Nutrition 30 (2014) 524–530

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

# Safe refeeding management of anorexia nervosa inpatients: an evidence-based protocol

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ARTICLE INFO

*Article history:*
Received 3 July 2013
Accepted 3 September 2013

*Keywords:*
Anorexia nervosa
Refeeding syndrome
Refeeding
Complications
Mortality

ABSTRACT

*Objective:* Anorexia nervosa is associated with several serious medical complications related to malnutrition, severe weight loss, and low levels of micronutrients. The refeeding phase of these high-risk patients bears a further threat to health and potentially fatal complications. The objective of this study was to examine complications due to refeeding of patients with anorexia nervosa, as well as their mortality rate after the implementation of guidelines from the European Society of Clinical Nutrition and Metabolism.

*Methods:* We analyzed retrospective, observational data of a consecutive, unselected anorexia nervosa cohort during a 5-y period. The sample consisted of 65 inpatients, 14 were admitted more than once within the study period, resulting in 86 analyzed cases.

*Results:* Minor complications associated with refeeding during the first 10 d (replenishing phase) were recorded in nine cases (10.5%), four with transient pretibial edemas and three with organ dysfunction. In two cases, a severe hypokalemia occurred. During the observational phase of 30 d, 16 minor complications occurred in 14 cases (16.3%). Six infectious and 10 non-infectious complications occurred. None of the patients with anorexia nervosa died within a follow-up period of 3 mo.

*Conclusions:* Our data demonstrate that the seriousness and rate of complications during the replenishment phase in this high-risk population can be kept to a minimum. The findings indicate that evidence-based refeeding regimens, such as our guidelines are able to reduce complications and prevent mortality. Despite anorexia nervosa, our sample were affected by serious comorbidities, no case met the full diagnostic criteria for refeeding syndrome.



## Introduction

In literature on anorexia nervosa (AN), psychosocial therapy often is the focus of attention, whereas treatment options for avoiding refeeding syndrome (RFS) and its complications are described by few [1,2]. AN is a lifelong illness with frequent relapses, and has two distinct subtypes: Restrictive and binge eating or purging [3]. The latter is characterized by self-induced vomiting and misuse of laxatives and diuretics [4]. According to a recent survey of 10 038 adults, the prevalence of AN in Switzerland is 1.2% for women and 0.2% for men [5]. AN is associated with several complications related to malnutrition, energy restriction, and severe weight loss [1,6]. Substance abuse,

The study was supported by research funds from the Department of General Internal Medicine of the University Hospital of Bern, Switzerland. MH and AP conceived and designed the study, analyzed and interpreted the data, and assisted in the drafting of the article. MJ analyzed and interpreted data, assisted in drafting the article, and revised it critically for important intellectual content. RO acquired, analyzed, and interpreted the data. FH acquired the data and assisted in drafting of the article. ML acquired data and assisted in drafting the article. RvK interpreted the data and assisted in drafting the article. ZS conceived and designed the study, analyzed, and interpreted the data, assisted in drafting the article, and revised it critically for important intellectual content. All authors approved of the final version of the article. None of the authors has a conflict of interest to declare.

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http://dx.doi.org/10.1016/j.nut.2013.09.019

**Table 1**
Risk factors for refeeding syndrome [17]

| One of the following | Two of the following |
|---|---|
| BMI <16 (kg/m$^2$) | BMI<18.5 (kg/m$^2$) |
| Unintentional weight loss >15% in preceding 3–6 mo | Unintentional weight loss >10% in preceding 3–6 mo |
| Very little or no nutritional intake for more than 10 d | Very little or no nutritional intake for more than 5 d |
| Low levels of serum potassium, phosphate or, magnesium before feed | History of alcohol or drug abuse |

BMI, body mass intake

as well as the amount of weight loss and the chronicity of the illness, are main risk factors for the development of complications [7,8].

Specific medical complications in AN (e.g., weight <70% of ideal weight, acute medical complications of malnutrition, bradycardia <30 beats/min, unstable vital signs, marked dehydration) require inpatient treatment in a combined internal medicine and psychosomatic unit [9]. In accordance with current guidelines, nutritional rehabilitation is one important aspect of Bern University Hospital's multimodal team approach to successfully treat inpatients with AN [2,10,11]. Behavioral therapy, psychotherapy, and incorporation of the family in the recuperation process are further important parts of the treatment.

Early nutritional replenishment with appropriate macro- and micronutrient intake and following weight gain is key in reducing AN morbidity and mortality [12]. The refeeding (RF) phase, however, poses a high risk for life-threatening and potentially fatal complications [2,11]. RFS is characterized by the occurrence of thiamine deficiency, fluid and electrolyte shifts, and their associated complications during nutritional rehabilitation [13]. It has been demonstrated that AN inpatients with phosphate levels <0.32 mmol/L during the RF phase were at higher risk for severe complications, which can lead to widespread dysfunction of cellular processes affecting almost every physiological system [14]. The most important issue concerning RFS prevention is to expect it, as its onset can be very rapid, sometimes within hours of RF. Common aggravating factors include severe malnutrition and overaggressive nutritional support in the early stages without adequate supplementation of micronutrients. Symptoms are observed generally within 3 d - after starting food intake and normally last no longer than 10 d [2,11,14,15].

Based on our long-term clinical experience, as well as on evidence-based literature, we developed guidelines for the prevention and management of the RFS in patients at risk, in collaboration with an international working group of specialists [2]. The guidelines (Table 2) also were adopted by the European Society of Clinical Nutrition and Metabolism (ESPEN) in 2011 [11].

**Table 2**
Guidelines for management of refeeding syndrome in adult patients at risk [2,11]

General recommendations

- Be aware of patients at risk
- Provide adequate assessment, interdisciplinary care plans, and follow-up
- Appreciate that risks apply whether patients are fed by oral, enteral, or parenteral route
- Carefully restore circulatory volume: monitor heart rate and fluid balance
- Energy intake should be instituted carefully and gradually increased over 1–10 d
- Empirical supplementation of electrolytes and vitamins should be started before feeding is initiated

| Days | Energy (by all routes; daily) | Electrolytes/vitamins/minerals | Fluids/sodium | Monitoring |
|---|---|---|---|---|
| 1–3 | 10 kcal/kg* and slowly increase to 15 kcal/kg* | Prophylactic electrolyte supplementation (unless prefeeding serum levels are high):<br>• Phosphate 0.5–0.8 mmol/kg daily<br>• Potassium 1–2.2 mmol/kg daily<br>• Magnesium 0.3–0.4 mmol/kg daily<br><br>Supplement micronutrients:<br>• 200–300 mg thiamine IV 30 min before first eating, and then 200–300 mg IV or PO daily<br>• Vitamins: 200% of RDI<br>• Minerals and trace elements: 100% of RDI (no iron supplementation in week 1) | Restrict daily fluids to 20–30 mL/kg (restrict to sufficient to maintain renal function, to replace deficits or losses, and to avoid weight gain → zero fluid balance)<br>Salt: restrict daily sodium intake <1 mmol/kg (if edema develops, restrict further) | Serum electrolytes (K, Mg, PO4) and glucose:<br>• Day 1: 2×/d<br>• Days 2-3: 1×/d<br><br>Monitor daily:<br>• Body weight (fluid balance)<br>• Clinical examination†<br>• Biochemistry‡<br>• Preferably ECG monitoring in severe cases |
| 4–6 | 15–20 kcal/kg* | Continue electrolyte supplementation to restore normal serum levels:<br>• If phosphate <0.6 mmol/kg daily → give 30–50 mmol phosphate IV over 12 h<br>• If potassium <3.5 mmol/kg daily → give >20–40 mmol KCl IV over 4-8 h<br>• If magnesium <0.5 mmol/kg daily → give 24 mmol MgSO4 IV over 12 h<br><br>Supplement micronutrients:<br>• Vitamins: 200% of RDI<br>• Minerals and trace elements: 100% of RDI (no iron) | Fluids 25–30 mL/kg daily (maintain zero fluid balance) | Serum electrolytes:<br>• 1×/d<br><br>Monitor daily:<br>• Body weight (fluid balance)<br>• Clinical examination†<br>• Biochemistry‡ |
| 7–10 | 20–30 kcal/kg* | Electrolyte, mineral, trace element, and vitamin substitutions as above.<br>Iron should be supplemented from day 7 onward. | Fluids 30 mL/kg daily | Body weight: 2×/wk<br>Clinical examination†: 1×/d<br>Biochemistry‡: 1×/wk |

ECG, electrocardiogram; IV, intravenous; PO, orally; RDI, dietary reference intake
* Nutrients: carbohydrates 50–60%, fat 30–40%, and protein 15–20%.
† Edema, blood pressure, heart rate, cardiovascular and respiratory systems.
‡ Phosphate, magnesium, potassium, sodium, calcium, glucose, urea, creatinine (thiamine: optional on day 1).

The year before the introduction of our new guidelines for the management of the RFS, we registered several patients with major complications (pulmonary edema, left ventricular heart failure, severe dyselectrolytemia, severe hypertransaminasemia, severe arrhythmia, symptoms of Wernicke encephalopathy) requiring stays in the intensive care unit (ICU) and two deaths resulting from fluid and salt overload in the RF phase. The aim of this study was to evaluate the effectiveness of the implemented guidelines, regarding complications and mortality in a sample of inpatients with AN during nutritional replenishment and with a follow-up period of 30 d.

## Materials and methods

### *Study design and patient selection*

This article describes a retrospective, observational case study of a cohort of patients with AN from Bern University Hospital (Department of Internal Medicine, Division of Psychosomatic Medicine). At admission, all patients with AN sign a contract including an individually tailored multimodal treatment program, that contains four main parts: 1) RF phase, 2) motivation and objective setting, 3) personal responsibility and sense of self, and 4) discharge preparation and organization of further treatment. Every week new goals are agreed on and integrated into the contract. The length of the program is 6 wk, but might change on an individualized basis in agreement with the medical staff.

In this study, all AN patients aged >16 y were included, if they met the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision, and had been hospitalized for multimodal AN therapy between January 2007 and December 2011 [4]. Patients who did not sign the multimodal treatment contract or who were younger than age 16 were excluded.

### *Data collection*

Data were extracted from paper and electronic medical records. We documented reason for admission, relevant medical history, demographic characteristics, and anthropometric and clinical data at hospital admission. Body mass index (BMI) was calculated as weight divided by height (kg/m$^2$). Energy intake (kcal/kg), liquids, and electrolyte substitutions were recorded during hospital stay. Ideal body weight was calculated based on height minus 100, multiplied by a sex factor (0.85 for women and 0.90 for men). Nutritional risk was assessed based on the international validated Nutrition Risk Screening System 2002 [16].

Hematologic and biochemical analyses were performed in the hospital's central laboratory with common methods, using reference measurements from the Department of Clinical Chemistry. Laboratory data were evaluated on days 1, 2, 9, and 30. In the electrocardiogram (ECG) on admission, the corrected QT interval (QTc) was defined as long at >440 ms for men and >460 ms for women. Bradycardia was defined as a resting heart rate <60 beats/min. Arterial hypotension was defined as systolic blood pressure <90 mm Hg.

### *Refeeding syndrome*

The RFS was defined using the three-faced diagnostic criteria previously developed (Fig. 1) [15]. Diagnosis of RFS was confirmed when all three critical facets were met. Risk factors for RFS are outlined in Table 1 [17].

### *Multimodal treatment*

After admission, a multidisciplinary and an interprofessional team, consisting of specialists in the field of psychosomatics, psychiatry, internal medicine, clinical nutrition, dietetics, psychology, recreational therapy, and physical therapy assessed all patients.

### *Nutritional replenishment therapy*

Nutritional replenishment therapy (energy and protein supply), fluids administration, electrolyte, and micronutrient supplementation were started on day 1 for a duration of 10 d (days 1–10), according to the ESPEN guidelines (Table 2) [2,11].

### *Adapted classification of complications*

The type and severity of complications that might occur during the RF phase were classified through adaptation of previous recommendations [18]:

Grade I Complications requiring deviation from the normal RF regimen, but without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions.
Allowed therapeutic regimens are electrolytes, multivitamins, thiamine supplementation (orally or intravenously as short-term infusion), oral nutritional supplements, enteral nutrition, psychotherapy, and physiotherapy, all of which are part of normal treatment and not necessary signs of complications.
Grade II Requiring pharmacologic treatment with drugs. Among them are therapeutically applied saline and/or glucose infusions (e.g., in symptomatic hypovolemia). Indication to switch from oral or enteral nutrition to total parenteral nutrition during hospital stay.
Grade III Complications requiring surgical, endoscopic, or radiologic interventions (with or without anesthesia), or prolongation of hospitalization due to grade II complications.
Grade IV Life-threatening complications (such as stroke, myocardial infarction, severe arrhythmia), or complications requiring intermediate/ICU management, single-organ dysfunction (including dialysis), and multiorgan dysfunction.
Grade V Death.

Complications data were reported during the 30-d observational period. Mortality rates were observed during a 3-mo follow-up period. Patients who left the program earlier were seen in the outpatient clinic or received follow-up calls.

### Ethical approval

The research was approved by the ethical committee of the University of Bern and State of Bern.

### *Statistical analysis*

The statistical assessment was performed with SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Continuous data was reported as means with SD. Some of the laboratory parameters were skewed (more than 3 SD away from the mean), and therefore these data were expressed as median with interquartile range (IQR). Categorical variables such as characteristics and morbidities were reported as counts (percentages). Statistically significant ($P < 0.05$) BMI and weight gain during hospitalization, were assessed with paired Student's $t$ test, whereas differences between BMIs of subgroups were analyzed with independent Student's $t$ tests, applying Levene's test for homogeneity of variances.

## Results

### *Patient characteristics*

The cohort consisted of 65 patients; of these, 14 were admitted more than once for different episodes of macro- and micronutrient replenishment during the study period. As a result, a total of 86 cases (100%) were analyzed. At admission, all patients committed to an individual multimodal treatment program. In the 3-mo follow-up period, the patients were monitored clinically (inclusive anthropometric parameters and psychological status) and through laboratory data in 14- to 28-d intervals by general practitioners or the specialized physicians in close collaboration with our medical team. During the follow-up period, no complications or deaths occurred and no rehospitalizations were needed. In nine cases (10.5% drop-out), the contract was violated after the RF phase, when the patients left the program after an average of 13.7 d. Due to the fact that all left after the RF phase and follow-up was successful, their data was incorporated in this study. Two of the nine patients in the drop-out group were readmitted four times, respectively, 9 mo later because of persistent catabolic state. No major complications or deaths were observed in this group.

The median hospital length of stay for all 86 cases was 49.5 d (IQR 52.3). The characteristics of the sample are shown in Table 3. All patients were malnourished (score ≥3) based on the validated Nutrition Risk Screening 2002 system [16]. Diagnosis and comorbidities of all cases are listed in Table 4. The median duration of a diagnosis of AN before hospital admission was 5 y (IQR 8.3).

Of all cases, 64 (74.4%) had a body weight <70% of ideal weight. At admission, patients with restrictive AN (66) had a

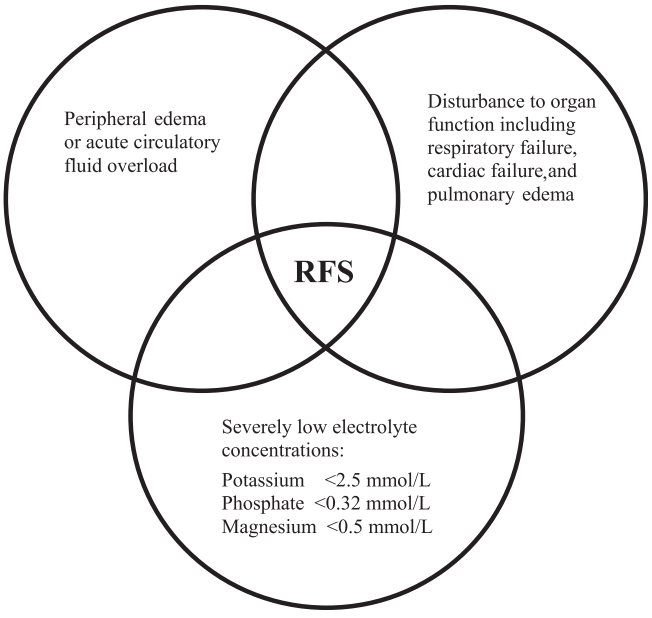


**Fig. 1.** The three critical facets defining a manifest refeeding syndrome (RFS) based on Rio et al. [15].

significantly lower mean BMI (13.2 ± 1.9 kg/m$^2$) than patients (20) with purging AN (15.4 ± 2.9 kg/m$^2$; $P < 0.001$; 95% confidence interval [CI], −3.4 to −1.0). BMI of patients (37) diagnosed with osteopenia or osteoporosis (12.7 ± 1.5 kg/m$^2$) was significantly lower than BMI of all other cases (14.0 ± 2.6 kg/m$^2$; $P = 0.039$; 95% CI, −2.5 to −0.1).

Within the first day of hospitalization, 66 (76.7%) of the cases received oral nutrition including snacks (i.e., fortified milk shakes, curd and fruits, cheese and bread); 7 (8.1%) received a combination of oral nutrition and oral supplements; 7 (8.1%) received a combination of oral nutrition and enteral feeding through a nasogastric tube (continuous over 24 h); 5 (5.8%) received enteral feeding; and 1 (1.2%) received a combination of oral and parenteral nutrition (continuously over 24 h). The single case receiving parenteral nutrition refused the insertion of a nasogastric tube. After the RF period with a given amount of administered nutrients based on our protocol, patients were encouraged to gradually increase oral intake. The mean total energy uptake rose from 437 to 1506 kcal/d and the mean liquid uptake increased from 1400 to 1550 mL/d during hospital stay in 77 cases (89.5%). After the refeeding phase, the general nutritional goal was to increase the energy intake according to the requirements and to maintain it. Therefore, nutritional protocols were periodically evaluated and if goals were not met the food components were adapted, fortified meals and oral nutritional supplements were served tailored to the patients' needs.

During the refeeding phase nearly all patients showed behavioral changes. We perceived psychosomatic symptoms mainly as discomfort on the emotional level as anxiety and confusion. Somatic complaints were a sense of overheating, fullness, bloating, abdominal distension, and abdominal cramps.

During the hospital stay mean body weight increased significantly from 37.9 ± 7.8 to 41.5 ± 7.1 kg ($P < 0.001$; 95% CI, −4.7 to −2.8) and BMI from 13.7 ± 2.4 to 15.0 ± 1.9 kg/m$^2$ ($P < 0.001$; 95% CI, −1.6 to −0.9). At discharge, restrictive AN cases still had a significantly lower mean BMI (14.6 ± 1.7 kg/m$^2$) than purging AN cases (16.1 ± 2.4 kg/m$^2$; $P = 0.002$; 95% CI, −2.4 to −0.6). Of all cases 50 (58.2%) were discharged to home, 34 (39.5%) to an institution/therapeutic living situation, and 2 (2.3%) to a peripheral hospital.

**Table 3**
Characteristics of observed cases at admission (N = 86)

| Characteristics | Data |
|---|---|
| Demographics | |
| Cases, N (%) | 86 (100) |
| Patients, n (%) | 65 (100) |
| Women, n (%) | 80 (93.0) |
| Men, n (%) | 6 (7.0) |
| Age (y) | 27.9 ± 9.5 |
| Body weight (kg) | 37.9 ± 7.8 |
| BMI (kg/m$^2$) | 13.7 ± 2.4 |
| History of AN | |
| Age at AN onset (y) | 19.8 ± 7.5 |
| Restrictive AN, n (%) | 66 (76.7) |
| Purging AN, n (%) | 20 (23.3) |
| Electrocardiogram | |
| Bradycardia, n (%) | 31 (36.0) |
| Abnormal repolarization, n (%) | 10 (11.6) |
| Long-QTc time, n (%) | 2 (2.3) |

AN, anorexia nervosa; BMI, body mass index

**Table 4**
Comorbidities registered at admission

| Comorbidities* | n (%) |
|---|---|
| Depression | 47 (54.7) |
| Osteopenia/osteoporosis | 37 (43.0) |
| Socioemotional problems | 21 (24.4) |
| Pretibial edema | 8 (9.3) |
| Anemia | 4 (4.7) |
| Cannabis and/or alcohol abuse | 3 (3.5) |
| Heart failure (cardiac ejection fraction ≈40%) | 2 (2.3) |
| Hypertension | 2 (2.3) |
| Diuretics and laxative abuse | 2 (2.3) |
| Severe hypophosphataemia (<0.32 mmol/L) | 1 (1.2) |
| Urinary infection | 1 (1.2) |
| Pneumonia | 1 (1.2) |
| Pneumothorax | 1 (1.2) |
| Polyneuropathy | 1 (1.2) |
| Chronic hepatitis C | 1 (1.2) |
| Atopic dermatitis | 1 (1.2) |

* More than one comorbidity per case possible.

### *ECG and laboratory measurements*

The ECGs at hospital admission were abnormal (bradycardia, abnormal repolarization, or long-QTc time) in 43 (50%) cases (see Table 2); of these cases, only 2 (2.3%) had long-QT intervals. The mean QT interval was 391 ± 31.6 ms (range 307–460 ms).

At admission, we registered 26 (30%) cases with high levels of aspartate aminotransferase (AST; max. 903 U/L) or alanine aminotransferase (ALT; max. 1017 U/L), or both. The increased transaminase levels improved in all cases and normalized in 16 within the first 30 d of hospitalization; however, the remaining 10 cases had persistently high transaminase levels at the end of the 30-d observation (AST max. 74 U/L; ALT max. 106 U/L). At admission, 31 (36%) patients had glycemic concentrations of <4 mmol/L, and all patients had thyroid-stimulating hormone levels within normal ranges.

### *Electrolytes and substitution*

Cases with dyselectrolytemia at admission and during the RF phase are listed in Table 5. During the RF phase, two cases (2.3%) showed severe hypokalemia (<2.5 mmol/L); none of the cases

**Table 5**
Cases with dyselectrolytemia on admission and during the refeeding phase

| Dyselectrolytemia | Admission | Day 1 | Day 2 | Day 9 |
|---|---|---|---|---|
| Hypophosphatemia, n (%) | 5 (5.8) | 4 (4.7) | 6 (7) | 6 (7) |
| Range (mmol/L) | 0.79–0.30 | 0.70–0.42 | 0.82–0.42 | 0.83–0.49 |
| Hypokalemia, n (%) | 17 (19.8) | 17 (19.8) | 9 (10.5) | 6 (7) |
| Range (mmol/L) | 3.4–1.8 | 3.4–2.1 | 3.4–2.5 | 3.4–3.1 |
| Hypomagnesemia, n (%) | 6 (7) | 4 (4.7) | 5 (5.8) | 3 (3.5) |
| Range (mmol/L) | 0.70–0.60 | 0.57–0.69 | 0.74–0.61 | 0.56–0.66 |

showed severe hypophosphatemia (<0.32 mmol/L) or severe hypomagnesemia (<0.5 mmol/L) as defined previously [15]. During RF, 41 (47.7%) cases received potassium (32 orally, 5 combined orally/intravenously, 1 intravenously), 28 (32.6%) received phosphate (25 orally, 1 combined orally/ intravenously, 2 intravenously), and 35 (40.7%) received magnesium (32 orally, 1 combined orally/intravenously, 2 intravenously). There was no need for supplementation of potassium in 45 patients (53.3%), phosphate in 57 (66.3%), or magnesium in 46 (53.5%). Mean values of the laboratory parameters during the observational period of 30 d are listed in Table 6. After the RF phase through day 30 of treatment, one patient received a combined substitution of phosphate and magnesium; three were substituted orally with magnesium, three with phosphate, and nine with potassium.

*Refeeding-related complications*

None of the 86 cases developed RFS based on an earlier definition (Fig. 1) [15]. However, complications in association with RFS were recorded in nine cases (10.5%): In four cases (4.7%) we observed transient pretibial edemas as soon as RF was started; in three cases (3.5%) a disturbance in organ function (transient mild pancreatitis, transient kidney failure stage 2, and urinary tract infection); and in two cases (4.7%) a severe hypokalemia <2.5 mmol/L. We did not observe severe hypophosphatemia (<0.32 mmol/L) or hypomagnesemia (<0.5 mmol/L) during RF. The persistently high transaminases in 10 cases (11.6%), mentioned previously, were not associated with RFS (see Discussion). In the two cases with preexisting cardiac failure (cardiac ejection fraction ≈40%, measured by ultrasound) the RF phase slightly increased severity of the underlying disease.

*Total complications*

During the observational period 30 d, a total of 16 grade I and II complications occurred in 14 cases (16.3%) (Table 7). No grade III, IV, and V complications were recorded [18]. No sex differences were observed. In two cases (2.3%) we found more than one complication. In total, 6 infectious and 10 non-infectious complications were registered (RFS-associated complications included).

Description of the complications: One case (1.2%) developed a urinary tract infection and a consequent slight transient kidney failure (stage 2, lowest creatinine clearance: 61 mL/min). Another case (1.2%) suffered from an upper arm fracture after a short syncope and had a concomitant phlegmon at the trauma site. Two further cases (2.3%) manifested superficial skin abscesses, one case (1.2%) an uncomplicated osteomyelitis of the tibia, one case (1.2%) a transient mild pancreatitis, and one case (1.2%) a self-limiting hematothorax that occurred during the insertion of a central venous catheter at admission. The two cases (2.3%) with preexisting cardiac failure suffered additional complications: One case (1.2%) developed aspiration pneumonia, and the other (1.2%) developed pretibial edemas. Three additional cases (3.5) manifested pretibial edema and two (2.3%) severe hypokalemia during the RF phase, as mentioned previously. All infectious complications, except the superficial skin abscess/ phlegmon, were treated with antibiotics at the ward. None of the patients had to be transferred to the intermediate care unit or ICU, and no one died during a follow-up phase of 3 mo.

## Discussion

After admission, all patients were assessed by a multimodal treatment team. The drop-out rate of only 10.3% in our sample in the short follow-up period of 3 mo, compared with other programs with 20% to 40% dropouts, is a good indicator for the success of the multimodal treatment approach at our institution; although comparisons are difficult due to different populations, treatments, duration, and drop-out criteria [19].

Sex, age, and BMI were similar to comparable samples from the literature [20,21]. In the presented cases, the BMI of patients with the purging type of AN was significantly higher than that of the restricting group, a perception that is supported by the literature [22]. AN cases with osteopenia or osteoporosis in our sample had a clearly lower average BMI compared with the average of non-affected cases [23].

Substance abuse (cannabis, alcohol, diuretics, and/or laxatives) was reported in five cases (5.8%) only, whereas in other AN study samples it was a common problem and strong predictor of mortality [7,23]. Additionally, legal and illegal drugs may have an accelerated negative effect on health, due to a reduced overall health status [24].

**Table 6**
Laboratory parameters during the observational period of 30 d (N = 86)

| Parameter | Day 1 | Day 2 | Day 9 | Day 30 | Normal serum ranges* |
|---|---|---|---|---|---|
| Sodium† | 137.8 ± 5.5 | 138 ± 4.8 | 140 ± 3.1 | 140 ± 3.3 | 132–142 mmol/L |
| Potassium† | 3.82 ± 0.51 | 3.83 ± 0.64 | 3.97 ± 0.39 | 3.94 ± 0.44 | 3.5–4.7 mmol/L |
| Phosphate† | 1.15 ± 0.24 | 1.08 ± 0.24 | 1.12 ± 0.25 | 1.21 ± 0.24 | 0.84–1.45 mmol/L |
| Magnesium† | 0.86 ± 0.01 | 0.87 ± 0.14 | 0.84 ± 0.09 | 0.84 ± 0.07 | 0.75–1.00 mmol/L |
| AST‡ | 28 (9–1017) | 29 (12–937) | 30 (13–379) | 23 (12–74) | <35 U/L§; <50 U/L‖ |
| ALT‡ | 25.5 (9–903) | 24.5 (10–777) | 28 (7–487) | 25.5 (9–155) | <35 U/L§;<50 U/L‖ |
| Alkal. phosphatase‡ | 51.5 (24–557) | 49.0 (21–501) | 47.0 (19–405) | 56.0 (22–223) | 35–103 U/L§; 40–130 U/L‖ |
| γ-GT‡ | 23.5 (8–529) | 28 (8–311) | 29 (7–579) | 23.5 (5–100) | 5–36 U/L§; 8–61 U/L‖ |
| Glucose† | 4.2 ± 0.75 | 4.12 ± 1.10 | 4.80 ± 1.56 | 4.43 ± 0.43 | 3.33–5.55 mmol/L |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma-glutamyltransferase
* Normal serum ranges based on the Clinical Chemistry Department of the University Hospital of Berne.
† Mean and SD.
‡ Median and range.
§ Values for female patients.
‖ Values for male patients.

At admission we found elevated concentrations of liver transaminases in 26 cases (~30%). This prevalence is in line with the literature [25]. The hypertransaminasemia was improved in all 26 cases during nutritional repletion therapy and normalized in 16 (60.2%) by day 30. The pathophysiological mechanism of high levels of AST and ALT in severely malnourished AN patients is multifactorial. Nonalcoholic steatohepatitis is one of the most common reasons for elevated transaminases [26]. Furthermore, abnormal transaminases can be caused by hepatic hypoxia, due to decreased portal pressure associated with a lower cardiac output [25]. Additionally, the glycogenic depletion and the general breakdown of tissues can lead in some patients to self-digestion of the liver [27].

In the literature, hypoglycemic serum levels are described as typical in AN, due to the glycogenic depletion. One study showed a prevalence of hypoglycemia in 44% of cases [20]. In our sample, 36% of the cases showed serum glucose levels <4 mmol/L at admission.

Contrary to our sample in which only two cases showed a prolonged QTc-time, a Japanese group found significantly longer QT-intervals and extensions in a majority of their patients with AN [28].

The ESPEN guidelines that helped determine our institution's treatment strategy, likely contributed to the positive effect of our approach [2,11]. The daily supervision of RF management may have contributed to low numbers of complications (Table 7). One of the important factors during the nutrient replenishment phase is the challenge of potential dyselectrolytemia that may occur within the first 10 d. Because our guidelines (Table 2) are geared toward the prevention of dyselectrolytemia through the precautional substitution with electrolytes, despite normal levels and ahead of RF, we did detect only two severe electrolyte deficiencies (hypokalemia <2.5 mmol/L; 2.3%) during the vulnerable RF phase. In our sample, 23 cases (26.7%) showed mild to moderate low levels of potassium, phosphate, or magnesium during day 1 of RF, which gradually normalized within the next few days.

Two previous studies [14,20] described a prevalence of 45% and 28% of RF-related hypophosphatemia in similar samples. In our sample, we solely observed a pathologically low level of serum phosphate in 4.7%, which supports the positive influence of our guidelines. This is likely due to an early and sufficiently high substitution and slow progression of renourishment as outlined in Table 2.

Compared with the literature, we registered considerably fewer RF-related complications. We believe the limitation of sodium on a daily basis (<1 mmol/kg) and fluids before starting the replenishment phase is a key factor in the reduction of edemas due to slow weight gain. Newer data indicate that sodium limitation should be extended longer, up to a BMI of 15 to 16 kg/m$^2$ [21]. Surprisingly, in one study no edemas occurred in patients with AN (BMI 11.3 ± 0.7 kg/m$^2$; nutritional support: High protein-caloric enteral formula or oral supplements), although replenishment was performed on a relatively fast track without any sodium restriction. However, the weight gain of 1.2 ± 1.3 kg within the first 7 d indicates that water retention was probably overlooked in that sample. In contrast, our cases had a high rate of preexisting comorbidities, not seen in a previous sample [29].

In our population, no major complications (grade III or IV) or deaths were registered [18]. During the observational period of 30 d, 16 grade I and II complications occurred in 14 cases (16.3%) (Table 7). Six infectious and 10 non-infectious complications were registered. During nutrient and fluid replenishment, we observed four cases (4.6%) with transient pretibial edemas as clinical signs related to the RFS. In our sample, two cases with preexisting cardiac failure showed more than one grade II complication. This demonstrates the prognostic value of serious concomitant morbidities. These high-risk patients need daily, close-meshed clinical checkups during the nutrient replenishment phase. Fluids and sodium restriction must be carefully monitored to avoid fluid overload, and consequently a critical increase of the extracellular volume. The infectious complications seen in our cases are probably more associated to the manifest severe protein–energy malnutrition, which alters the cellular and the humoral immune system than to the RFS [30]. Some of the complications are attributable to AN; others are not directly related to the underlying disease, such as upper arm fracture, self-limiting hematothorax, osteomyelitis, or aspiration pneumonia.

**Table 7**
Complications and mortality data during the 30-d observational period (N = 86)

| Total complications | n (%) |
|---|---|
| Total cases with complications* | 14 (16.3) |
| Infectious complications | 6 (7.1) |
| Abscess/phlegmon | 3 (3.5) |
| Aspiration pneumonia | 1 (1.2) |
| Urinary tract infection† | 1 (1.2) |
| Oesteomyelitis (tibia) | 1 (1.2) |
| Non-infectious complications | 10 (11.7) |
| Transient pretibial edemas† | 4 (4.6) |
| Hypokalemia <2.5 mmol/L† | 2 (2.3) |
| Transient kidney failure, stage 2† | 1 (1.2) |
| Transient mild pancreatitis† | 1 (1.2) |
| Fracture (upper arm) | 1 (1.2) |
| Hematothorax | 1 (1.2) |
| Total cases of mortality‡ | 0 (0) |

* Total of 16 complications in 14 cases (2 cases manifested >1 complication).
† Associated with refeeding syndrome.
‡ Follow-up period of 3 mo.

In comparison to our unpublished data gained in the years before the introduction of the evidence-based RF guidelines (two deaths and several major complications requiring ICU stay), the data presented here show that seriousness and rate of complications during the replenishment phase in frail and vulnerable AN patients with serious comorbidities can be held to a minimum. Therefore, it can be stated, that RF management of AN inpatients by this evidence-based protocol is safe [11].

The limitations of the study are the retrospective data collection that relies on accuracy of record charts written by the medical staff. Moreover, we performed only clinical anthropometric parameters without bioimpedance measurements of the body composition.

## Conclusions

This data indicate that evidence-based RF regimens are able to avoid mortality and reduce RFS-related complications to a minimum in high-risk patients with AN [2]. Additionally, complications among our patient cohort were limited to those of only minor severity, with no patients suffering severe complications or death [18].

## Acknowledgments

The authors acknowledge Dr. Thomas Fischer for his support in collecting data.

All authors declare that this work has been composed by themselves, and describes their own work, unless otherwise acknowledged in the text. All sentences or passages quoted in this paper from other people's work have been specifically acknowledged by clear cross-referencing to author, work and page(s). All authors have participated sufficiently, intellectually

or practically, in the present work and take public responsibility for the content of the article.

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