacin.[32] Even though we could not demonstrate that certain 'logical' patient characteristics were predictive,

knowledge regarding anatomy can be helpful in some cases to decide whether oral antimicrobial agents are safe or whether TDM is mandatory.

For two participants with ultra-SBS (remaining small bowel length of 5 and 7 cm), the bioavailability of flucloxacillin (43% and 14%, respectively) and fluconazole (65% and 49%, respectively) was, as expected, below that of healthy individuals (flucloxacillin: 55% and fluconazole: 90%).[7,33]

Concerning the strength of our study, this is the first prospective investigation evaluating (inter) individual bioavailability after oral administration of antimicrobial agents in SBS patients at a high inclusion rate since only a few patients were eligible for inclusion, and most of these were willing to participate. The latter emphasises that these patients consider this an important treatment issue.

Conclusion

In conclusion, our study shows that oral clindamycin and fluconazole are likely possible treatment options in many SBS patients. Ciprofloxacin should probably be used at a higher dose. Due to substantial interindividual differences, TDM is advised as part of the treatment with flucloxacillin or in patients with duodenal resection and/or ultra-short remaining bowel. Future clinical studies should explore the feasibility of oral antimicrobial agent therapy in SBS patients with mild infections, with the ultimate goal of providing an effective, safe, cost-saving and minimally invasive treatment.

Acknowledgements

We thank the patients who participated and the nursing staff who cared for them.

Financial disclosures

This work was supported by the Dutch Governmental Organization for Health Research and Development (ZonMw; reference number 848015009). The funder had no involvement in the study design, collection, analysis, and interpretation of data, writing of the report, and the decision to submit the article for publication.

Conflict of interest

None

Conference presentation

Oral presentation ECCMID April 2023

Supplementary data

Supplementary files are available at:
https://academic.oup.com/jac/article/78/8/2008/7214002

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Chapter 7

Superior vena cava syndrome in chronic intestinal failure patients: When the going gets tough

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Clinical Nutrition, January 2024

Abstract

Background

Catheter-related venous thrombosis is a severe complication of home parenteral nutrition (HPN) with potentially devastating consequences such as superior vena cava syndrome (SVCS). Early recognition and awareness of factors leading to its development are of paramount importance. However, studies are lacking in HPN patients focusing on this topic. In this study, we aimed to determine the incidence of SVCS in HPN patients and describe SVCS-related outcomes.

Methods

This retrospective cohort study comprised all adult HPN patients who developed SVCS between 2000 and 2022 at our national HPN referral centre. The primary outcome was the incidence of SVCS. Secondary outcomes include SVCS-related symptoms, tip location of central venous access device (CVAD) post-insertion and at time of SVCS, diagnostics and treatment.

Results

SVCS was diagnosed in 38 of 616 patients (6%), with an annual cumulative incidence rate ranging between 0 and 4.2%. Most common presenting symptoms were facial oedema (82%) and arm oedema (50%). Post-insertion, 17% (6/36) of patients had a correct position of the CVAD tip and 11% (4/36) during SVCS diagnosis. Computed tomography was the most used diagnostic imaging technique (66%). Sixty-three percent of patients started, 11% switched, and 21% continued anticoagulant treatment.

Conclusion

The incidence of SVCS is relatively high in our vulnerable HPN population. It is key to recognise whenever such patients present with vascular obstruction-related symptoms and treat them in an early stage by a multidisciplinary team.

Introduction

Patients with chronic intestinal failure (CIF) lifelong depend on home parenteral nutrition (HPN), which requires the presence of a permanent central venous access device (CVAD).[1] Current guidelines recommend the tip of such CVAD to be placed as close as possible to the junction of the superior vena cava (SVC) and the right atrium to prevent catheter-related venous thrombosis (CRVT).[2] Obstruction at the level of the SVC may lead to superior vena cava syndrome (SVCS), which comprises a variety of symptoms, depending on the localisation of the thrombus, severity, and speed of onset of obstruction.[3,4] Most common symptoms are facial and neck swelling and dilated neck and chest veins.[4] However, up to 10% of patients are asymptomatic.[5] A previous study showed SVCS prevalence of 5.1% in HPN patients.[6] Although malignancies account for 70% of SVCS, the overall incidence of device-related SVCS is around 30% and increasing, mainly because of the rising use of CVADs.[4,7]

In general, the development of thrombosis is often related to Virchow's triad (hypercoagulability, stasis of blood flow, and endothelial injury).[8] In the case of SVCS, this mostly concerns endothelial damage due to multiple catheter placement attempts, incorrect positioning, and multiple CVADs in the past.[9,10]

Loss of access options to insert a CVAD, as is frequently seen with SVCS, poses a threat to both the patient and the continuation of HPN as a technique. Nonetheless, following SVCS, the remaining options for a CVAD are limited to less favourable sites such as the femoral vein, liver vein, or inferior vena cava. Construction of an arteriovenous fistula as a rescue to obtain venous access is often not an option because of the increased venous return in the acute situation of SVCS. In some cases, even direct placement into the right atrium through thoracotomy has to be considered.[9,11] Moreover, SVCS may have additional serious risks, for instance, a thrombotic infection or pulmonary embolism, the latter being a potentially life-threatening complication.[7,12]

The rationale behind the present study is that we were under the impression that SVCS occurred in increasing numbers during the COVID-19 pandemic, with its associated thrombotic risk.[13] Also, due to the subtle onset of symptoms, the diagnosis of SVCS, in hindsight, is often missed in its early stage, often with devastating consequences. In the present study, we therefore seek to address this apparent lack of awareness by reporting our experience, and we provide suggestions on how to deal with SVCS in these vulnerable patients.

Methods

Study design and patient selection

This retrospective cohort study was conducted at Radboud university medical center (Radboudumc), a tertiary referral centre for CIF patients. Patients were selected from the Nijmegen intestinal failure (IF) Registry, a web-based Castor EDC database.[14] Patients aged ≥18 years were eligible for inclusion if they met the criteria for CIF.[1]

Study outcomes, definitions, and data collection

The primary outcome was the incidence of SVCS. Secondary outcomes included SVCS-related symptoms, time to SVCS, tip location of CVAD post-insertion and at the time of SVCS, diagnostics, treatment, consequences, and follow-up.

The following variables were collected from the Nijmegen IF registry: patient characteristics (sex, age, underlying disease, and co-morbidities), medication (anticoagulants and oral contraceptive pill), CVAD characteristics (type, number of lumen, site, and side of vein insertion, date of insertion, and removal), HPN characteristics (duration of HPN), small bowel transplantation (no transplantation, referral to a transplantation centre, or small bowel transplantation) and follow-up at 1, 5, and more than 10 years after SVCS diagnosis (including imaging and symptoms related to SVCS). For this study, we assessed all patients' medical records, and all clinical data related to SVCS were collected. Two investigators (JK and VG) independently assessed SVCS cases and discussed them with a third investigator (GW). The tip location at post-insertion radiography and during SVCS diagnosis, luminal occlusion and collateral formation were revised for every patient and discussed with an interventional radiologist (SJ).

SVCS was defined as a (partly) obstruction of the SVC on diagnostic imaging with or without associated symptoms. We included the percentage of luminal occlusion and collateral formation to establish the degree of SVC occlusion. The percentage of luminal occlusion was divided into categories: non-significant occlusion (<70%), significant occlusion (70-99%), and total occlusion (100%).

For some patients, diagnostic imaging was not available for revision because imaging was dated, conducted in an external hospital, or insufficient to provide the needed variables. Incidence rates were calculated in two ways: first, by dividing the number of new SVCS cases by the number of CIF patients at risk, and second by the number of new SVCS cases per 1000 catheter days.

Persistent symptoms were defined as SVCS symptoms that were present continuously, intermittent, or progressive after SVCS diagnosis and also included symptoms that were classified as volume load-related to the degree that TPN volume had to be decreased or infusion time extended. Decreased options for CVAD placement implied that a CVAD had to be inserted at a less favourable site (femoral vein, inferior vena cava or direct placement in the right atrium) after SVCS diagnosis.

A correct placement of the CVAD tip was considered at positions two, three, or four (Figure 2).[2,15]

Statistical methods

Baseline characteristics were summarised using descriptive statistics. Continuous variables were presented as mean with standard deviation (SD) or median and interquartile range (IQR) if not normally distributed. Missing data were excluded from analyses. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp. Armonk, NY, USA).

Ethical approval

This study was approved by the research ethics committee of Radboudumc in Nijmegen, the Netherlands (reference number 2020-6119) and was reported according to the STROBE guidelines.[16]

Results

Demographics

Between 2000 and 2022, a total of 616 patients were under treatment for 1.16 million catheter days in Radboudumc, of whom 38 (6%) individual patients were diagnosed with SVCS. Most patients were female (74%), and the mean age at diagnosis was 54 years. Baseline characteristics are presented in Table 1. In total, 25 patients had a history of venous thrombosis, of which 18 CRVTs, 4 pulmonary embolisms, 3 deep venous thromboses, and 10 other thromboses. Some patients had multiple thromboses.

Superior vena cava syndrome incidence

Figure 1 shows the SVCS cumulative annual incidence rate ranging between 0 and 4.2% over the years 2000-2022, with an outlier of eight cases in 2021. Since 2020, three of eleven (27%) patients were diagnosed with COVID-19 within three months

prior to SVCS diagnosis. The incidence of SVCS was 0.03 per 1000 catheter days. Patients had a mean of four HPN catheters before SVCS was diagnosed. The median time between CVAD placement and diagnosis was five months (IQR 2–17) (Table 2).

Superior vena cava syndrome symptoms

Thirty-seven out of 38 (97%) patients presented with symptoms at the time of their SVCS diagnosis. Patients presented with 31 facial oedema (82%), 19 arm oedema (50%), 10 headache (26%), 8 dyspnea (21%), 8 distended chest veins (21%), 5 facial plethora (13%), 5 increased central venous pressure (13%), 4 distended neck veins (11%), 3 occlusion alarm of feeding pump (8%), 3 visual symptoms (8%), 3 facial/neck pain (8%), 2 dizziness (5%), and 5 other symptoms (13%). Other symptoms included 1 snoring, 1 stridor, 1 syncope, 1 hoarseness, and 1 central cyanosis. The median symptomatic period until diagnosis was 14 days (IQR 3–28), with five outliers of 49, 106, 122, 130, and 137 days.

CVAD tip during insertion and diagnosis

Seventeen percent (6/36) of patients who presented with SVCS had a correct position of the CVAD's tip on the post-insertion radiograph, and 11% (4/36) of patients had a correct position of the CVAD's tip on SVCS diagnosis imaging (Figure 2).

Superior vena cava syndrome diagnosis and treatment

Table 2 presents all SVCS-related outcomes. A diagnosis was made in 66% using a computed tomography (CT) scan. At diagnosis, 30 patients had a significant occlusion, of which six had a total occlusion, and one had a non-significant occlusion. Diagnostic imaging was missing in seven patients. In addition, collateral vein formation was identified in 29 patients, while one did not have signs of collateral vein formation. In eight patients, diagnostic imaging was not available.

Subsequently, 63% of the patients started with anticoagulants; coumarin derivatives in 19 patients (83%), and four patients with low molecular weight heparin (LMWH, 17%). Four patients switched anticoagulant therapy, all from coumarin derivatives to LMWH. Eight patients continued their current anticoagulant (four patients (50%) coumarin derivatives and four patients their LMWH (50%)).

In total, 13 patients (34%) needed endovascular therapy after diagnosis. The most frequently used procedures were percutaneous transluminal angioplasty (PTA, 16 times) and stenting (11 times). The median time till endovascular therapy was 15 weeks (range 0–58 weeks). Endovascular treatment was performed repeatedly in six patients due to recurrent or persistent symptoms.

Superior vena cava syndrome consequences and follow-up

In total, 24 (63%) CVADs were removed, 19 (79%) due to SVCS-related symptoms or consequences, and 5 (21%) because of another reason (3 infections, 1 mechanical damage, and 1 stop HPN). Most CVADs were removed within 30 days after diagnosis, but two CVADs after a longer period (115 and 189 days) due to persisting symptoms.

Table S1 shows the long-term follow-up and illustrates patients reporting symptoms and/or whether imaging was available during follow-up. At 1 year of follow-up, 11 patients had a significant occlusion on imaging, of whom four had a completely occluded SVC, and two had a non-significant occlusion. Subsequently, at 5 years of follow-up, three patients had a significant occlusion, of whom two had a completely occluded SVC, and two had a non-significant occlusion. At 10 years of follow-up, all five patients had a significant occlusion, of whom four had a completely occluded SVC.

Of all patients, seven were referred to a transplantation centre, of which only one eventually underwent a small bowel transplantation. The other six patients are still on the transplantation list, did not want a transplantation, or were deceased.

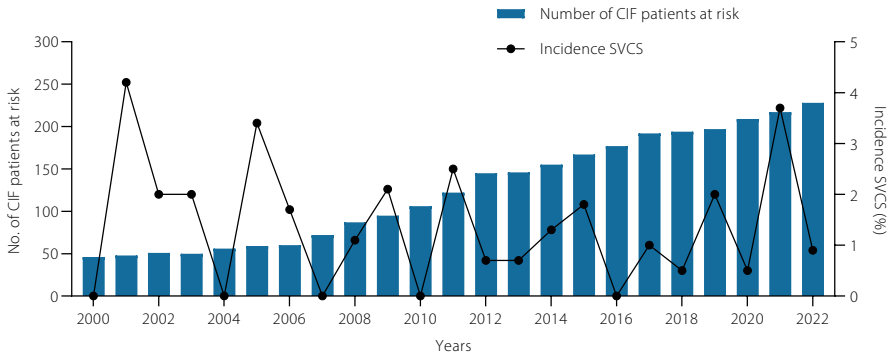
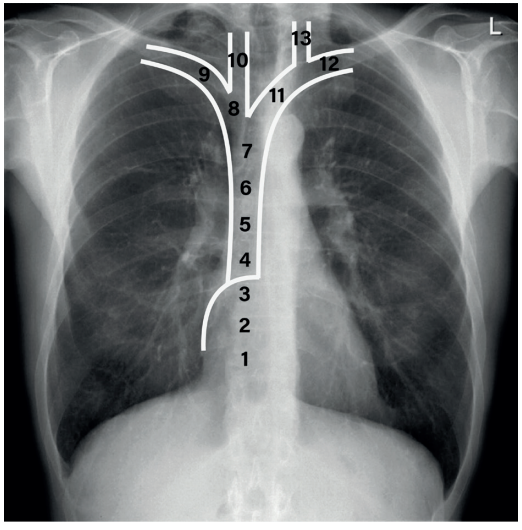
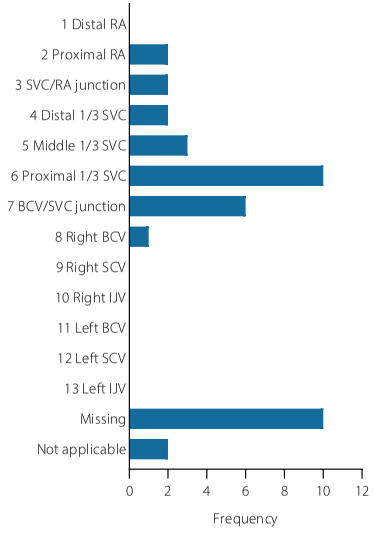


Figure 1. Cumulative annual incidence rate of superior vena cava syndrome over the years 2000-2022. Abbreviations: CIF, chronic intestinal failure; No, number; SVCS, superior vena cava syndrome.

A) A chest radiograph with an outline of the venous system superimposed



B) CVAD tip position on post-insertion radiograph



C) CVAD tip position on SVCS diagnosis imaging

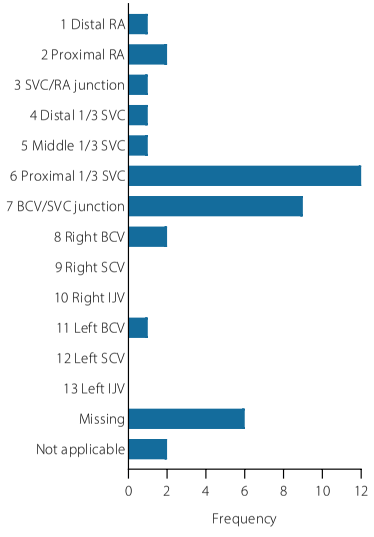


Figure 2. A chest radiograph with an outline of the venous system superimposed (A) and CVAD tip position on post-insertion radiograph (B) and on SVCS diagnosis imaging (C). Line tip position given as 1 distal RA, 2 proximal RA, 3 SVC/RA junction, 4 distal 1/3 SVC, 5 middle 1/3 SVC, 6 proximal 1/3 SVC, 7 brachiocephalic vein (BCV)/SVC junction, 8 right BCV, 9 right subclavian vein (SCV), 10 right internal jugular vein (IJV), 11 left BCV, 12 left SCV, 13 left IJV.[17]

Not applicable: patients with arteriovenous fistula or CVAD located in the femoral vein. Missing: no diagnostic imaging available.

Abbreviations: BCV, brachiocephalic vein; CVAD, central venous access device; IJV, right internal jugular vein; RA, right atrium; SCV, subclavian vein; SVC, superior vena cava.

Table 1. Patient characteristics.

Patient characteristics		***n* = 38**
Female, n (%)		28 (74)
Age at start HPN, mean (SD), years		49 (17)
Age at SVCS diagnosis, mean (SD), years		54 (16)
Cause of intestinal failure, n (%)		
	Short bowel syndrome	17 (45)
	Gastrointestinal motility disorder	14 (37)
	Extensive small bowel mucosal disease	2 (5)
	Intestinal fistula	1 (3)
	Mechanical obstruction	1 (3)
	Other	3 (8)
Number of previous CVADs, mean (SD)		4 (4)
Medical history, n (%)		
	Inflammatory bowel disease	11 (29)
	Active malignancy	2 (5)
	History of venous thrombosis	25 (66)
	Inherited hypercoagulable state	3 (8)
Medication use prior to SVCS, n (%)		
	Oral contraceptive pill	4 (11)
	Anticoagulant use	14 (37)
CVAD characteristics		***n* = 38**
Type of CVAD, n (%)		
	Tunneled catheter	29 (76)
	Subcutaneous port system	6 (16)
	Non-tunnelled	1 (3)
	Arteriovenous fistula	1 (3)
	Unknown	1 (3)
CVAD lumen, n (%)		
	Single lumen	21 (55)
	Multi-lumen	3 (8)
	Unknown	7 (18)
	Not applicable	7 (21)
Side of vein insertion, n (%)		
	Left	21 (55)
	Right	17 (45)

Table 1. Continued

Vein used for insertion, n (%)		
	Jugular	14 (37)
	Subclavian	20 (53)
	Femoral	1 (3)
	Arteriovenous fistula	1 (3)
	Basilica	1 (3)
	Unknown	1 (3)

Abbreviations: CVAD, central venous access device; SD, standard deviation; SVCS, superior vena cava syndrome.

Table 2. Superior vena cava syndrome-related outcomes

Superior vena cava-related outcomes		**n = 38**
Time between CVAD placement and diagnosis, median (IQR), months		5 (2–17)
Time between start HPN and diagnosis, median (IQR), months		39 (13–80)
Difficult CVAD placement, n (%)		5 (13)
Imaging technique used for diagnosis, n (%)		
	Computed tomography scan	25 (66)
	Fluoroscopy	6 (16)
	Phlebography	5 (13)
	Ultrasound	1 (3)
	Unknown	1 (3)
Treatment with anticoagulants, n (%)		
	New	24 (63)
	Switch	4 (11)
	Continue	8 (21)
	None	1 (3)
	Unknown	1 (3)
Endovascular therapy, n		
	PTA	16 in 8 patients
	Stent	11 in 9 patients
	Recanalization	5 in 4 patients
	Snare	1 in 1 patient
	Thrombolysis	1 in 1 patient
	Thrombectomy	1 in 1 patient
Consequences/complications of SVCS, n (%)		
	CVAD removal	24 (63)
	Decreased options for CVAD placement	25 (66)
	Persisting symptoms	23 (61)

Table 2. Continued

Stent thrombosis	5 (13)
Bleeding while on anticoagulant use	4 (11)
Vena cava inferior syndrome	4 (11)
Septic lung embolism	1 (3)
Infected thrombosis	9 (24)

Abbreviations: CVAD, central venous access device; IQR, interquartile range; PTA, percutaneous transluminal angioplasty; SD, standard deviation; SVCS, superior vena cava syndrome.

Discussion

Since HPN patients lifelong depend on their vascular access, which they often see as their lifeline, SVCS is a major threat in this regard. Because data on catheter-related SVCS are mostly anecdotal, we aimed to provide more robust data on the incidence and management of catheter-related SVCS in our large HPN referral centre cohort. As shown in Figure 1, we identified a cumulative annual SVCS incidence ranging from 0 to 4.2% per year. Although it has been suggested that the overall SVCS incidence seems to increase in this population in recent years, this was not corroborated by our findings.[7]

Overall, our data support previous findings in HPN settings. Buchman et al. diagnosed 22 patients who developed either inferior vena cava syndrome or SVCS (4.2% of 527 HPN patients) with an incidence of 0.02 per catheter year.[18] Barco et al. reported SVCS in 12 patients out of 236 receiving HPN (5.1%), while Beers et al. diagnosed 15 cases in 107 HPN patients (14%; incidence 0.04 per patient-year).[6,9] Interestingly, in 2021 we observed an outlier of eight SVCS cases (Figure 1), of whom three were diagnosed with COVID-19 within three months prior to SVCS diagnosis. Obviously, the global pandemic may play a role here, given the known increased thrombosis risk of this infection as well as the associated immobility.[19,20]

Most SVCS patients were symptomatic (97%), in contrast to the findings of Beers et al., who reported that 40% of patients were asymptomatic.[9] Most reported symptoms in our patients, in line with the literature, were facial (82%) and arm oedema (50%).[4,21,22] The median (IQR) symptomatic period until diagnosis was quite substantial at 14 days (3–28), with five outliers, reasons for which were other possible mimicking diagnoses considered (e.g. allergies, peripheral thrombosis, frontal sinusitis, and Cushing's syndrome), nontypical presentation, or lacking signs of (peripheral) thrombosis on ultrasound imaging. In the latter group, no other diagnostic modality, such as computed tomography (CT), had been used.

In addition, it is important to mention that one patient had a non-significant occlusion at imaging because all vessels draining the SVC were occluded, causing SVCS. The above findings emphasise that whenever a patient with a CVAD presents with possibly vascular obstruction-related symptoms, SVCS should always be ruled out using accurate radiological techniques, such as a CT scan.

In general, to decrease the CRVT risk, vessel wall damage should be minimised by using ultrasound-guided catheter insertion, with the tip of the CVAD placed at the atrio-caval junction.[2] The latter should be verified with diagnostic imaging (e.g., X-rays) during placement of the CVAD. We previously found that a right-sided approach is preferable over a left-sided placement to reduce the risk for CRVT.[23,24] SVCS in HPN patients is considered to be triggered by vascular damage and/or luminal obstruction with diminished blood flow due to the presence of a CVAD. An incorrect position with the tip too far away from the atrio-caval junction may increase the CRVT risk because the suboptimal alignment of the CVAD in the vessel causes the tip to damage the vessel wall and alter blood flow in the SVC.[9,25] In our cohort, in hindsight, only 17% of CVAD tips met the criteria for optimal placement, and even fewer patients at the time of SVCS diagnosis (11%, Figure 2). This contrasts with findings by Beers et al., who reported only 13% atypical CVAD placements, but most likely relates to accepting a higher tip position (mid to distal SVC) by these authors and because insertion was only verified intra-operatively.[9] All CVAD tip positions in our study were revised by post-insertion radiography because the catheter position may alter upon changing to an upright position.[25] The origin of thrombosis may also originate from vascular damage following previous CVAD placement. This was suggested during revision by signs of pre-existing thrombosis, mainly septation and venous collaterals. These findings emphasise the urge for correct tip placement and (when feasible) considering an arteriovenous fistula as access mode rather than a new catheter in case of thrombotic central vessel damage.

In our cohort, in two-thirds of cases, a CT scan was used to diagnose SVCS; other options included fluoroscopy, phlebography, or ultrasound (Table 2). CT scan provides the most optimal visualisation of the SVC and is, therefore, preferable for diagnosing SVCS.[4,26] Other imaging modalities may be sufficient in some cases, but these may lead to missed diagnoses. In our study, there was a diagnostic delay in three patients. One had SVCS clinical symptoms without such evidence on ultrasound. Four months later, a CT scan was performed due to persisting symptoms, and SVCS was diagnosed. This case exemplifies the importance of adequate imaging to avoid any delay in diagnosis and the start of appropriate treatment.

The treatment approach in HPN patients with SVCS is multidisciplinary and includes the treating HPN physician, (interventional) radiologist, vascular surgeon, and vascular specialist.[4] Initial management for HPN patients with SVCS includes tilting the head-side of the bed to decrease hydrostatic pressure in the superior body, lowering TPN volume, and/or extending infusion time. Next, anticoagulation is the mainstay of treatment.[27] Almost every patient in our cohort started or continued anticoagulant treatment. In one patient, CVAD removal proved sufficient for symptom control, although we usually do not remove CVADs upon SVCS development unless there is catheter dysfunction. Persistent symptoms can be managed using PTA, stenting, and recanalization, the most frequently used endovascular therapies in our cohort (Table 2).

The development of SVCS frequently has major consequences. We found that 95% of patients had remaining issues, the most prevalent being reduced options for CVAD placement (66%) and persistent symptoms (61%). Since the SVC is the final common pathway for all venous return to the heart, a problem at this level usually leads to serious problems for any new CVAD insertion. Although the femoral vein is often used as an alternate approach, this is less ideal due to the risk of infections and its location, especially in patients with an ostomy.[24] Moreover, these patients face the risk of developing inferior vena cava syndrome, which occurred in 4 (11%) of our patients. In case of reduced vascular access options, there are other exotic options like the placement of a CVAD through the thrombus or insertion of a CVAD through the hepatic veins into the caval vein or directly into the right atrium. In case of total loss of options for vascular access, intestinal transplantation is the last resort and in line with concurrent guidelines of IF and HPN care, timely referral to such a specialised unit should be urgently considered once SVCS develops.

This study comes with strengths and limitations. SVCS remains an underexposed topic in HPN care, and this is the first study that completely focuses on this topic. In addition, this is the first study that thoroughly revised all catheter tip positions with an expert interventional radiologist, and we provide guidance for such evaluation and further research. Our retrospective approach precludes statements on causality and carries a risk of underreporting information on SVCS, although we rigorously analysed all patient data from our comprehensive HPN patient population. The available literature is seriously hampered by the absence of a uniform definition of SVCS. Future research would benefit from a uniform definition of new or recurrent SVCS.

Conclusion

In conclusion, in our CIF population, in contrast with our initial impression, we found no evidence of an increase in SVCS incidence in recent years, including the period that covers the COVID-19 pandemic. We describe the devastating consequences of SVCS, which should - whenever suspected - be recognised and treated as early as possible in HPN patients by a multidisciplinary expert approach. In addition, it is crucial to check for adequate placement of the CVAD tip to prevent or limit the development of this adversity.

Financial disclosure
None

Conflict of interest
None

Supplementary data
Supplementary files are available at:
https://www.sciencedirect.com/science/article/pii/S0261561423004053

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Chapter 8

General discussion

The primary objective of this thesis is to improve the care for chronic intestinal failure (CIF) patients. This general discussion will concentrate on the main findings, their clinical implications, and the future perspectives of the individual studies addressed in this thesis. Table 1 provides an overview of the research aims and main findings, while Table 2 presents the strengths and limitations of each study included in this thesis.

Chapter 2: Body composition of chronic intestinal failure patients

Knowledge gap

Measuring changes in body composition in CIF patients provides valuable information on the effectiveness of total parenteral nutrition (TPN) and the overall health status, which is underscored by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommendation to use this tool at every scheduled visit.[1] In our tertiary referral centre for intestinal failure care, we have measured body composition using single-frequency bioelectrical impedance analysis (SF-BIA) as part of routine care since 2019. Here, we share these results to evaluate the therapeutic effects of TPN on body composition, detect patterns and trends, guide clinical practice, and set aims for future research.

Findings

Our data show that regardless of the assumed adequate nutritional intake via TPN infusions, most CIF patients remain to have an unfavourable body composition that is characterised by a high fat percentage and low fat-free mass index (FFMI) despite having a normal body mass index (BMI).

Clinical implications and future perspectives

The results of this study emphasise the importance of incorporating body composition monitoring as a routine in CIF patients using advanced methods such as BIA measurements, as mentioned in the guideline. Regular assessments of body composition allow clinicians to monitor the effects of their TPN regimen and make any necessary adjustments in a timely manner. For example, optimising the protein and caloric contents of TPN helps to address muscle wasting while preventing excessive fat accumulation.

Our results suggest that reliance on BMI alone might lead to the erroneous conclusion that the body composition of CIF patients is adequate. BIA

measurements in this study reveal an unfavourably high fat percentage and low FFMI, highlighting the inadequacy of BMI measurements as the single tool to assess body composition. While BMI is a useful general screening tool, it lacks the detailed information needed for a thorough nutritional assessment. As such, body composition measurements provide a more nuanced insight into a patient's health status, enabling more detailed, effective, and personalised care.

As a limitation, we could not include data on accelerometry and muscle function here because these were not yet routinely performed during the study period. Accelerometry provides valuable data on physical activity levels,[2] while muscle function data enables the identification of sarcopenia, which is common in CIF due to malnutrition and reduced physical activity.[3,4] Integrating these assessments into our future routine care will provide a more robust nutritional assessment.

We hypothesised that most CIF patients will likely have a suboptimal body composition, apart from their underlying condition, because of insufficient physical exercise. Hence, our next step will be to conduct research on tailored exercise interventions for CIF patients, aiming to improve body composition by increasing muscle mass and enhancing physical functions, such as balance and proprioception. Understanding the effects of exercise on body composition and function will enable the development of more targeted rehabilitation programs encompassing personalised treatment plans that not only address nutritional deficits but will also improve the overall quality of life because of increased functional independence of CIF patients.

Chapter 3: Fasting bioelectrical impedance analysis

Knowledge gap

The ESPEN guideline on BIA suggests fasting prior to measurements to ensure accuracy.[5] However, apart from the fact that this measure perpetuates malnutrition, it substantially complicates matters in clinical practice. Importantly, adequate evidence to strongly support this fasting criterion for BIA is lacking.

Findings

Our study found that breakfast consumption before BIA measurements only marginally affects fat-free mass (FFM) outcomes. The largest mean difference observed was a FFM increase of 0.2 kg at 3 hours, which was statistically but not clinically significant. 90% of participants showed less than a 1 kg difference in FFM between fasting and non-fasting measurements.

Clinical implications and future perspectives

These results suggest that fasting prior to BIA measurements does not appear to be required since consuming a standardised breakfast does not lead to clinically relevant changes in body composition estimates for most individuals. A limitation of this study was the homogeneity of the included population, predominantly females aged 24-39 with a normal BMI, this may reduce external validity. However, there is no evidence to suggest different findings in other populations. Therefore, based on this study and the currently available literature,[6,7] we have revised the Dutch BIA guideline of the Nutritional Assessment Platform and removed the fasting statement.[7,8] This guideline update has resulted in a more patient-friendly approach that seems particularly beneficial for patients who preferably should not fast for medical reasons.

The revised guideline also opens new logistic avenues since it is now possible to analyse non-fasted subjects without compromising the quality of results. This change also enables an increased measurement frequency and broader access to body composition assessment with more effective patient monitoring and management. Taken together, these aspects should enable more personalised patient care. The next hurdle and critical step will be the translation at the international level into an adaptation of existing guidelines with the goal to ensure analytical consistency in clinical practice and -hopefully- improved patient outcomes worldwide.

Chapter 4: Parenteral nutrition infusion and bioelectrical impedance analysis

Knowledge gap

Standardisation of BIA measurements is essential, yet the guideline does not provide specific recommendations for patients receiving TPN.[5] It remains unclear whether TPN should be (dis)continued during a measurement or what would be the optimal time of day to perform BIA. This may lead to inconsistencies in the assessment of body composition in CIF patients, given that TPN infusion usually takes place overnight. Research was needed to standardise pre-measurement conditions and ensure accurate and reliable BIA in CIF patients.

Findings

Our study in CIF patients found that overnight TPN infusion does not significantly affect FFM estimation as assessed by BIA.

Clinical implications and future perspectives

These findings have direct implications for clinical practice. Our data suggest that TPN infusion does not significantly affect FFM estimation as assessed by BIA. As a limitation, we only have a modest sample size. However, the observed 95% confidence intervals fall within the predefined clinically acceptable range (±1 kg in FFM). While increasing the number of study participants would narrow the confidence interval, the current results are already within the clinically acceptable range; therefore, including additional patients in future studies seems unnecessary. Thus, despite the exploratory design and modest sample size, this study suggests that BIA measurements in CIF patients can be performed at any time of the day. This practical hint guides clinicians in their daily patient management and improves efficiency.

Bioelectrical impedance analysis

Our research on BIA measurements in Chapters 2, 3, and 4 highlights the importance of BIA as a tool for assessing the body composition of CIF patients. This is in line with the growing trend towards the use of body composition measurements in clinical practice, which is reflected in the increased attention at medical congresses and symposia on this matter. Also, due to these advances, there is a growing need for guidance to integrate body composition measurements further into standard care and practice and improve patient management and outcomes.

Standardising measurement procedures is essential to improve the reliability and comparability of BIA results. Even minor variations in measurement conditions, such as patient positioning, electrode placement, and pre-measurement conditions, can lead to discrepancies in data.[10] Adopting uniform standards for conducting BIA will help mitigate these issues and ensure that measurements are accurate and reproducible. In that vein, the current ESPEN BIA guideline dates from 2004 and is obviously due for an update.

Besides the issues mentioned in Chapters 3 and 4, the revised guideline must also address what constitutes a clinically acceptable variation in FFM. In designing our research, we encountered challenges related to defining this variation. The existing literature on this variation referred to in the guideline is scarce.[5] Additionally, most studies use impedance or resistance as primary outcome measures, which are not clinically relevant. Healthcare providers are rather interested in parameters such as FFM and fat percentage, which provide actionable insights into a patient's

nutritional status. The American tutorial (2015) on body composition tools denotes that the decision as to what level of 'precision' is considered clinically acceptable is likely to vary depending on the application, and there is yet no consensus on this point.[10] This tutorial underlines the broader issue: the lack of consensus on what constitutes an acceptable range of FFM variation. Given these challenges, future guidelines must include specific recommendations on the maximum clinically acceptable range for FFM variation. Establishing these standards will allow for more consistent application of BIA measurements in research settings.

While BIA is a valuable tool, it should not be the sole determinant to describe a patient's nutritional status. A comprehensive nutritional assessment includes three domains: 1) intake, consumption and losses, 2) body composition, and 3) body function, providing a holistic view of the patient's health.[11] Moreover, BIA results should be interpreted with some caution. We performed measurements in a healthy colleague using three BIA devices in five minutes (SF-BIA (Kyle equation), multi-frequency bioelectrical impedance analysis (MF-BIA) SECA 555, and MF-BIA Inbody S10). We found a range of 7.7 kg in FFM and 19% in fat percentage. We therefore should keep in mind that the measurement does not necessarily reflect the actual situation. BIA measurements should always be considered alongside other clinical information and the clinician's judgement. Logical reasoning and consideration of the patient's complete clinical picture will ensure that BIA results are used appropriately.

Further research should also focus on improving technological aspects of BIA to increase its accuracy and reliability. Advances in such technology could reduce the influence of external factors and provide more accurate assessments of body composition. Additionally, new algorithms should be developed to refine the interpretation of BIA data in clinical practice.

In conclusion, the use of BIA to assess body composition represents a growing trend with significant benefits in the management of CIF patients. However, it is essential to standardise the measurement procedures, update BIA guidelines, and ensure that BIA is part of a comprehensive nutritional assessment.

Chapter 5: Taurolidine-related adverse events

Knowledge gap

While taurolidine is generally considered as a safe antiseptic agent to prevent catheter-related bloodstream infections, there remains a gap in our understanding of potential adverse events (AEs) that may be specific to its use as a catheter lock solution (CLS). Furthermore, clinical practice so far lacked practical guidance on how to manage taurolidine-related AEs.

Findings

Our retrospective study found that 89 out of 470 CIF patients reported a total of 103 taurolidine-related AEs (incidence rate 0.15 per 1000 catheter days). 53% of the AEs were related to problems with the catheter, such as thrombosis, malposition, and infection, and 85% of symptoms in this group concerned infusion-related pain. Importantly, the majority of patients could resume taurolidine as a CLS once the underlying catheter-related problem had been resolved.

Clinical implications and future perspectives

This study, which presents the most comprehensive dataset on taurolidine-related AEs to date, highlights the urgent need for critical assessment and careful management of patients experiencing such AEs. We propose a clinical algorithm for the management of taurolidine-related AEs, a tool that could significantly impact the management of CIF patients. Given the high percentage of patients with infusion-related pain, it is essential to educate patients to recognise such symptoms. This knowledge will enable patients to rapidly identify potential problems with their catheter, leading to faster interventions.

Taurolidine plays an important role in the prevention of CRBSIs due to its broad-spectrum antimicrobial properties.[12-14] Its efficacy is well documented, making it a preferred CLS in CIF patients.[15-17] Given its benefits, the decision to rechallenge with taurolidine in patients who have experienced AEs should be carefully considered. Discussions between treating physicians and patients are essential to weigh the benefits against potential AEs.

More research is needed to understand the true causes of intolerance or allergy when using taurolidine. It is unlikely that intolerance due to an allergy is caused by taurolidine, as it is rapidly metabolised into bodily taurine, carbon dioxide, and water. One potential culprit could be the stabiliser polyvinylpyrrolidone (PVP) used in taurolidine formulations. One study investigated the pharmacokinetics and

safety of taurolidine in healthy dogs and found that when given 2% taurolidine without PVP, no dogs experienced any AE.[18] Pharmaceutical companies should consider developing taurolidine solutions without PVP or with alternative stabilisers to prevent possible AEs.

As the retrospective assessment of AEs is suboptimal and underreporting may have played a role in our study, a prospective (multicentre) registry is needed to collect taurolidine-related AEs to comprehensively understand the prevalence and causes. Moreover, this registry can validate the usefulness of the clinical algorithm for clinicians managing home parenteral nutrition (HPN) patients to ensure that it supports decision-making and improves patient care.

In summary, the future perspective for the management of taurolidine-related AEs includes patient education, careful consideration of rechallenge protocols, more research on the cause of allergic reactions when using taurolidine, and prospective data collection on AEs. These steps will help further optimise the use of taurolidine while ensuring patient safety and improving the overall management of catheter-related complications.

Chapter 6: Enteral absorption of antimicrobial agents in short bowel syndrome patients

Knowledge gap

Despite the frequent necessity of using antimicrobials in CIF patients because of suspected (mostly catheter-related) infections, currently there are no recommendations to guide the use and dosing of antimicrobial drugs in short bowel syndrome (SBS) patients, where anatomical and physiological changes to the digestive system affect drug pharmacokinetics.

Findings

In this exploratory study, we included 18 SBS patients who received frequently used antimicrobial drugs in CIF care, i.e., clindamycin and ciprofloxacin or flucloxacillin and fluconazole both orally and intravenously. The results show a median oral bioavailability of 36%, 93%, 50%, and 98% for ciprofloxacin, clindamycin, flucloxacillin, and fluconazole. We observed considerable variability in the oral bioavailability of these drugs among the participants. No correlation was found between oral bioavailability and several patient characteristics.

Clinical implications and future perspectives

The results of this study may have several important implications and highlight areas for future research. Contrary to what might be expected in SBS patients, specific oral antimicrobial agents showed acceptable levels of bioavailability. This suggests that oral therapy may be a promising option for treating (especially mild) infections in this population. If implemented, it could reduce reliance on prolonged intravenous therapy, thereby decreasing associated complications and costs.

The observed variability in drug absorption in SBS patients portrays the heterogeneity of this condition and the multitude of factors that can influence drug absorption. This variability necessitates the implementation of therapeutic drug monitoring (TDM). TDM ensures tailored patient care with individualised dosing and adequate drug exposure, thereby optimising therapeutic outcomes and minimising the risks associated with undertreatment or drug toxicity. It is important to emphasise that TDM is currently necessary when using oral antimicrobials in SBS patients to ensure adequate drug exposure.[19,20]

The study presented in this thesis concerned stable patients without active infection. It is unknown whether SBS patients with infections can achieve therapeutic drug levels. It would be interesting to conduct a randomised trial in which SBS patients with a mild infection are treated, with one group receiving oral antimicrobial agents while the other gets standard intravenous treatment. These studies are needed to investigate the feasibility of oral antimicrobial agent therapy in SBS patients.

This is the first prospective study investigating individual bioavailability after oral administration of antimicrobial agents in SBS patients, but due to its explorative nature we only have a modest sample size. Therefore, it is essential that we conduct multicentre studies to enlarge the study population and thereby capture more varied patient characteristics. These studies should focus on identifying patient-specific characteristics that can predict drug absorption in SBS patients and explore the underlying mechanisms that contribute to variability in drug absorption. Factors such as residual bowel length, presence of the ileocecal valve, intestinal transit time, and the degree of mucosal adaptation may be critical determinants of drug absorption. By identifying patient-specific characteristics, we can further improve the accuracy of oral antimicrobial therapy, enabling more personalised and effective treatment plans.

Another interesting topic would be the inclusion in such research of intestinotrophic hormones, such as the recently introduced synthetic glucagon-like peptide-2 (GLP-2) analogues, that promise to enhance drug absorption by promoting the growth and functionality of the intestinal mucosa.[21-25] Using a within-patient design, we could investigate whether GLP-2 analogues can improve oral drug absorption. Understanding how GLP-2 therapy modulates drug bioavailability will be critical to optimising dosing regimens and improving therapeutic outcomes in this patient population.

In conclusion, our study underlines the potential of oral antimicrobial therapy in SBS patients and highlights the need for personalised treatment approaches. By improving our understanding of oral drug absorption in SBS patients and exploring the effects of adjunctive therapies such as GLP-2 analogues, we can improve infection management and overall care for these patients to provide an effective, safe, cost-saving, and minimally invasive treatment.

Chapter 7: Superior vena cava syndrome in chronic intestinal failure patients

Knowledge gap

The primary issue addressed in this study is the incidence and management of superior vena cava syndrome (SVCS) in CIF patients. SVCS is often only recognised at a late stage and leads to significant morbidity (swelling of the upper body and headache) and may compromise the remaining options to obtain central venous access.

Findings

SVCS was diagnosed in 6% (38/616) of CIF patients between 2000 and 2022, with an annual cumulative incidence ranging from 0 to 4.2%. The most common symptoms of SVCS in these patients included facial oedema (82%) and arm oedema (50%). In hindsight, only 17% of these patients had a correct position of their CVAD tip on post-insertion imaging.

Clinical implications and future perspectives

Due to the high incidence of SVCS in this vulnerable CIF population, we aim to highlight the need for vigilant monitoring and early recognition of vascular obstruction symptoms, emphasising a multidisciplinary approach for timely diagnosis and treatment. Therefore, it is essential to educate CIF patients and their medical

teams on (especially early) SVCS symptoms. Teaching patients to recognise vascular obstruction-related symptoms such as facial and arm oedema and encouraging them to seek prompt medical contact when these symptoms occur can lead to earlier detection and treatment, potentially reducing the severity of complications.

We found that most CVADs had an incorrect tip location upon insertion and even more so when SVCS was diagnosed. A more robust prospective multicentre evaluation of this is needed to corroborate whether the risk of catheter-related venous thrombosis and, consequently, SVCS is higher in patients with incorrectly placed CVADs. This evaluation should also explore optimal techniques for CVAD placement and identify the most qualified personnel to perform the insertion. These findings could significantly improve clinical practice and patient outcomes by ensuring the safest and most effective use of CVADs in CIF patients.

General conclusions

With the data from this thesis, we aim to further optimise the care provided to CIF patients. Patients with CIF benefit significantly from the personalised care approach that our research has contributed to in various ways. We showed that despite adequate nutritional intake via TPN infusions, CIF patients often have an unfavourable body composition that is characterised by a high fat percentage and low FFMI. While BMI was normal, these BIA characteristics highlight the importance of a detailed nutritional assessment. Of note the possible effect of exercise interventions in this patient group remains to be established. We found that intake of breakfast and overnight TPN infusions had no clinically relevant effect on FFM estimates evaluated by BIA. This novel finding substantially increases the practicability of BIA and paves the way for their more easy and standardised use of this technique in CIF patients. We demonstrated that long-term use of taurolidine as a CLS is generally safe and that most supposed taurolidine-related AEs are, in fact, CVAD-related problems. In our ABSORB study, we show that the oral bioavailability of antimicrobial agents is better than expected, which offers possibilities for less invasive and more cost-effective treatment options for SBS patients. Lastly, the incidence of SVCS is relatively high in our vulnerable CIF population. Given the consequences, it is key to recognise this condition at an early stage.

Overall, this thesis covers an array of studies that provide relevant new insights concerning major issues in CIF care and HPN support, some of which remain to be bolstered in other clinical and multicenter settings.

Table 1. Overview of aims and main findings of each study in this thesis.

Chapter	Research aims	Main findings and conclusion
2	Determine the body composition of our adult CIF patient cohort	Most CIF patients have unfavourable body composition characterised by high fat percentage and low FFMI, despite a normal mean BMI
3	Investigate the impact of breakfast on FFM estimation as assessed by SF-BIA	Eating affects SF-BIA measurements, but differences in FFM mostly remain below clinical relevance Performing BIA measurements in fasting state is not required
4	Describe the effect of PN infusion on FFM estimation as assessed by SF-BIA	PN infusion lacks impact on FFM as assessed by SF-BIA
5	Quantify the number of CIF patients experiencing taurolidine-related AEs Identify which taurolidine-related AEs are observed in CIF patients. Investigate the causes of taurolidine-related AEs Develop an algorithm for managing taurolidine-related AEs in clinical practice	89 (19%) patients experienced a total of 103 mild to severe taurolidine-related AEs Many reported presumed taurolidine-related AEs signify catheter-related problems rather than intolerance or allergy to taurolidine We provide an algorithm on how to address taurolidine-related AEs in clinical practice
6	Determine the bioavailability of orally administered antimicrobial agents in SBS patients.	The bioavailability of selected antimicrobial agents was better than expected in some SBS patients, providing a potential treatment option Due to large differences observed between patients, therapeutic drug monitoring should be part of the treatment to ensure adequate exposure in all patients
7	Determine the incidence of SVCS in CIF patients Investigate SVCS-related symptoms Determine CVAD tip location post-insertion and at SVCS diagnosis	Between 2000 and 2022, cumulative SVCS incidence rates ranged from 0 to 4.2% Most common symptoms were facial oedema (82%) and arm oedema (50%) 17% of patients had a correct CVAD tip position post-insertion, and 11% during SVCS diagnosis. The incidence of SVCS is relatively high in our CIF population and requires early recognition and multidisciplinary treatment

Abbreviations: AE, adverse event; BIA, bioelectrical impedance analysis; BMI, body mass index; CIF, chronic intestinal failure; CVAD, central venous access device; FFM, fat-free mass; FFMI, fat-free mass index; PN, total parenteral nutrition; SBS, short bowel syndrome; SF-BIA, single-frequency bioelectrical impedance analysis; SVCS, superior vena cava syndrome.

Table 2. Overview of strengths and limitations each study in this thesis.

Chapter	Strengths	Limitations
2	Standardised BIA measurements from a substantial group of CIF patients Use of BIVA plots for hydration status assessment	Lack of accelerometry and muscle function data
3	Standardised BIA measurements All measurements performed by the same researcher Consistent calibration of BIA device on each study day	Homogeneity of study population
4	First study exploring the effect of PN infusion on FFM estimation	Modest sample size
5	Most robust patient cohort using taurolidine from a single centre Identification of a frequent underlying cause Provided an algorithm for taurolidine use in clinical practice	Potential underreporting of AEs Retrospective grading of AEs is suboptimal
6	First prospective study on individual bioavailability of oral antimicrobial agents in SBS patients	Modest sample size Not optimal sample collection
7	First study to focus completely on SVCS in CIF patients Thorough revision of catheter tip positions by an expert interventional radiologist	Risk of underreporting information on SVCS Absence of uniform definition of SVCS in the literature

Abbreviations: AE, adverse event; BIA, bioelectrical impedance analysis; BIVA, bioelectrical impedance vector analysis; CIF, chronic intestinal failure; FFM, fat-free mass; PN, parenteral nutrition; SBS, short bowel syndrome; SVCS, superior vena cava syndrome.

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Chapter 9

Summaries

English summary

Patients with chronic intestinal failure (CIF) rely on total parenteral nutrition (TPN), which is typically administered through a central venous access device (CVAD). Due to the chronic nature of this condition, patients and caregivers receive training on how to prepare the TPN bag, connect and disconnect the CVAD, and maintain the equipment in the home setting, this strategy is called home parenteral nutrition (HPN). HPN is a complex and time-consuming treatment that requires careful coordination between healthcare providers, patients, and caregivers to be successful. Moreover, optimal care and coordination by a multidisciplinary nutrition support team are essential to reduce the risks of complications. This thesis presents several studies that aim to improve the overall care provided to CIF patients.

As part of an extensive nutritional assessment, body composition plays a crucial role in understanding the nutritional status of CIF patients. In **Chapter 2**, we conducted a retrospective cohort study to determine the overall body composition of our adult CIF patient cohort (n=147), which was evaluated by assessing body mass index (BMI), fat-free mass index (FFMI) and fat percentage. Despite assumingly adequate nutritional intake via TPN infusions, most CIF patients have an unfavourable body composition. Sixty-three percent of patients had an FFMI below reference, and 48% had a high fat percentage despite the mean BMI being 22.1 kg/m^2. These data highlight the necessity for in-depth nutritional assessment, including bioelectrical impedance analysis (BIA).

Without clear supporting evidence, current guidelines recommend that BIA should be performed in a fasting state. However, this is impractical in clinical practice and undesirable in already malnourished patients. Therefore, in **Chapter 3**, we performed an explorative prospective study in 39 healthy volunteers to assess the impact of breakfast on fat-free mass (FFM) estimation as evaluated by BIA. For 90% of the participants, having breakfast did not significantly affect the estimated FFM. The largest mean difference was an increase of 0.2 kg 3 hours after breakfast ingestion, which was statistically but not clinically significant. These data suggest that fasting before BIA is not necessary.

Current BIA guidelines provide no recommendations concerning patients receiving TPN because the impact on BIA is unknown. Therefore, in **Chapter 4**, we explored the effect of TPN infusion on FFM estimation evaluated by BIA in a prospective study of 20 CIF patients. We found no significant change in FFM estimation after

TPN infusion. This suggests that BIA can be performed at any time during the day to assess FFM in patients receiving TPN.

Taurolidine is an antiseptic catheter lock solution (CLS) that has proven relevant in preventing catheter-related bloodstream infections. Nevertheless, some patients report adverse events (AEs) after CLS (re)placement that may be related to taurolidine. In **Chapter 5**, we conducted a retrospective cohort study to identify the incidence and cause of taurolidine-related AEs. In our cohort, 470 CIF patients used taurolidine during 700.232 catheter days. Eighty-nine (19%) patients experienced 103 mild to severe taurolidine-related AEs. 51% of the reported AEs were related to problems with the CVAD and predominantly presented with infusion-related pain (85%), and 49% concerned taurolidine-related problems. An algorithm was developed to guide the management of taurolidine-related AEs in clinical practice. The data indicate that taurolidine as CLS is generally safe and that most supposed taurolidine-related AE frequently points towards an underlying CVAD problem.

Patients with short bowel syndrome (SBS) have a significant loss of absorptive small intestine surface and, therefore, a presumed impaired oral drug uptake. However, successful treatment with oral antimicrobials has been reported in case studies. **Chapter 6** further explored the oral bioavailability of four frequently prescribed antimicrobial agents in 18 SBS patients. We found median oral bioavailabilities of 36%, 93%, 50%, and 98% for ciprofloxacin, clindamycin, flucloxacillin, and fluconazole, respectively. Even though oral bioavailability in certain patients appeared better than expected, therapeutic drug monitoring should be part of treatment to ensure sufficient exposure in all patients. Moreover, the feasibility of oral antimicrobial agents in SBS patients with (mild) infections remains to be established.

Superior vena cava syndrome (SVCS) is a severe complication in CIF patients, most often related to the presence of their CVAD. In **Chapter 7**, a retrospective cohort study was performed to determine the incidence of SVCS in our CIF patient cohort. Secondary outcomes were to determine SVCS-related symptoms and CVAD tip location during insertion and at the time of SVCS diagnosis. SVCS was diagnosed in 38 out of 616 patients (6%), with an annual incidence rate varying from 0 to 4.2%. The most common symptoms were facial (82%) and arm (50%) oedema. 17% of SVCS patients had a CVAD tip that was correctly positioned at post-insertion radiography and 11% during SVCS diagnosis. The relatively high incidence of SVCS in our CIF population calls for increased attention.

Nederlandse samenvatting

Patiënten met chronisch darmfalen zijn afhankelijk van intraveneuze toediening van totale parenterale voeding (TPV), die meestal wordt toegediend via een centraal veneuze katheter (CVK). Vanwege de chronische aard van deze aandoening krijgen patiënten en mantelzorgers training in het klaarmaken van de TPV-zak, het aansluiten en loskoppen van de CVK en het onderhouden van de apparatuur in de thuissituatie, deze behandeling wordt thuis-TPV genoemd. Thuis-TPV is een complexe en tijdrovende behandeling die een zorgvuldige coördinatie tussen zorgverleners, patiënten en mantelzorgers vereist om succesvol te zijn. Bovendien zijn optimale zorg en coördinatie door een multidisciplinair voedingsondersteuningsteam essentieel om het risico op complicaties te verminderen. Dit proefschrift presenteert diverse onderzoeken die als doel hebben om de algehele zorg voor patiënten met chronisch darmfalen te verbeteren.

Als onderdeel van een uitgebreide nutritional assessment speelt het bepalen van de lichaamssamenstelling een cruciale rol om de voedingsstatus van chronisch darmfalen patiënten te begrijpen. In **Hoofdstuk 2** hebben we een retrospectieve cohortstudie uitgevoerd om de algehele lichaamssamenstelling van ons volwassen chronisch darmfalen cohort (n=147) te bepalen, die werd geëvalueerd aan de hand van de body mass index (BMI), de vetvrije massa index (VVMI) en het vetpercentage. Ondanks veronderstelde adequate voedingsinname via TPV bleken de meeste patiënten met chronische darmfalen een ongunstige lichaamssamenstelling te hebben. Drieënzestig procent van de patiënten had een VVMI onder de referentie, 48% had een hoog vetpercentage ondanks dat de gemiddelde BMI 22.1 kg/m^2 was. Deze gegevens laten het belang zien van een volledig nutritional assessment, inclusief bio-elektrische impedantieanalyse (BIA).

Zonder duidelijk bewijs wordt in de huidige richtlijnen aanbevolen om een BIA uit te voeren in nuchtere toestand. Dit is echter onpraktisch in de klinische praktijk en zelfs ongewenst bij patiënten die ondervoed zijn. In **Hoofdstuk 3** hebben wij een exploratieve prospectieve studie uitgevoerd bij 39 gezonde vrijwilligers om de invloed van het ontbijt op de schatting van de vetvrije massa (VVM), geëvalueerd met BIA, te beoordelen. Bij 90% van de deelnemers had het ontbijt geen klinisch relevant effect op de geschatte VVM. Voor de groep was het grootste gemiddelde verschil een toename van 0,2 kg in VVM 3 uur na inname van het ontbijt, hetgeen wel statistisch maar niet klinisch significant was. De resultaten van deze studie suggereren dat vasten voor de BIA niet nodig is.

De huidige BIA-richtlijnen geven geen aanbevelingen voor patiënten die TPV krijgen, omdat de invloed van TPV toediening op de BIA uitslag onbekend is. In **Hoofdstuk 4** hebben we de invloed van nachtelijke TPV-infusies op de VVM-schatting, geëvalueerd met BIA, onderzocht in een exploratieve prospectieve studie bij 20 patiënten met chronisch darmfalen. We vonden geen significante verandering in VVM-schatting na nachtelijke TPV-infusie. De resultaten van deze studie suggereren dat BIA op elk moment van de dag betrouwbaar uitgevoerd kan worden om de VVM te beoordelen bij patiënten die TPV krijgen.

Taurolidine is een antiseptisch middel dat als katheterslot relevant is gebleken bij het voorkomen van katheter-gerelateerde bloedbaaninfecties. Desondanks melden sommige patiënten bijwerkingen bij het plaatsen van het katheterslot die waarschijnlijk gerelateerd zijn aan taurolidine. In **Hoofdstuk 5** hebben we een retrospectieve cohortstudie uitgevoerd om de incidentie en oorzaak van taurolidine-gerelateerde bijwerkingen te identificeren. In ons cohort gebruikten 470 chronisch darmfalen patiënten taurolidine gedurende 700.232 katheterdagen. Negentachtig patiënten rapporteerde 103 milde tot ernstige taurolidine-gerelateerde bijwerkingen. 51% van de bijwerkingen was gerelateerd aan problemen met de CVK en deze patiënten presenteerde zich voornamelijk met infusie-gerelateerde pijn (85%), terwijl 49% verband hielden met taurolidine. Nadat het onderliggende CVK-probleem aangepakt was, kon een aanzienlijk aantal patiënten het gebruik van taurolidine hervatten. Gebaseerd op deze resultaten hebben we een algoritme ontwikkeld om handvatten te bieden bij de aanpak van taurolidine-gerelateerde bijwerkingen in de klinische praktijk. Deze gegevens impliceren dat het gebruik van taurolidine als katheterslot over het algemeen veilig is en dat de meeste vermeende taurolidine-gerelateerde bijwerkingen in feite wijzen op een probleem met de CVK.

Patiënten met het kortedarmsyndroom hebben een aanzienlijk tekort aan absorptiecapaciteit van de dunne darm en daardoor een verondersteld verminderde opname van orale geneesmiddelen. Succesvolle behandeling met orale antimicrobiële middelen is echter desondanks gerapporteerd in casestudies. In **Hoofdstuk 6** hebben we de orale biologische beschikbaarheid van vier vaak voorgeschreven antimicrobiële middelen bij 18 patiënten met het kortedarmsyndroom onderzocht. De mediane orale biologische beschikbaarheid van ciprofloxacine, clindamycine, flucloxacilline en fluconazol was respectievelijk 36%, 93%, 50% en 98%. Ondanks dat de orale biologische beschikbaarheid bij bepaalde patiënten beter was dan verwacht, moet therapeutische drug monitoring naar onze mening deel uitmaken van de behandeling om voldoende opname van

cruciale geneesmiddelen bij alle patiënten met een te korte darm te garanderen. Zo moet de haalbaarheid van orale antimicrobiële middelen bij patiënten met kortedarmsyndroom met (milde) infecties nog worden vastgesteld.

Het vena cava superior syndroom (VCSS) is een ernstige complicatie bij patiënten met chronisch darmfalen, en die meestal gerelateerd is aan de aanwezigheid van hun CVK. In **Hoofdstuk 7** hebben we een retrospectieve cohortstudie uitgevoerd om de incidentie van VCSS te bepalen. Secundaire uitkomsten waren VCSS-gerelateerde symptomen en de locatie van de CVK-tip tijdens het inbrengen en op het moment van de VCSS-diagnose. Een VCSS werd vastgesteld bij 38 van de 616 patiënten (6%), met een jaarlijkse incidentie die varieerde van 0 tot 4,2%. De meest voorkomende symptomen waren zwelling van het gelaat (82%) en van de armen (50%). Bij slechts 17% van de patiënten bleek de tip van CVK correct te zijn gepositioneerd na plaatsing en bij 11% ten tijde van de VCSS-diagnose. Aangezien de incidentie van VCSS dus relatief hoog is in onze chronisch darmfalen populatie is vroegtijdige herkenning en behandeling cruciaal.


1.0

Chapter 10

Appendices

Research data management

Ethics and privacy

This thesis is based on research involving human participants conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct, and Radboudumc policy.

The study described in Chapter 6 was subjected to the Medical Research Involving Human Subjects Act (WMO). The recognised Medical Ethics Review Committee 'METC Oost-Nederland' has given approval to conduct this study (file number NL70700.091.19). Informed consent was obtained from participants to collect and process their data for this research project. Technical and organisational measures were followed to safeguard the availability, integrity, and confidentiality of the data (these measures include the use of independent monitoring, pseudonymisation, access authorisation and secure data storage).

A statement that the studies described in Chapters 2, 3, 4, 5, and 7 were not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) was obtained from the recognised Medical Ethics Review Committee 'METC Oost-Nederland' (reference number: 2023-16161, 2022-15782, 2021-13266, 2020-6524, 2020-6524). Informed consent, if necessary, was obtained from research participants. Technical and organisational measures were followed to safeguard the availability, integrity, and confidentiality of the data (these measures include the use of pseudonymisation, access authorisation and secure data storage).

Data collection and storage

To ensure the interpretability of the data, all file names, primary and secondary data, metadata, descriptive files and program code and scripts used for the analyses of studies are stored in the departments' shared drive. Data for Chapters 2, 3, 4, 5, 6, and 7 were collected through an electronic Case Report Form (eCRF) using Castor EDC or Excel. From Castor EDC, data were exported to SPSS (SPSS Inc., Chicago, Illinois, USA). Pseudonymised data were stored on the department server and in Castor EDC and are only accessible by project members. Paper (hardcopy) data is stored in department cabinets.

Availability of data

The studies described in Chapters 2, 3, 4, 5, 6, and 7 are published with open access. The data will be archived for 15 years after termination of the study. While permission was not obtained for sharing the data after research, the data from

Chapters 2, 3, 4, 5, 6, and 7 are archived in a 'closed access' Data Acquisition Collection (DAC) of the Radboud Data Repository, from which the metadata are publicly available via DOI:

https://doi.org/10.34973/4s95-6v49
https://doi.org/10.34973/r7w7-xs60
https://doi.org/10.34973/ghbp-bb97
https://doi.org/10.34973/e2m9-5m04
https://doi.org/10.34973/0q2y-rj43
https://doi.org/10.34973/n4ck-tj22

List of publications

This thesis

Korzilius JW, Gillis V, Wouters Y, Wanten GJA. Taurolidine-related adverse events in patients on home parenteral nutrition frequently indicate catheter-related problems. Clin Nutr. 2022;41(10):2178-84.

Korzilius JW, Gompelman M, Wezendonk GTJ, Jager NGL, Rovers CP, Brüggemann RJM, Wanten GJA. Oral antimicrobial agents in patients with short bowel syndrome: worth a try! J Antimicrob Chemother. 2023;78(8):2008-14.

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* Authors share first authorship

Other publications

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Zweers H, **Korzilius J**, Kruizenga H, Visser W, Jans I, Droop A. Standard Operating Procedures: single-frequency bioelectrical impedance analysis: Nutritional Assessment Platform; 2024.

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Acknowledgements (dankwoord)

Met veel plezier heb ik de afgelopen jaren met veel verschillende mensen samengewerkt. Ik wil graag iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift. Allereerst wil ik mijn dank uitspreken naar alle patiënten en vrijwilligers die hebben deelgenomen aan de verschillende studies. Daarnaast wil ik ook een aantal mensen in het bijzonder bedanken voor hun steun.

Beste **Geert**, 12 april 2021 stuurde ik jou mijn eerste mail met de vraag of we een keer in gesprek konden gaan over een mogelijk promotietraject. 1.5 uur later kreeg ik de volgende reactie: Tuurlijk, woe ochtend gesprek plannen? G. Een efficiënte start van onze fijne samenwerking. In de loop der jaren heb ik nog heel wat efficiënte mails van jou mogen ontvangen, zoals: Ja Ja G, Ter info G, OK G, Vind je dit wat? G, Dank! G, Iets voor jou? G, Bij deze G, Eens G, Ha Julia Shoot Geert, Prima! G, En succes!! G, Mooi werk!, Bij deze alvast wat gekras van mijn kant G, HJ wat vind je hier van? G.

Het was altijd een plezier om deze e-mails te openen. Je hebt een talent voor het krassen in mijn manuscripten en maakt daarbij gebruik van prachtige woordkeuzes. Je bent zeer laagdrempelig benaderbaar: van even iets vragen naar 1.5 uur aan het kletsen zijn over van alles en nog wat. Je reageert altijd snel en weet voortdurend je enthousiasme voor het vakgebied over te brengen. Dank voor jouw goede begeleiding tijdens mijn promotietraject. ''Ben je nou nog niet gepromoveerd?'' Nu kan ik eindelijk antwoorden: ''Ja wel Geert, ik ben gepromoveerd!

Beste **Heidi**, samenwerken met jou gaat heel natuurlijk. Dat komt waarschijnlijk vanwege onze vele overeenkomstige eigenschappen, zoals onze directheid – wat vooral voor heldere en eerlijke gesprekken zorgt. Ik heb de begeleiding van studenten samen met jou altijd als erg plezierig ervaren. Je bent een heel fijne begeleider en ik heb heel veel van je geleerd, dus ik ben blij dat jij gedurende het traject mijn copromotor bent geworden.

Beste **Joost**, hoewel je niet altijd direct betrokken was bij mijn dagelijkse werkzaamheden, waardeerde ik enorm dat je altijd beschikbaar was voor vragen en het overzicht over mijn traject wist te behouden. Jouw aanwezigheid en bereidheid om te helpen waren van grote waarde tijdens mijn promotietraject. Dank voor je steun en begeleiding.

Leden van de manuscriptcommissie: **prof. dr. D.M. Burger**, **prof. dr. S. Middeldorp** en **prof. dr. G. Dijkstra** en opponenten **dr. L. Wauters**, **prof. dr. H. Jager-Wittenaar** en **dr. B.A.E. de Koning** hartelijk dank voor het beoordelen van mijn proefschrift en het investeren van uw kostbare tijd.

Beste coauteurs, hartelijk dank voor jullie input, het includeren van patiënten, het beoordelen van samples en jullie kritische blik op het onderzoek en de manuscripten. In het bijzonder dank voor alle coauteurs die bij hebben gedragen aan de ABSORB-studie: **Roger Brüggemann**, **Nynke Jager** en **Chantal Rovers**. Zonder jullie expertise hadden we dit artikel niet kunnen publiceren.

De andere promovendi van Geert: **Michelle**, je was aanwezig bij mijn eerste gesprek met Geert en gaf me vanaf het begin het vertrouwen dat alles goed zou komen, ondanks dat de financiering voor drie jaar nog niet rond was (zoals ook bij jou het geval was en uiteindelijk goed kwam). Je liet me weten dat je beschikbaar zou zijn voor vragen en overleg en dat heb je ook waargemaakt. Ik ben blij dat we samen de ABSORB studie tot een succes hebben kunnen afronden. **Veerle**, jij bent mijn darmfalen-maatje. Ik ben heel blij dat je jouw tijd bij de MDL hebt kunnen verlengen, zodat we nog wat langer team darmfalen konden zijn. Samenwerken met jou verloopt niet alleen soepel, maar is ook ontzettend gezellig. De afgelopen jaren hebben we samen veel mooie momenten beleefd, waarbij onze tripjes naar Athene en Wenen absoluut de hoogtepunten waren. Ik waardeer je enthousiasme en ik kijk met plezier terug op onze samenwerking. **Yannick**, jij bent de copromotor van Veerle en zo heb ik ook van jouw expertise gebruik mogen maken. Hartelijk dank voor al je inhoudelijke feedback op mijn manuscripten, hierdoor is de kwaliteit aanzienlijk verbeterd. Bedankt nog voor de gezellige tijd in Milaan tijdens het ESPEN congres en Manchester tijdens de darmfalen workshop. **Angelique**, dankzij jou projecten heb ik in de eerste fase van mijn promotietraject extra veel contact met patiënten kunnen hebben. Dit heeft mijn traject aanzienlijk verrijkt en veel leuker gemaakt. Hartelijk dank daarvoor!

Ook al mijn mede (arts)-onderzoekers verdienen een speciale vermelding in dit dankwoord. Dank voor alle gezellige borrels, congressen, weekendjes weg, activiteiten, vierdaagse stap avonden, lunch sessies en de gezamenlijke besprekingen. Jullie hebben mijn promotietraject extra bijzonder gemaakt. **Britt**, ik kende jou al voordat we collega's werden en ik ben blij dat we nog een periode samen konden werken, ik genoot van onze roddelsessies tijdens de pauze over ons gezamenlijke verleden op het gebied van voetbal en dates. **Jasmijn**, ik bewonder jouw ijzeren discipline zowel op sport- als onderzoekersgebied. Het is

indrukwekkend hoe jij verzonken kunt raken in je werk. Ondanks vele pogingen van mij en Gijs lukte het ons niet om jou uit je concentratie te krijgen. Gelukkig had je af en toe wel tijd voor een potje worstelen. **Gijs**, jij bent mijn favoriete kamergenoot en gesprekspartner. Ik ben je dankbaar voor alle fijne gesprekken die we samen hebben gehad en alle adviezen die je me hebt gegeven, ook al werd ik af en toe gek van je als je me weer eens ging verbeteren. **Lia**, ik ken weinig mensen die zo chaotisch zijn als jij. Ik vergeet nooit het moment dat we overgingen naar het nieuwe besturingssysteem en jij afscheid moest nemen van alle mappen en losse bestanden die op jouw bureaublad stonden. Hoe kan iemand zo werken? Maar ondanks al die chaos, ben je bovenal een supergezellige collega met wie ik veel mooie momenten heb beleefd. **Lieke**, dokter de KOGEL, dank voor alle eerlijke en gezellige momenten. We hopen ooit nog een bevestiging te krijgen dat je officieel een relatie hebt. **Daan**, jij bent standaard aanwezig op alle borrels en zorgt ervoor dat het altijd gezellig is, dankzij de regel om niet over werk te praten en je geweldige dansmoves. **Monica**, jij bent echt een gezelligheidsdier met eindeloze energie. Je weet altijd alles te combineren en bent overal bij. Dat komt waarschijnlijk omdat je enorm veel FOMO hebt. **Michiel**, prof. Maas, dank voor de gezellige échte borrel momenten met jou erbij was het altijd een feest. **Romée**, ik vind het bijzonder hoe jij al je activiteiten in je leven weet je combineren en vast te leggen op beeld. Gelukkig had je ook af en toe tijd om in het Radboudumc over champagneproblemen te kletsen onder het genot van een goede kop koffie. **Milou**, dank voor de gezellig tijd samen als collega's en voor het inwerken op de MDL van het Rijnstate, ik mis de koffies samen nu al. **Fenna** Beeren, hoewel je vaker in Arnhem was, waardeer ik je enorm als collega en de fijne gesprekken die we samen hebben gehad. **Sabien**, als er dan maar één andere collega op werk is, dan kies ik jou. Fijn dat je altijd een rondje mee wilde wandelen en gezellig wilde bijkletsen. ESPEN 2023 was ook erg gezellig samen. **Renée**, je bent een wandelende encyclopedie, iedereen kan bij jou terecht voor cake en adviezen. Ook ik mocht daarvan profiteren en dan met name in de vorm van gezamenlijke klaagmomenten, altijd lekker om alles eruit te gooien. **Naomi**, hoewel je niet vaak in Nijmegen was, konden we altijd gezellig praten over de inrichting van onze nieuwe huizen en samen hard lachen om onze slaapgewoontes. **Dorien**, dank voor alle gezellige momenten samen. **Mike**, dank voor jouw werkzaamheden als CDC en de tomatenplanten. **Joris**, **Lotte Hazeleger**, en **Larissa** wat leuk dat jullie je in mijn laatste maanden nog bij het onderzoekersteam hebben gevoegd. Jullie brachten een hoop gezelligheid met jullie mee, en dat konden we goed gebruiken!

Verder dank aan alle andere onderzoekers voor de mooie tijd: **Edo**, **Fenna Jansen**, **Koen**, **Lotte Huijbertse**, **Maarten**, **Melissa**, **Pepijn**, **Stijn**, **Thijs**, **Yonne**. Dank

Cynthia, **Eva** en **José** van de Research Unit voor al jullie expertise. Dank **Lionne**, **Linda** en **Rachelle** van het stafsecretariaat MDL voor alle ondersteuning en gezelligheid tijdens mijn promotietraject. Dank aan alle studenten van de TPV-database voor hun werkzaamheden: **Guus**, **Raisa**, **Britt**, **Thijs** en **Bram**. Master studenten: **Sosha**, **Melina** en **Manon**, dank voor al jullie inspanningen, jullie hebben een belangrijke bijdrage geleverd aan meerdere projecten. **Reinier Akkermans**, hartelijk bedankt voor de waardevolle bijdragen en het geduldige advies bij de statistische analyses. Ook bedankt aan alle **stafleden** en **arts-assistenten** van de afdeling Maag-, Darm- en Leverziekten van het Radboudumc. Ik wil in het bijzonder iedereen van het Darmfalen team bedanken: **Anneleen**, **Chrissy**, **Doreen**, **Hester**, **Judith**, **Karen**, **Marriëtte**, **Monique**, **Renate** en **Sophie**. Jullie deur stond altijd open, voor studievragen, overleg over patiënten, maar bovenal voor gezelligheid. Zonder jullie extra hulp bij de inclusie van patiënten was het nooit zo voorspoedig gegaan. Bedankt Darmfalen Nederland voor de samenwerking, en in het bijzonder: **Gerard Dijksta**, **Mireille Serlie**, **Miriam van der Werf** en **Cora Jonkers- Schuitema**.

Lieve **Myrthe**, **Lisa** en **Eline**. Mijn PhD-maatjes. Ik ben enorm blij dat wij in dezelfde periode aan het promoveren waren in het Radboudumc. Lekker samen kletsen onder het genot van een goede kop koffie, gezamenlijk sparren over onze PhD-trajecten of gewoon lekker roddelen. Met als hoogtepunt dat we onze publicaties vierden tijdens de PUBLIBOOSS, wat overigens soms onmogelijk was om te plannen, ik denk dat we nog een beetje achterlopen, maar soms konden we allemaal opeens dezelfde avond nog. En niet te vergeten onze geweldige gala avond tijdens DTHR, of was dat nu een grap? Mijn dank en liefde voor jullie is groot!

Lieve **familie** en **vrienden**, dank voor jullie interesse in mijn onderzoeksprojecten en voor de nodige afleiding en ontspanning. En in het bijzonder: **Pap**, **Mam**, **Nikki** en **Fleur**, dank voor al jullie liefde en onvoorwaardelijke steun. Tegenwoordig is de fysieke afstand tussen ons groter, maar ik weet dat jullie ondanks alles altijd voor mij klaarstaan. Ik hou van jullie!

Lieve Daphne, wij hebben de afgelopen jaren een enorme groei samen doorgemaakt, dit was niet altijd makkelijk, maar heeft onze band wel enorm versterkt. Natuurlijk word ik nog steeds af en toe gek van je, bijvoorbeeld als ik weer eens je persoonlijke encyclopedie moet zijn terwijl ik juist een rustige avond wil. Maar ik ben je heel dankbaar dat je altijd zoveel interesse toonde in mijn PhD leven en dat je altijd beschikbaar was voor advies. Ik ben heel blij met ons nieuwe huis in Lent (ja ja ik heb de oversteek moeten maken) en ik kijk uit naar alle avonturen die we nog samen gaan beleven. Ik hou van je!

Curriculum vitae

Julia Korzilius werd geboren op 1 september 1996 in Nijmegen. Samen met haar zussen Nikki en Fleur en ouders Ankie en Hubert groeide ze hier op. In 2014 behaalde zij haar atheneumdiploma aan het Kandinsky College in Nijmegen. Aansluitend startte zij haar studie Geneeskunde aan de Radboud Universiteit in Nijmegen, waar zij in 2018 haar bachelor en in 2021 haar artsendiploma behaalde. Tijdens haar studie ontwikkelde zij een sterke interesse in Maag-, Darm- en Leverziekten, wat haar ertoe bracht haar wetenschappelijke stage op het gebied van gastro-oesofageale refluxziekte aan Stanford University te doen. Deze interesse werd verder versterkt tijdens haar coschappen, waarna zij haar senior coschap op de afdeling Maag-, Darm- en Leverziekten van het Radboudumc succesvol afrondde. Direct vanuit de studiebanken begon zij haar promotietraject op de afdeling Maag-, Darm- en Leverziekten van het Radboudumc over het verbeteren van de zorg rondom patiënten met chronisch darmfalen. Dit proefschrift is het resultaat van haar promotieonderzoek, dat zij uitvoerde onder leiding van dr. Geert Wanten, dr. Heidi Zweers en prof. dr. Joost Drenth. Na haar promotieonderzoek vervolgde ze haar carriere als ANIOS op de Maag-, Darm- en Leverziekten in het Rijnstate ziekenhuis in Arnhem en daarna in het Radboudumc in Nijmegen.

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Portfolio

Department: Gastroenterology and Hepatology
PhD period: 01/09/2021 – 30/09/2024
PhD Supervisor: Prof. dr. J.P.H. Drenth
PhD Co-supervisors: dr. G.J.A. Wanten and dr. H.E.E. Zweers- van Essen

	Year(s)	Hours
Courses & workshops		**403**
Radboudumc – Introduction Day	2021	6
Radboudumc – eBROK course	2021	42
Radboud University – Statistics for PhD candidates using SPSS	2021	60
Workshop – Multi-frequency bio-electrical impedance analysis	2021	3
RIHS – Introduction course for PhD candidates	2022	15
Webinar – Vascular accesses for parenteral nutrition	2022	3
Good Clinical Practice	2022	12
Salford Intestinal failure Workshop	2022,2024	32
JUMPstart programme – Energize your research in Clinical Nutrition	2022,2023	60
Radboudumc – Scientific Integrity	2023	20
Workshop – Multi-frequency bio-electrical impedance analysis	2023	3
RU – Zelfinzicht: de sleutel voor je loopbaan	2023	7
RU – Presentation Skills	2023	42
Radboudumc – Peer review and rebuttal writing	2023	2
RU – Academic English Conversation and Pronunciation	2024	43
RU – Mindfulness-Based Stress Reduction	2024	45
Radboudumc – Managing Your Internship Students	2024	2
Radboudumc – Re-registration BROK	2024	5
Seminars		**35**
Soeterbeeck GI lectures	2021-2024	26
GI-Hep meetings with international experts	2021-2022	6
Research Integrity Round (2x)	2022, 2023	3
Conferences		**312**
ESPEN, Vienna, Wien (poster tour presentation)	2022	48
WoCoVa, Athens, Greece (oral presentation)	2022	40
Digestive Disease Days, Veldhoven, Netherlands	2023	16
ECCMID, Copenhagen, Denmark (oral presentation)	2023	48
PhD retreat, 's-Hertogenbosch, Netherlands	2023	16
ESPEN, Lyon, France (poster presentation)	2023	48
After-ESPEN, 's-Hertogenbosch, Netherlands (oral presentation)	2023	16
Intestinal failure day, Utrecht, Netherlands (oral presentation)	2023,2024	32
ESPEN, Milano, Italy (poster presentation)	2024	48

Other		**354**
Journal club Gastroenterology & Hepatology (weekly)	2021-2024	138
Research meeting (weekly)	2021-2024	138
Intervision sessions PhD students (4x yearly)	2021-2024	24
Organising intervision sessions PhD students	2022-2024	10
Organising research meeting	2023-2024	40
Reviewing a scientific article	2024	4
Supervision of internships / other		**210**
Supervision research internship (Master student, 6 months)	2022-2023	60
Supervision research internship (Master student, 6 months)	2022-2023	60
Supervision research internship (Master student, 3 months)	2024	30
Supervision students retrospective database	2021-2024	60
Total hours		**1313**
ECTS (hour/28)		**46.9**

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