Journal of Parenteral and Enteral Nutrition
Volume 45 Number 6
August 2021 1259–1267

DOI: 10.1002/jpen.2006
wileyonlinelibrary.com
WILEY

Hypophosphatemia in a Specialized Intestinal Failure Unit: An Observational Cohort Study

Marcel Kjærsgaard Eriksen, MD[1]; Simon Mark Dahl Baunwall, MD[1]; Simon Lal, MD, PhD[2]; Jens Frederik Dahlerup, MD, DMSc[1]; and Christian Lodberg Hvas, MD, PhD[1]

Abstract

Background: Patients with intestinal failure (IF) are prone to hypophosphatemia and shifts in magnesium and potassium levels. Although these shifts are often attributed to refeeding syndrome (RFS), the incidence of electrolyte shifts among patients with IF is unknown. We evaluated the occurrence of hypophosphatemia and other electrolyte shifts according to the functional and pathophysiological IF classifications. *Methods:* We consecutively included all patients' first admission to an IF unit from 2013 to 2017. Electrolyte shifts were defined as severe hypophosphatemia <0.6 mmol/L (mM) or any 2 other shifts below reference range, comprising hypomagnesemia <0.75 mM, hypophosphatemia <0.8 mM, or hypokalemia <3.5 mM. Outcomes included length of stay, central line–associated bloodstream infection, and other infections. Mortality was evaluated 6 months after discharge. *Results:* Of 236 patients with IF, electrolyte shifts occurred in 99 (42%), and 127 (54%) of these patients received intravenous supplementation with either phosphate, magnesium, or potassium. In patients who started parenteral nutrition, up to 62% of early-onset shifts (<5 days) related to refeeding, and up to 63% of late-onset shifts (≥5 days) could be ascribed to infections. Derangements occurred in 7 (18%) with type 1 IF, 53 (43%) with type 2 IF, and 39 (53%) readmitted patients with type 3 IF. Of 133 patients with IF secondary to short-bowel syndrome, 65 (49%) developed shifts. *Conclusion:* In patients with IF, electrolyte shifts are frequent but not always due to RFS. Electrolyte shifts are common in patients with type 2 and those readmitted with type 3 IF. (*JPEN J Parenter Enteral Nutr.* 2021;45:1259–1267)

Keywords

enteral nutrition; hypophosphatemia; intestinal failure; parenteral nutrition

Clinical Relevancy Statement

Intestinal failure (IF) is defined by the patients' need of parenteral support. Parenteral nutrition renders patients with IF prone to hypophosphatemia, hypomagnesemia, and hypokalemia. These are often attributed to refeeding syndrome, but may be related to other factors. This study evaluated the occurrence, causes, and risk factors of electrolyte shifts in a consecutive cohort of patients with IF admitted to a specialized IF unit.

Introduction

Hypophosphatemia and shifts in magnesium and potassium may occur in malnourished patients when nutrition is commenced following a period of inadequate nutrition.[1–16] Hypophosphatemia is often attributed to refeeding syndrome (RFS), although hypophosphatemia does not always imply that RFS has occurred.[17] Other causes include infections, renal disorders, disturbances in cellular redistribution, and poor intake.[17,18]

Intestinal failure (IF) is a condition defined by reduced gut function and a need for parenteral support (PS).[19] IF may be separated into 3 subtypes. Acute type 1 IF is often self-limiting, requiring only short-term PS.[20–22] Type 2 IF

From the [1]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; and the [2]Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Salford, United Kingdom.

Financial disclosure: None declared.

Conflicts of interest: None declared.

Received for publication June 9, 2020; accepted for publication August 17, 2020.

This article originally appeared online on September 10, 2020.

Corresponding Author:
Marcel Kjærsgaard Eriksen, MD, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark.
Email: marcer@rm.dk

occurs in metabolically unstable patients and requires PS over periods of weeks or months.[19,23] Type 3 IF is a chronic condition in metabolically stable patients who require PS over months or years.[19,24] On admission, patients with IF often present with infections, undiagnosed comorbidity, and metabolic instability.[25] Reestablishment of feeding in patients with IF is lifesaving but carries significant risks. These include a risk for electrolyte shifts when recommencing nutrition.[26–28] Although prone to these, the incidence of hypophosphatemia and other biochemical derangements among patients with IF remain unknown.

The aim of the present study was to evaluate the occurrence of hypophosphatemia, hypomagnesemia, and hypokalemia and the relation to clinical outcomes in a cohort of consecutive patients with IF during their first admission to a dedicated IF unit (IFU).

Materials and Methods

Study Design and Cohort

This was a single-center observational study conducted at Aarhus University Hospital, Denmark. Adult patients with IF were consecutively included on their first admission from January 1, 2013, to December 31, 2017, to evaluate the incidence of electrolyte shifts, including hypophosphatemia during admission. Clinical characteristics of the patients have been published previously.[25] All patients were followed up 6 months after discharge to review mortality.

A research database was established for prospective inclusion of patients with IF, using the research data capture software REDCap (www.redcap.au.dk). All patients were classified according to the European Society for Clinical Nutrition and Metabolism (ESPEN)–endorsed functional and pathophysiological IF classification.[19] Using the patients' medical records, collection of supplementary data was carried out retrospectively.

Electrolyte Shifts and Clinical Outcome Measures

Laboratory parameters included plasma levels of phosphate, potassium, and magnesium. In all patients, regardless of admission length, time and value of lowest measured levels were documented. Electrolyte shifts were defined in 4 groups, adapted from Reber et al.[7,8]

1. Group 1: Severe hypophosphatemia <0.6 mmol/L.
2. Group 2: Hypophosphatemia <0.8 mmol/L and hypomagnesemia <0.75 mmol/L.
   Assumptions: Phosphate ≥ 0.6 mmol/L and potassium ≥ 3.5 mmol/L.
3. Group 3: Hypophosphatemia <0.8 mmol/L and hypokalemia <3.5 mmol/L.
   Assumptions: Phosphate ≥ 0.6 mmol/L and magnesium ≥ 0.75 mmol/L.
4. Group 4: Hypomagnesemia <0.75 mmol/L and hypokalemia <3.5 mmol/L.
   Assumptions: Phosphate ≥ 0.6 mmol/L.

To evaluate the incidence of refeeding, time from central venous catheter (CVC) placement to timing of derangements was calculated in all patients who commenced parenteral nutrition (PN) during admission. Patients with electrolyte shift extremes before CVC placement were excluded. To examine interdepartmental differences in electrolyte shift occurrence, patients admitted from other departments or hospitals were referred to as "externals." Accordingly, patients admitted by the local gastroenterological department housing the IFU were referred to as "internals."

Outcome variables included length of stay, diagnosis of central line–associated bloodstream infection (CLABSI), and other infections. CLABSI was defined by clinical signs of systemic infection, a central line in situ for >48 hours, laboratory-confirmed bloodstream infection in qualitative peripheral blood cultures, and no evidence of infection from another site.[29–31]

Nutrition Commencement Regimens

PN was administered as SmofKabiven (Fresenius Kabi): a standard 3-chamber bag containing amino acids, lipid, and glucose. On admission, individual nutrition requirements were estimated based on body mass index (BMI) and unique metabolic properties, including level of activity and/or presence of fever. Typically, PN was initiated at 50 mL/h and given as continuous pump feeding over a 10- to 12-hour duration. Supplementary electrolytes were only administered in case of deficiencies. PN commencement followed a step-up protocol starting at one-third of the nutrition requirements on the first day, half the nutrition requirements on the second day, and two-thirds of the nutrition requirements on the third day until complete coverage of daily nutrition requirements the fourth day.

Enteral nutrition (EN) was given by tube as either Peptamen (Nestlé) or Nutrison Protein Plus (Nutricia). EN was administered as either bolus feeding over a halfhour's duration or as continuous pump feeding according to individual nutrition requirements using a similar step-up protocol as above. In patients with a high risk of refeeding, infusion rate of artificial nutrition was reduced and dosage frequency or speed was increased over 6–8 days in concordance with National Institutes for Health and Care Excellence (NICE) guidelines. All patients were supplied with intravenous (IV) vitamin B complex (recommended daily doses of vitamin B_1, B_2, and B_6) and thiamin (400 mg per 24 hours).

After commencement of EN or PN, venous blood biochemistry of patients was monitored daily for 3 days

Table 1. Definition of Electrolyte Shifts and Patient Characteristics of Patients with IF admitted to an IF Unit.

Characteristics	All patients (n = 99)	Group 1 (n = 30)	Group 2 (n = 14)	Group 3 (n = 8)	Group 4 (n = 47)	*P*-value
Definitions of groups						
P < 0.6 mmol/L		+	–	–	–	
P < 0.8 mmol/L		–	+	+	–	
Mg < 0.75 mmol/L		–	+	–	+	
K < 3.5 mmol/L		–	–	+	+	
Patient characteristics						
Gender, n (%)						<.001
Male	46 (46)	22 (73)	9 (64)	2 (25)	13 (28)	
Female	53 (54)	8 (27)	5 (36)	6 (75)	34 (72)	
BMI, n (%)						
≥ 18.5 kg/m^2	70 (71)	23 (77)	11 (79)	6 (75)	30 (64)	.218
<18.5 kg/m^2	28 (28)	6 (20)	3 (21)	2 (25)	17 (36)	
<16 kg/m^2	11 (11)	0 (0)	1 (7)	1 (13)	9 (19)	
Alcohol abuse (ever), n (%)	4 (4)	1 (3)	1 (7)	0 (0)	2 (4)	.747
CCI score						
Median (IQR),	3 (1–6)	4 (1–6)	6 (2–6)	0 (0–4)	2 (1–4)	.021
Range	0–10	0–9	1–10	0–6	0–7	
Admission length, n (%)						
<2 wk	22 (22)	6 (20)	2 (14)	5 (63)	9 (19)	
2–4 wk	34 (34)	10 (33)	7 (50)	2 (25)	15 (32)	.080
>4 wk	43 (43)	14 (47)	5 (36)	1 (13)	23 (49)	
Deaths 6 months after discharge, n (%)	21 (21)	8 (27)	3 (21)	0 (0)	10 (21)	.494

BMI, body mass index (missing values, n = 1); CCI, Charlson Comorbidity Index; IQR, interquartile range; K, potassium; Mg, magnesium; P, phosphate.

followed by 3 times weekly, including measurement of sodium, potassium, ionic calcium, phosphate, magnesium, alanine transaminase, triglyceride, creatinine, and serum albumin levels.

Statistical Analysis

Descriptive statistics were performed on all patient characteristics and IF-related outcomes stratified by defined electrolyte shift groups. Numerical, nonparametric data were presented as medians with interquartile ranges (IQRs) and evaluated using Mann-Whitney or Kruskal-Wallis tests. When reporting the length of stay outcomes, these were plotted as means with 95% CI. Dichotomous data were presented as numbers with percentages and evaluated using χ^2 tests or Fisher exact test. *P*-values below .05 were considered statistically significant. All statistical analyses were performed using GraphPad Prism version 8.2.1 (279) for Mac (GraphPad Software, La Jolla, CA, USA, www.graphpad.com) or STATA version 16 for Windows (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Ethics Statement

The IF database was established as part of a clinical quality-improvement program. The database was approved by and fulfilled the requirements of the Danish Data Protection Agency (jr.no. 2012-58-006). Because this was a quality-improvement study and the head of the department approved the protocol, no formal ethics committee approval was required according to Danish law.

Results

Hypophosphatemia and Other Electrolyte Shifts

In total, 236 adult patients with IF were admitted during the 5-year study period. Of these, 99 (42%) had significant electrolyte imbalances at least once during their admission. These included 30 (30%) patients with plasma phosphate <0.6 mmol/L and 69 (70%) patients with plasma phosphate ≥ 0.6 mmol/L and 2 of the following: plasma magnesium <0.75 mmol/L and phosphate <0.8 mmol/L (n = 14), plasma potassium <3.5 mmol/L and phosphate <0.8 mmol/L (n = 8), or combined plasma magnesium <0.75 mmol/L and potassium <3.5 mmol/L (n = 47) (Tables 1 and 2). The cohort comprised 133 (56%) females and the median age was 61 years (IQR, 46–71 years; range, 16–90 years). The overall occurrence of electrolyte shifts was evenly distributed between women and men with 53 (54%) and 46 (46%) cases of derangements,

Table 2. Electrolyte Shifts According to IF Characteristics or IF-Related Pathology in Patients Admitted to an IF Unit.

Characteristics	All patients (n = 99)	Group 1 (n = 30)	Group 2 (n = 14)	Group 3 (n = 8)	Group 4 (n = 47)	*P*-value
IF characteristics and IF-related pathology						
Functional IF type, n (%)						.136
Type 1	7 (7)	1 (3)	2 (14)	2 (25)	2 (4)	
Type 2	53 (54)	19 (63)	5 (36)	2 (25)	27 (57)	
Type 3	39 (39)	10 (33)	7 (50)	4 (50)	18 (38)	
Pathophysiological IF classification, n (%)						.073
SBS	65 (66)	22 (73)	9 (64)	3 (38)	31 (66)	
ECF	3 (3)	2 (7)	1 (7)	0 (0)	0 (0)	
Dysmotility	11 (11)	0 (0)	2 (14)	2 (25)	7 (15)	
Obstruction	8 (8)	2 (7)	1 (7)	0 (0)	5 (11)	
SB mucosal disease	12 (12)	4 (13)	1 (7)	3 (38)	4 (9)	
Ileostomy, n (%)	49 (49)	16 (53)	9 (64)	2 (25)	22 (47)	.361
Gastrostomy (any), n (%)	30 (30)	10 (33)	3 (21)	3 (38)	14 (30)	.821
Feeding during admission, n (%)						.495
EN/OR	24 (24)	6 (20)	5 (36)	3 (38)	10 (21)	
PN	75 (76)	24 (80)	9 (64)	5 (63)	37 (79)	
IV supplementation, n (%)						
Phosphate	51 (52)	29 (97)	5 (36)	3 (38)	14 (30)	<.001
Magnesium sulphate	48 (48)	14 (47)	9 (64)	0 (0)	25 (53)	.018
Potassium	36 (36)	11 (37)	2 (14)	3 (38)	20 (43)	.276
Infections, n (%)						
One or more	49 (49)	16 (53)	10 (71)	0 (0)	23 (49)	.009[a]
LRTI	26 (26)	9 (30)	5 (36)	0 (0)	12 (26)	
UTI	14 (14)	4 (13)	3 (21)	0 (0)	7 (15)	
GI	17 (17)	8 (27)	3 (21)	0 (0)	6 (13)	
Non-GI	7 (7)	0 (0)	3 (21)	0 (0)	4 (9)	
CLABSI	8 (8)	3 (10)	0 (0)	0 (0)	5 (11)	
Exit-site infections	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)	

CLABSI, central line–associated bloodstream infection; ECF, enterocutaneous fistula; EN/OR, enteral or oral nutrition; GI, gastrointestinal; IF, intestinal failure; IV, intravenous; LRTI, lower respiratory tract infection; PN, parenteral nutrition; SB, short bowel; SBS, short-bowel syndrome; UTI, urinary tract infection.
[a] Statistics based on 1 or more infections.

respectively ($P = .46$). Severe hypophosphatemia occurred more frequently in men (73%) ($P = .0004$), and men more often had an ileostomy on admission compared with women ($P = .006$). Patients with electrolyte shifts had a higher Charlson Comorbidity Index score (median, 3; IQR, 1–6; range, 0–10) than patients without shifts ($P = .02$), with no differences between women and men ($P = .91$).

A total of 127 (54%) patients commenced IV supplementation with either phosphate-, magnesium sulphate–, or potassium-containing substances, comprising 57 (24%), 88 (37%), and 44 (19%) patients, respectively. Of patients supplemented with IV phosphate, 51 (89%) had significant electrolyte imbalances, whereas significant shifts were present in 48 (55) treated with IV magnesium, and 36 (82%) patients treated with IV potassium.

Prior to admission, 78 (33%) patients had received PN. Of these, 67 (86%) patients ("externals") came from other departments or hospitals without accredited experience in the prevention of catheter- and feeding-related complications. The remaining 11 (14%) patients ("internals") were admitted by the local gastroenterological department housing the IFU and thus adhering to the same quality standards. Whereas only 2 (18%) internals receiving PN developed severe hypophosphatemia during admission, 33 (49%) externals receiving PN developed significant electrolyte imbalances during admission (Figure 1), including 11 (33%) with severe hypophosphatemia and 22 (67%) with mixed phosphate, magnesium, or potassium imbalances. Although numerically different, the difference did not reach statistical significance ($P = .10$). Among 160 (68%) patients in which PN was

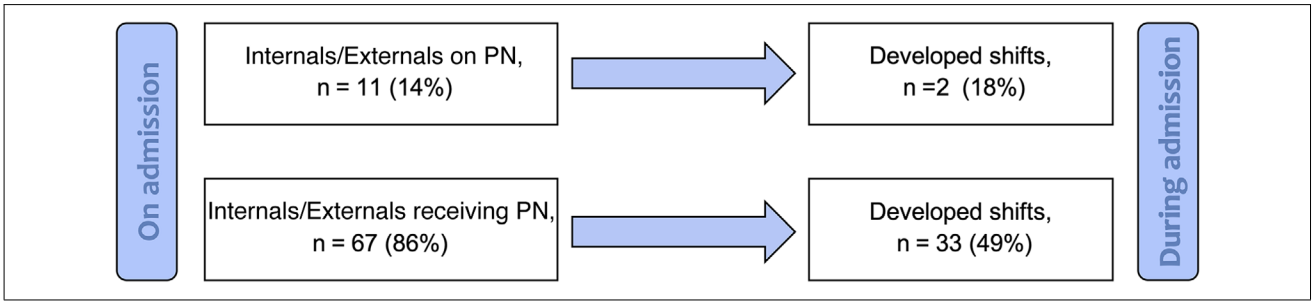

Figure 1. Electrolyte shifts during admission among internal and external patients receiving PN. PN, parenteral nutrition.

established during admission, 75 (47%) patients developed derangements.

Electrolyte Shifts Related to Refeeding and Length of Stay

The timing of electrolyte shifts was recorded in all patients. For phosphate, the lowest level was measured at median 4.5 days after admission (IQR, 1–17 days; range, 0–42 days). The lowest levels were measured at median 4 days after admission for both magnesium (IQR, 0–25 days; range, 0–65 days) and potassium (IQR, 1–12 days; range, 0–82 days). In total, 158 (67%) patients received EN or oral nutrition on admission. Of these, 70 (44%) patients commenced PN during admission with a CVC placed after median 2 days (IQR, 1–6; range, 0–41 days) of admission, and 33 (47%) developed shifts. Patients with shifts prior to CVC placement included 12 (36%) with hypophosphatemia, 17 (52%) with hypomagnesemia, and 15 (45%) with hypokalemia. After CVC placement and exclusion of electrolyte shifts prior to this, median time to electrolyte shift extremes were 5, 10, and 5 days for phosphate (n = 21), magnesium (n = 16), and potassium (n = 18), respectively (Figure 2). Within 5 days after PN commencement, a total of 13 (62%) patients developed shifts in phosphate, 7 (44%) developed shifts in magnesium, and 9 (50%) developed shifts in potassium. Accordingly, up to 62% of early-onset electrolyte shifts (<5 days) after PN commencement may relate to refeeding.

During the 5-year study period, mean length of stay was 22 days (95% CI, 19.9–24.9). Stratified by admission length, 22 (25%) patients with a length of stay below 2 weeks developed electrolyte shifts. In patients admitted for a total of 2–4 weeks, electrolyte shifts were present in 34 (43%) patients. Forty-three (61%) patients with a total length of stay above 4 weeks developed derangements. Accordingly, electrolyte shifts were more frequent in patients with longer stays (Figure 3) ($P < .0001$).

Electrolyte Shifts Related to Infections

One or more infections developed in 92 (39%) patients on or during admission, comprising lower respiratory tract infections (n = 39), urinary tract infections (n = 31), gastrointestinal (GI) infections (n = 30), other non-GI infections (n = 14), CLABSI (n = 12), and exit-site infections (n = 4).

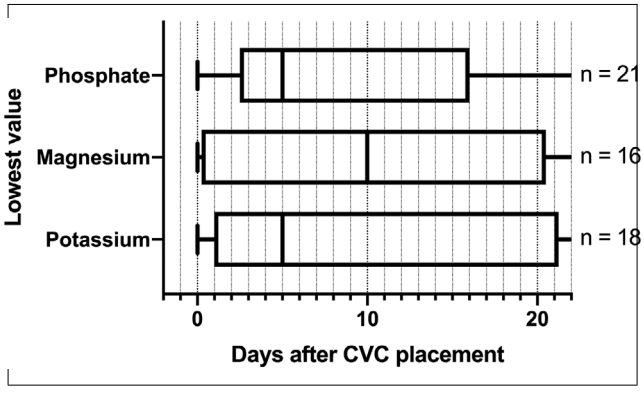

Figure 2. Box plot of time to lowest measured electrolyte levels after CVC placement. Median time to shifts were 4, 7.5, and 4.5 days for phosphate, magnesium, and potassium, respectively. CVC, central venous catheter.

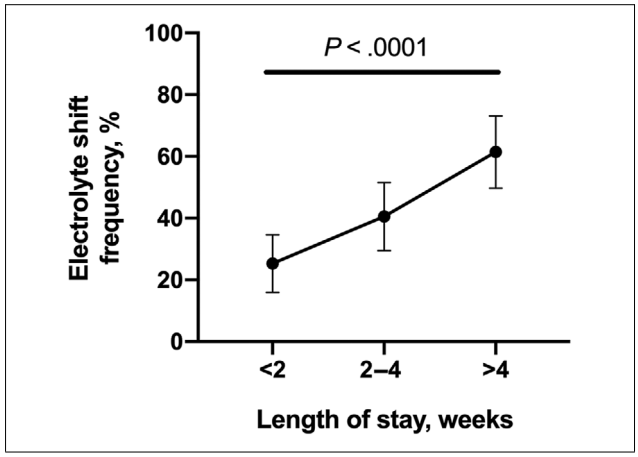

Figure 3. Frequency of electrolyte shifts stratified by length of stay in an intestinal failure unit. Mean length of stay was 22 days (95% CI, 19.9–24.9 days).

Forty-nine (53%) of these, or 49% of patients with shifts, developed biochemical derangements during admission. These included 16 (53%) patients with severe hypophosphatemia, 10 (71%) with combined hypophosphatemia and hypomagnesemia, and 23 (49%) with combined hypomagnesemia and hypokalemia (Table 2). Compared with the remaining cohort, electrolyte shifts were more common in patients with 1 or more infections during admission ($P = .002$).

On admission, 91 had a CVC, and CLABSI was present in 11 (12%). Eight (73%) of these also developed electrolyte shifts during admission. One patient with CLABSI on admission also developed CLABSI in a new CVC during admission. Accordingly, the CLABSI occurrence during admission was 2 (1%) of 173 patients with a CVC. One (50%) patient with CLABSI developed severe hypophosphatemia during admission.

During admission, 70 patients commenced PN, and 33 (47%) developed shifts. Regarding phosphate, 21 developed hypophosphatemia after and 12 had shifts prior to CVC placement. Excluding the latter, 18 (86%) had infections during admission. Of these, 7 (39%) had shifts ≥5 days after PN commencement, and 11 (61%) had shifts within 5 days. Regarding magnesium, 16 developed hypomagnesemia after and 17 had shifts prior to CVC placement. Excluding the latter, all had infections during admission. Of these, 10 (63%) had shifts ≥5 days after PN commencement, and 6 (38%) had shifts within 5 days. Regarding potassium, 18 developed hypokalemia after and 15 had shifts prior to CVC placement. Excluding the latter, 16 (89%) had infections during admission. Of these, 9 (56%) had shifts ≥5 days after PN commencement and 7 (44%) had shifts within 5 days after PN commencement. Accordingly, up to 63% of late-onset (≥5 days) electrolyte shifts after PN commencement may be ascribed to infections. Although numerically different, the difference did not reach statistical significance ($P = .35$).

Electrolyte Shifts According to ESPEN IF Classification Template

All 236 patients were classified according to ESPEN functional IF type, comprising 39 (17%) patients with type 1 IF, 123 (52%) with type 2 IF, and 74 (31%) patients with type 3 chronic IF (CIF). Electrolyte shifts developed in 7 (18%) patients with type 1 IF, 53 (43%) patients with type 2 IF, and 39 (53%) patients with type 3 CIF, suggesting that patients with type 2 and 3 IF are at higher risk of developing electrolyte derangements (Figure 4) ($P = .004$). Secondary sensitivity analyses (Supplementary Table S1) including only patients with type 2 and 3 IF did not change the significant differences within groups, except for differences in IV supplementation of magnesium sulphate becoming marginally insignificant ($P = .068$).

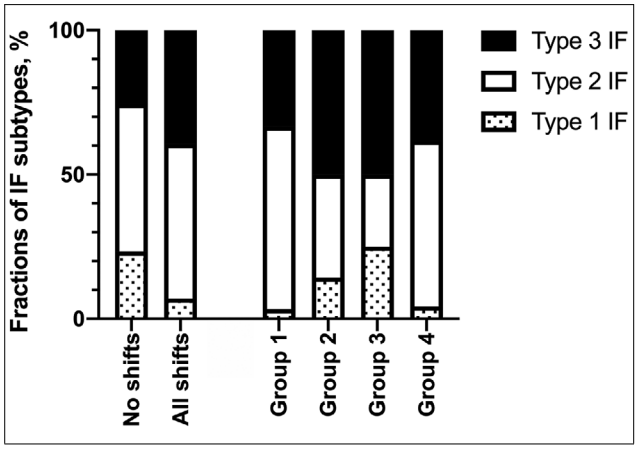

Figure 4. Functional IF classification of patients with and without electrolyte shifts during admission. IF; intestinal failure.

According to the pathophysiological IF type, 133 (56%) patients had IF due to short-bowel syndrome (SBS). Other causes included enterocutaneous fistula (ECF) in 7 (3%), intestinal dysmotility in 41 (17%), mechanical obstruction in 16 (7%), and extensive short-bowel (SB) mucosal disease in 39 (17%) patients. Among patients with SBS, 65 (49%) developed electrolyte imbalances during their first admission. Electrolyte shifts were present in 3 (43%) with ECF, 11 (27%) with intestinal dysmotility, 8 (50%) with obstructive disorders, and 12 (31%) patients with SB mucosal disease.

Electrolyte Shifts and Mortality After 6 Months

Among all patients with IF, the mortality rate 6 months postdischarge was 17% (n = 39) whether electrolyte imbalances were present during admission or not. Among all patients who died within 6 months after discharge, 21 (54%) had significant electrolyte derangements during admission, comprising 9 (43%) patients who died from cancer, 6 deaths (29%) due to non–catheter-related infections or thromboembolic events, and 6 deaths (29%) caused by various organ failures and systemic diseases. The 6-month mortality rate among patients with derangements was 21% (95% CI, 14.3%–30.3%), which is comparable to the general patient cohort (Figure 5).

Discussion

In this consecutive cohort of patients with IF, we found that electrolyte shifts occurred in 42% during admission. Our study demonstrates that electrolyte shifts are common in this patient group, and up to 62% of early-onset shifts in patients commencing PN related to refeeding. Infections may explain up to 63% of late-onset shifts in patients with PN commencement.

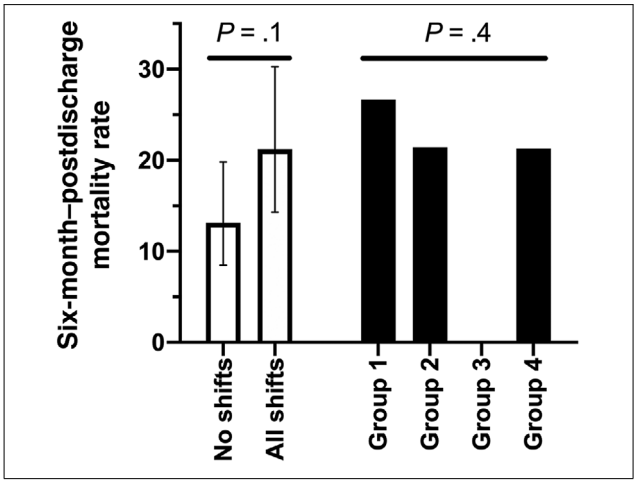

Figure 5. Mortality 6 months postdischarge among patients with and without electrolyte shifts during admission.

No previous study evaluated the incidence of electrolyte shifts in an IFU, nor did previous studies evaluate these according to functional and pathophysiological IF classification. In the present study, we included and classified patients with IF admitted to a university hospital IFU in concordance with current IF classifications. Consecutive patient inclusion was chosen to establish a representative patient cohort and eliminate the risk of selection bias.

In the present study, electrolyte shifts mainly occurred in patients with functional type 2 IF, readmitted type 3 IF, and in patients with IF pathophysiologically caused by SBS. Electrolyte shifts were defined using refeeding-related definitions adapted from Reber et al.[7,8] It is noteworthy that biochemical shifts were measured in patients regardless of recent artificial nutrition commencement. Some developed shifts due to infections, and data regarding clinical symptoms were unavailable. Residual explanations remain unknown but may include electrolyte disturbances due to renal disorders. Consequently, measured electrolyte shifts may have various causes and may not exclusively represent RFS.

Concerning RFS, no well-accepted definition exists. Despite numerous reviews, there is no consensus whether RFS is a sole laboratory diagnosis or a combined clinical and biochemical diagnosis.[32] Because of the lack of a standardized definition and sparse research on RFS among patients with IF, comparison of refeeding-related electrolyte shifts is difficult. A systematic review found an RFS incidence ranging from 15% to62% among patients receiving PN or EN.[32] Other studies reported a prevalence of 0.43%–34% in different hospital populations.[17,33,34] The studies used different biochemical definitions of RFS, comprising different cutoffs and types of electrolyte shifts. A Swiss-UK collaborative review stated that the cutoff point at which the RFS can be said to be present is somewhat arbitrary, and it proposes the adaptation of the terms "symptomatic RFS" and "potential or biochemical RFS".[9] Although hypophosphatemia is often attributed to RFS, the occurrence of hypophosphatemia in undernourished patients does not necessarily imply RFS.[17] Assuming that up to 62% of shifts in patients with PN commencement may represent refeeding, our lack of data regarding clinical symptoms may overestimate the true incidence of RFS.[9] Also, we applied the lowest electrolyte values measured throughout all of the patients' admission, and not necessarily in relation to artificial nutrition provision. This may further lead to an overestimate of the incidence of refeeding-related shifts, and the definition of RFS solely by biochemistry is an important limitation to the study. Our findings that electrolyte shifts are frequent may also reflect patient selection because of the impaired nutrition status of patients with IF. Most patients with IF are admitted because of metabolic instability or chronic need of artificial nutrition with subsequent risks of complications.

In the present study, electrolyte shifts were more frequent in patients with longer lengths of stay. This was seen despite a careful step-up protocol used during PN or EN initiation. These findings may reflect an increased number of drawn blood samples and, thus, increased risk of abnormal laboratory values unrelated to refeeding. Electrolyte shift extremes were measured at median 4–7.5 days after CVC placement and the initiation of PN. According to the Swiss-UK collaborative review, biochemical changes primarily occur within the first 72 hours after initiation of nutrition therapy, and longer length of stay is seen in patients showing signs or symptoms of RFS.[32] Consistent with our results, hypomagnesemia has been reported to occur later than the onset of hypophosphatemia.[12] Standard 3-chamber PN bags were given without measurement of pre-PN electrolyte levels, and deficiencies were corrected as they occurred. This may also contribute to overestimation of refeeding-related shifts. Our data indicate that continued electrolyte monitoring after initiation of artificial nutrition beyond 72 hours may be required. Prompt identification and management of electrolyte shifts and malnutrition are pivotal to prevent and treat refeeding-related symptoms and thereby reduce complication rates and complication-related length of stay.[34–36]

Multiple studies apply or recommend the classification of refeeding risk according to the NICE criteria.[4,7,8,17,26,27,32,35,37–39] Reported sensitivities and specificities of NICE risk criteria range from 30% to 87% and 20% to 76%, respectively.[4,7,32,37] In the present study, only a few risk criteria were measured because valid data regarding weight loss and nutrition intake prior to admission could not be obtained. According to available criteria from the medical records (BMI <16 kg/m^2 or alcohol abuse), only 11% of patients with high risk of refeeding developed electrolyte shifts.

In conclusion, we found electrolyte shifts common among patients with IF during their first admission to an

IFU. Despite the use of a careful step-up protocol when commencing PN or EN, all patients with IF had high risk of developing electrolyte imbalances, but only in a fraction of patients did these reflect RFS. The functional and pathophysiological IF classifications were useful to identify types and causes of IF at increased risk of derangements. Also, a long length of stay was a risk factor. Standardized definitions of RFS could potentially facilitate more accurate predictors of clinical deterioration secondary to biochemical abnormalities.

Statement of Authorship

M. K. Eriksen, S. M. D. Baunwall, S. Lal, J. F. Dahlerup, and C. L. Hvas equally contributed to the conception and design of the study; M. K. Eriksen contributed to the acquisition and analysis of the data; all authors contributed to the interpretation of the data; and M. K. Eriksen drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplementary Information

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

References

1. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 2017;36:(1):49-64.
2. Goyale A, Ashley SL, Taylor DR, et al. Predicting refeeding hypophosphataemia: insulin growth factor 1 as a diagnostic biochemical marker for clinical practice. *Ann Clin Biochem*. 2015;52:(1):82-87.
3. Gaudiani JL, Sabel AL, Mehler PS. Low prealbumin is a significant predictor of medical complications in severe anorexia nervosa. *Int J Eat Disord*. 2014;47:(2):148-156.
4. Zeki S, Culkin A, Gabe SM, Nightingale JM. Refeeding hypophosphataemia is more common in enteral than parenteral feeding in adult in patients. *Clin Nutr*. 2011;30:(3):365-368.
5. Marvin VA, Brown D, Portlock J, Livingstone C. Factors contributing to the development of hypophosphataemia when refeeding using parenteral nutrition. *Pharm World Sci*. 2008;30:(4):329.
6. Redgrave GW, Coughlin JW, Schreyer CC, et al. Refeeding and weight restoration outcomes in anorexia nervosa: Challenging current guidelines. *Int J Eat Disord*. 2015;48:(7):866-873.
7. Aubry E, Friedli N, Schuetz P, Stanga Z. Refeeding syndrome in the frail elderly population: prevention, diagnosis and management. *Clin Exp Gastroenterol*. 2018;11:255-264.
8. Reber E, Friedli N, Vasiloglou MF, Schuetz P, Stanga Z. Management of refeeding syndrome in medical inpatients. *J Clin Med*. 2019;8:(12):2202.
9. Stanga Z, Brunner A, Leuenberger M, et al. Nutrition in clinical practice - the refeeding syndrome: illustrative cases and guidelines for prevention and treatment. *Eur J Clin Nutr*. 2008;62:(6):687-694.
10. Sobotka L. Basics in clinical nutrition: refeeding syndrome. *e-SPEN*. 2010;5:(3):146-147.
11. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect*. 2018;7:(4):135-146.
12. Raj KS, Keane-Miller C, Golden NH. Hypomagnesemia in adolescents with eating disorders hospitalized for medical instability. *Nutr Clin Pract*. 2012;27:(5):689-694.
13. Jahnen-Dechent W, Ketteler M. Magnesium basics. *Clin Kidney J*. 2012;5:(suppl 1):3-14.
14. Fan C-G, Ren J-A, Wang X-B, Li J-S. Refeeding syndrome in patients with gastrointestinal fistula. *Nutrition*. 2004;20:(4):346-350.
15. Flesher ME, Archer KA, Leslie BD, McCollom RA, Martinka GP. Assessing the metabolic and clinical consequences of early enteral feeding in the malnourished patient. *JPEN J Parenter Enteral Nutr*. 2005;29:(2):108-117.
16. Solomon S, Kirby D. The refeeding syndrome: a review. *JPEN J Parenter Enteral Nutr*. 1990;14:(1):90-97.
17. Crook MA. Refeeding syndrome: problems with definition and management. *Nutrition*. 2014;30:(11-12):1448-1455.
18. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition*. 2001;17:(7-8):632-637.
19. Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clin Nutr*. 2015;34:(2):171-180.
20. Lal S, Teubner A, Shaffer JL. Review article: intestinal failure. *Aliment Pharmacol Ther*. 2006;24:(1):19-31.
21. Brandt CF, Tribler S, Hvistendahl M, Staun M, Brobech P, Jeppesen PB. Single-center, adult chronic intestinal failure cohort analyzed according to the ESPEN-endorsed recommendations, definitions, and classifications. *JPEN J Parenter Enteral Nutr*. 2017;41:(4):566-574.
22. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. *Aliment Pharmacol Ther*. 2013;37:(6):587-603.
23. Bond A, Teubner A, Taylor M, et al. Catheter-related infections in patients with acute type II intestinal failure admitted to a national centre: incidence and outcomes. *Clin Nutr*. 2019;38:(4):1828-1832.
24. Pironi L. Definitions of intestinal failure and the short bowel syndrome. *Best Pract Res Clin Gastroenterol*. 2016;30:(2):173-185.
25. Eriksen MK, Jørgensen SMD, Lemming LE, Lal S, Dahlerup JF, Hvas CL. Patient characteristics and clinical outcomes in a specialised intestinal failure unit: an observational cohort study. *Clin Nutr ESPEN*. 2020; 38:253-262. https://doi.org/10.1016/j.clnesp.2020.04.002.
26. Rio A, Whelan K, Goff L, Reidlinger DP, Smeeton N. Occurrence of refeeding syndrome in adults started on artificial nutrition support: prospective cohort study. *BMJ Open*. 2013;3:(1):e002173.
27. National Institute for Clinical Excellence (NICE). Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition. Published 2006. Accessed November 2, 2019https://www.nice.org.uk/guidance/cg32/evidence/full-guideline-194889853
28. Boateng AA, Sriram K, Meguid MM, Crook M. Refeeding syndrome: treatment considerations based on collective analysis of literature case reports. *Nutrition*. 2010;26:(2):156-167.
29. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control*. 2011;39:(4):1-34.
30. Smith RN, Nolan JP. Central venous catheters. *BMJ*. 2013;347:(nov11 4):6570.
31. Centers for Disease Control and Prevention. National healthcare safety network patient safety component manual. Published 2018. Accessed January 3, 2020.https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf
32. Friedli N, Stanga Z, Sobotka L, et al. Revisiting the refeeding syndrome: results of a systematic review. *Nutrition* 2017;35:151-160.
33. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. *Arch Surg*. 1996;131(10):1043-1047.

34. Schuetz P, Fehr R, Baechli V, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet*. 2019;393:(10188):2312-2321.
35. Owers EL, Reeves AI, Ko SY, et al. Rates of adult acute inpatients documented as at risk of refeeding syndrome by dietitians. *Clin Nutr*. 2015;34:(1):134-139.
36. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003;22:(3):235-239.
37. Walmsley RS. Refeeding syndrome: screening, incidence, and treatment during parenteral nutrition. *J Gastroenterol Hepatol*. 2013;28(suppl 4):113-117.
38. Nunes G, Brito M, Santos CA, Fonseca J. Refeeding syndrome in the gastroenterology practice: how concerned should we be? *Eur J Gastroenterol Hepatol*. 2018;30:(11):1270-1276.
39. Friedli N, Stanga Z, Culkin A, et al. Management and prevention of refeeding syndrome in medical inpatients: an evidence-based and consensus-supported algorithm. *Nutrition*. 2018;47:13-20.