Revisiting the Refeeding Syndrome:

Results of a Systematic Review

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Abstract

Introduction:

Although described more than 70 years ago, the refeeding syndrome remains understudied with lack of standardized definition and treatment recommendations. The aim of this first systematic review was to gather evidence regarding standardized definition, incidence rate and time course of occurrence, association with adverse clinical outcomes, risk factors and therapeutic strategies to prevent or treat this condition.

Methods:

We searched MEDLINE and EMBASE for interventional and observational clinical trials focusing on refeeding syndrome, excluding case reports and reviews. We extracted data based on a predefined case report form and assessed bias.

Results:

Out of 2207 potential abstracts, 45 records with a total of 6608 patients were included (3 interventional trials, 16 studies focusing on anorexic patients). Definitions for refeeding syndrome were highly heterogeneous with most studies relying on blood electrolyte disturbances only and others also including clinical symptoms. Incidence rates varied between 0% and 80% depending on the definition and patient population studied. Occurrence was mostly within the first 72 hours of start of nutritional therapy. Most of the risk factors were in accordance with NICE guidelines, with older age and enteral feeding being additional factors. There was no strong evidence regarding associations of refeeding syndrome and adverse outcomes, as well as regarding preventive measures and treatment algorithms.

Discussion:

This first systematic review focusing on refeeding syndrome found consensus regarding risk factors and timing of occurrence, but wide variations regarding definition, reported incidence rates, preventive measures and treatment recommendations. Further research to fill this gap is urgently needed.

Keywords: Nutritional therapy, nutritional support, hypophosphatemia

Introduction

Disease-related malnutrition is a common condition in medical and surgical inpatients and is associated with detrimental clinical outcomes including mortality, complications and prolonged hospital stay [1-3]. Instigating nutritional therapy is commonly recommended in malnourished patients in order to prevent these adverse outcome, although large clinical trials demonstrating benefit in the polymorbid inpatient population are largely lacking [4-6]. A potential risk of nutritional therapy in malnourished patients is the refeeding syndrome (RFS) with electrolyte disturbances leading to clinical deterioration and possible sudden cardiac death [7, 8]. Yet, as of today, the importance of the RFS in the polymorbid inpatient population is understudied lacking a common definition and treatment recommendation.

For the first time, RFS was described in prisoners liberated from concentration camps at the end of World War II after a long period of starvation. Despite allegedly adequate nutritional support these prisoners showed an unexpectedly high mortality rate of up to 20% [9, 10]. To date the pathophysiology of RFS is still incompletely understood. Proposed mechanisms include starvation and catabolic state-induced reduction in insulin and increased glucagon secretion [11] with resulting activated gluconeogenesis and proteolysis, as well as depletion of intracellular vitamin and electrolyte supplies [12, 13]. After the initial start of nutritional intake in patients in such a starved and catabolic state, glucose concentration and insulin secretion rises suddenly leading to an overwhelming shift in electrolytes with increased sodium and water retention and extracellular volume expansion [11]. The potential clinical consequences are volume overload with risk of heart failure and peripheral edema [14], as well as transcellular shift and redistribution of phosphate, potassium and magnesium[15] with life-threatening complications such as spasm, or cardiac arrhythmias [12, 15-17]. Additionally the hypophosphatemia also affects the phosphate-dependent ATP production [18, 19], resulting in possible muscle weakness, rhabdomyolysis, and impaired hematopoiesis with symptoms of anemia and reduced oxygen supply [12].

Numerous reviews regarding RFS have been published focusing each on specific aspects of RFS. Yet, there is lack of a systematic literature search to better understand the current state of knowledge regarding RFS. The aim of this first systematic review was to provide evidence in regard to a standardized definition,

incidence rate and time course of occurrence, association with adverse clinical outcome, risk factors and therapeutic strategies to prevent or treat this condition in adult or adolescent patients.

Methods

Study objectives

This systematic review adheres to the PRISMA guidelines [20]. Our aim was to investigate the importance of the RFS in adult or adolescent patients. Particularly we focused on the following six research questions:

- I. *What are the definitions used for RFS?*
- II. *What is the incidence of RFS?*
- III. *When does RFS occur?*
- IV. *Is RFS associated with adverse clinical outcome?*
- V. *What are the risk factors for RFS?*
- VI. *What are therapeutic strategies to prevent or treat RFS?*

Eligibility Criteria

Randomized clinical and observational studies investigating refeeding and RFS in anorexic and non-anorexic adult or adolescent patients (medical and surgical), were considered eligible for this review. There was no restriction in regard to publication date. We did not include case reports, narrative reviews, audits, surveys, animal studies and unpublished records. Also, we excluded studies with pediatric and neonate patient populations.

Information sources and search strategy

Electronic libraries were searched in order to identify all abstracts written in English. The search was performed with MEDLINE and EMBASE library and in cooperation with a subject specialist in Medicine & Life Sciences of the University Library of the University of Basel. The searches were performed using keyword search and also Mesh Term search, they were run on 20th, 23rd and 27th of March 2015. Two updated searches were performed in mid-September and mid-December 2015.

The following search terms were used to perform the literature search in the two databases: “refeeding”, “NOT review”, “NOT child”, “NOT children”, “NOT neonates” “NOT neonatal”, “NOT animal”, “English”. The full electronic search protocol is presented in **Appendix 1**.

Study selection and data collection process

Eligibility assessment was performed by one of the authors (NF) in discussion with the study team. All search results were assessed by short review of abstracts. Records, which did not meet our inclusion criteria, were excluded. For data extraction a predefined case report form (**Appendix 2**) was used after undergoing a testing period. During the process of data extraction, the individual risk of bias of each study was assessed. Final extraction results were checked and discussed among the research team. We also contacted authors from abstracts and posters for international congresses by email to obtain final reports and further information.

From each included trial we extracted the following information: (1) name, year and title of the trial, (2) number of included patients and patients characteristics (e.g. whether patients were anorectic or not, adult or elderly patients, oral, enteral or parenteral refeeding, state of illness, reason for hospital admission, etc.), (3) definition of RFS if used, (4) methods including inclusion and exclusion criteria, (5) outcome measures, (6) main results including information concerning our main investigation questions, (7) conclusions, (8) limitations and (9) information about the nutritional treatment consisting of energy, protein, electrolytes, fluids, micronutrients, days and rate of nutritional rehabilitation.

We reported phosphate, potassium and magnesium in mmol/L (1mg/dl phosphate equals 0.323mmol/L phosphate, 1mg/dl potassium equals 0.256mmol/L potassium and 1mg/dl magnesium equals 0.411 mmol/L magnesium).

Risk of Bias Assessment of Individual Studies and across studies

In order to assess the risk of bias we conducted an evaluation for each single trial using the SIGN checklists [21] for bias assessment (**Appendix 3/4**).

Data Synthesis and Analysis

Due to the lack of quantitative data and wide heterogeneity among trials we decided post-hoc not to perform a quantitative meta-analysis, but focused on presentation of data qualitatively corresponding to each of the objectives.

Results

Trials identified through the search strategy

Our systematic search identified 2910 titles and abstracts of potentially eligible studies through database searching. After duplicate removal, 2205 records were screened and 69 full texts were assessed for eligibility. Through two updated searches in mid-September and mid-December 2015 two additional studies were added. A total of 45 studies with a total of 6608 patients were included in the analysis including 3 interventional trials (**Figure 1**). A total of 16 studies focused on anorexic patients and 29 on non-anorexic patients.

Study characteristics and risk of bias

Most of the included studies were smaller, single-center studies including heterogeneous adult or adolescent medical or mixed medical/surgical patients with disease-related malnutrition. Studies were conducted between 1989 and 2015 in different countries (**Table 1**). In regard to bias assessment (**Appendix 3**), there was a high risk of bias resulting from the observational / retrospective study design used in most studies, as well as high risk for attrition bias due to incomplete outcome reporting. Also many trials did not deal with RFS as their main research aspect but reported RFS data as secondary aims.

Definitions and incidence rates for RFS

Among the 45 studies, 38 studies reported a definition for RFS (**Table 1**). Definitions were highly heterogeneous among studies with some studies only relying on electrolyte disturbances with again different cut-offs, and others also integrating clinical parameters into the definition. Most studies had hypophosphatemia, either as a cut-off or as a relative decrease from baseline, as part of the definition. Cut-offs used for hypophosphatemia differed among studies (the range varied from phosphate <1mmol/L and below normal range to <0.32 mmol/L or decreased rate from baseline >30% or >0.16mmol/L). Of note, the definition used by RIO's study [22] was later used by 2 other studies [23, 24]. Also Marik's [25] definition was reused by another study [26] and slightly adapted in 2 other studies [27, 28]. These definitions are thus the most commonly used definitions.

Incidence rates for RFS were highly dependent on the definition used and similar in anorexic and non-anorexic patient populations. As shown in **Table 1**, 11/32 studies (34%) did not find any patient with either signs or symptoms of RFS. These studies, however, used a more rigorous definition with clinical and electrolyte abnormalities. Incidences of up to 80% [29] were reported in studies using a broader definition based on electrolyte disturbances only.

Time course and association with adverse outcomes

Only 11 studies reported on the time point when RFS occurred (**Table 1**). In most of these studies, it occurred within the first 72 hours after start of nutritional therapy. Out of these 11 studies providing information regarding the timely occurrence of RFS, 7 used only hypophosphatemia as their definition criteria of RFS. Except for one, all studies reported that RFS occurred within 84 hours. Two studies using clinical symptoms for their definition reported time of occurrence of RFS within 24 hours and after 5 days, respectively.

A total of 11 studies reported outcomes in their RFS patient population compared to patients without RFS, mainly all-cause in hospital mortality and length of hospital stay (**Table 2**). Of 8 studies reporting mortality, 5 reported a tendency to higher mortality rates with one study finding a mortality rate of 71% in anorexic RFS patients from critical care [30]. However, these studies did not adjust for confounders and in most of these studies p-values were not reported or did not show a significant result. No association of RFS and mortality or a mortality rate of 0% was reported in the 4 remaining studies. A total of 4 studies reported LOS with all studies finding longer LOS in patients showing signs or symptoms of RFS. Again, no adjustment for confounding was done in these studies.

When separating studies based on the criteria used to define RFS, there was no differences regarding association of RFS and mortality. In all three definition groups (hypophosphatemia, electrolyte disturbances or clinical symptoms) some studies showed a mortality rate of 0% and others an increased risk of mortality in patients showing signs and symptoms of RFS. Of note, the highest mortality rate was reported in one study [30] using clinical symptoms as a definition criteria. Studies reporting on length of hospital stay used either hypophosphatemia or general electrolyte disturbances as definition criteria.

Risk factors for RFS

Several studies focused on risk factors for development of RFS (**Table 3 / 3a**). Most risk factors are in accordance with the NICE guidelines [31], i.e. low BMI, unintentional weight loss, starvation, history of alcohol abuse and low initial electrolyte concentrations. Most of the studies relying on NICE guidelines as risk factors for RFS used clinical symptoms as part of their RFS definition. Additionally to criteria included in the NICE guidelines, higher age was reported to be a risk factor in one study [32] and showed a non-significant trend in another study [27]. Other parameters not included in the NICE guidelines were low albumin or pre-albumin, higher nutritional intake during feeding, low insulin-like growth factor (IGF)-1, nutritional risk screening (NRS) 2002 [33] ≥ 3 points and enteral feeding as part of the nutritional therapy. A total of 3 studies did not validate the above risk factors to be associated with RFS. Of note, in two studies [34, 35] NICE guidelines had a low sensitivity and only 30% of patients were identified.

Therapeutic strategies to prevent or treat RFS

Different studies evaluated preventive strategies for RFS, mainly substitution of electrolytes, thiamin infusions and hypocaloric nutrition. As shown in **Table 4**, 5 studies showed a preventive effect of hypocaloric feeding whereas 6 studies did not find such an effect. Regarding substitution of electrolytes and vitamins, 6 studies found a reduced risk of RFS while 3 studies found no such effect. One study [36] proposes monitoring of electrolytes whereas another [37] did not show a reduction in risk for RFS in this measure. There was no correlation between criteria used to define RFS and effect of preventive measurements.

Three studies reported on the treatment of RFS [26, 36, 38]. In two of these the investigators used phosphate supplementation in order to treat signs and symptoms of RFS and concluded that these measures were helpful (**Table 4**). In the most recent RCT involving critically-ill patients [26], protocolised caloric restriction proofed to be a suitable option for treatment of patients with improvement in mortality and overall survival time although the primary outcome (the number of days alive after ICU discharge) was not significantly improved.

Discussion

Summary of evidence

Although described more than 70 years ago, RFS remains incompletely understood. The main findings of this first systematic and comprehensive literature review are threefold. First, there is no well-accepted definition of RFS and no consensus whether the definition should rely only on laboratory parameters or additionally include clinical symptoms. Most studies, however, had a low or decreasing phosphate concentration as part of their definition. Depending on the definitions used, incidence rates showed wide heterogeneity. Second, in regard to risk factors, the current NICE guidelines seem to adequately reflect findings of the included studies with some additional factors (i.e. higher age, low albumin or pre-albumin, higher nutritional intake during feeding, low IGF-1, NRS ≥ 3 and enteral feeding) being described. Third, only a few studies have investigated the clinical consequences and therapeutic measures of RFS. Within these studies, there was a lack of association of this syndrome and adverse clinical outcomes, as well as preventive measures and improved outcomes. Similarly, there was only one randomized study [26] evaluating therapeutic approaches of RFS as the main outcome. In this recent RCT Doig et al. reported caloric restriction to be a suitable therapeutic measure for RFS in ICU patients. Further randomized studies confirming these findings are largely lacking.

Interestingly, our results did not find strong differences for the anorexic and non-anorexic populations. For this reason, we pooled these two populations in our analysis. Still, from a pathophysiological standpoint, it can be argued that anorexic patients without an acute illness would be different compared to acutely ill malnourished patients. The lack of differences found in our review may also be the result of the low study quality and it is thus possible that anorexic patients need particular attention in regard to the RFS.

The lack of common definitions for RFS is problematic and makes a comprehensive comparison of different study populations challenging or even literally impossible. Most studies used electrolyte disturbances as part of their definition – with, however, differences in cut-offs and types of electrolytes included. In acute illness electrolyte disturbances are common and may be the result of different nutritional and non-nutritional factors lowering their specificity for RFS. There is no general consensus

whether electrolyte disturbances seen in RFS are part of the normal metabolic response to disease, or a maladaptation which need therapeutic action. From a biological perspective, concentration gradients of electrolytes between intracellular and extracellular compartments are basic conditions seen in most eukaryotes and promote different metabolic functions. Phosphate is essential for different metabolic and regulatory processes like protein phosphorylation/de-phosphorylation and energy production (generation of adenosine triphosphate [ATP]) [39]. Similarly, magnesium is an essential component for ATP stabilization and various enzymatic processes [40]. Also, sodium - potassium membrane gradient is important for membrane excitation, signal transduction and for transport processes [41]. During catabolism, the intracellular ion storage is being depleted while intracellular sodium increases in exchange. This is reversed after refeeding [12, 13]. Yet, the change in ion composition of currently-used processed food (i.e., higher amount of sodium, but lower concentrations of potassium, phosphate and magnesium) may interfere with this natural reaction leading to a more pronounced electrolyte disturbances with adverse clinical effects. Thus, the observation of low plasma electrolytes during illness may in fact be a consequence of lower nutritional intake of these ions rather than RFS. These speculations would favor using clinical symptoms in addition to electrolyte disturbances as a goldstandard diagnosis of RFS.

A rational approach to devise up with a standard definition of RFS may also be to focus on factors associated with adverse clinical outcome, as targets of preventive and therapeutic measures. Only a few studies, however, have focused on such premises. For example Heimburger et al. [42] reported a lower survival probability in patients with hypophosphatemia independent of other metabolic parameters. This study, however, was conducted in a HIV infected study population limiting generalizability of their findings. There is need for further high quality research in regard to better understanding the importance of RFS in the medical patient population.

There is some consensus among studies in regard to the time point of RFS occurrence, namely within the first 72 hours. Thus, particular attention may be drawn to at risk patients within this initial time period. Still, due to the limited study quality, we cannot exclude that in certain patients a later development of the syndrome can occur.

Even though most studies agree with the NICE criteria as risk factors for RFS, the use of this guidelines by itself has low sensitivity and specificity as Goyale et al [34] and Zeki et al [35] stated in their studies.

This review has several limitations, mostly associated with the limited quality of included studies. First, we found only three interventional studies, two of them not having RFS as their main trial focus. Second, most included studies had small sample sizes (26 studies included <100 patients) and low quality according to the SIGN methodology [20], with high heterogeneity in regard to the type of interventions and patient populations. The risk of bias analysis revealed high risks for performance bias, attrition bias, and reporting bias. We can therefore not draw firm conclusions regarding the definition, prevention, risk factors, incidence and treatment of RFS. There is currently a large, multi-center randomized controlled intervention study ("EFFORT"-study) ongoing focusing on nutritional therapy in inpatients which will help to fill this gap (<https://clinicaltrials.gov/ct2/show/NCT02517476>) [4, 5].

Conclusion

Although there is consensus in regard to risk factors and timely occurrence of RFS, there is still wide variation in definition, reported incidence rates and preventive measures and treatment recommendations. This first systematic review is an important step towards a better understanding of the current state of knowledge regarding RFS and its clinical consequences. Further prospective high-quality research is warranted to fill this gap.

Contributors:

NF and PS wrote the initial protocol. NF performed the literature search and the data extraction. PS and ZS reviewed and commented on the final data extraction. NF drafted the manuscript. All authors amended and commented on the manuscript and approved the final version. PS and ZS oversaw the study and act as guarantors.

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Tables and Figures

Figure 1 – Flow Chart

Table 1 – Definition, incidence and timely occurrence of RFS

	Firstauthor	Y	N=	Population	Definition of RFS	Incid.	When did it occur?
HYPOPHOSPHATEMIA as definition criteria	Goyale, A. [34]	2015	52	patients receiving PN	PO4 drop of >30% during the first 36h of PN administration.	62%	NR
	Coskun, R. [43]	2014	117	ICU patients receiving EN or PN	PO4 $\leq$ 0.78 mmol/L	52.14%	NR
	Gaudiani, L. [44]	2012	25	AN patients	PO4 < 0.87mmol/L	45%	3.4 days
	Gaudiani, L. [45]	2014	132	AN patients	hypophosphatemia	37%	NR
	Marik, P. E. [25]	1996	62	ICU patients starved for at least 48h	drop of PO4 by > 0.16mmol/L to below 0.65mmol/L accompanied by possible other electrolyte disturbances	34%	1.9 +/- 1.1 days
	Marvin, V. [28]	2007	250	patients receiving PN	PO4 drop of $\geq$ 0.15mmol/L to < 0.80mmol/L from baseline in the first 7days of PN in patients with a period of > 48h without food	34%	3 days
	Brown, CA. [46]	2015	123	female AN patients	PO4 < 0.87mmol/L	33%	2 days
	Lubart, E. [47]	2009	40	frail elderly patients with feeding problems >72h	PO4 < 0.52mmol/L	25%	2 - 3 days
	Gonzalez Avila, G. [32]	1996	106	cancer patients receiving EN or PN	PO4 < 0.81mmol/L	24.5%	Within 72h
	Zeki, S. [35]	2011	321	patients receiving PN or EN	PO4 < 0.6mmol/L	15%	NR
	Garber, A.K. [48]	2012	56	AN patients	shifts in electrolytes	0%	NR
	Grasso, S. [49]	2013	34	patients with cancer of the upper aerodigestive tract, doing an 12 hours over night fast	HP and/or other shifts in electrolytes during RF	NR	NR
	Terlevich, A. [38]	2003	30	patients with refeeding syndrome	PO4 < 0.50 mmol/L	NR	NR
	Nagata, J.M. [50]	2015	356	AN patients	PO4 < 0.97 mmol/L	NR	NR
	Kagansky, N. [51]	2005	651	patients >65yrs with at least one episode of HP compared with patients without HP	PO4 < 0.77 mmol/L	NR	10.9+/- 21.5 days after hospitalisation
SHIFT IN ELECTROLYTE	Marvin, V. [27]	2008	140	patients receiving PN	PO4 drop of $\geq$ 0.15 mmol/L to < 0.80 mmol/L from baseline in the first 7days of PN in patients with a period of > 48h without food	NR	NR
	Doig, G. [26]	2015	339	ICU critically ill adult patients	PO4 drop >0.16mmol/L to < 0.65 mmol/L within 72h after starting nutritional support	NR	Within 72h
	Hernandez-Aranda, J.C. [52]	1997	50	patients with mild and severe malnutrition receiving EN or PN for >7d	drop of any electrolyte value under the reference range	48%	3 days
	Redgrave, G.W. [53]	2015	461	AN patients	PO4 < 0.87 mmol/L, for patients $\leq$ 16yrs < 1mmol/l, hypomagnesaemia, hypokalemia and hypoglycemia	18.5%	NR
	Manning, S. [37]	2014	36	alcoholic patients	changes in fluid and electrolyte balance in malnourished receiving intensive feeding	0%	NR
CLINICAL SYMPTOMS	Luque, S. [54]	2007	11	malnourished patients receiving PN	severe shifts in electrolytes in patients that are underweight, severely malnourished or starved and started on refeeding	0%	NR
	Whitelaw, M. [36]	2010	46	AN patients	electrolyte and fluid shifts during refeeding	NR	NR
	Flesher, M.E. [29]	2005	51	malnourished patients receiving EN	shifts in electrolytes associated with complications during early EN	80%	NR
	Chen, L. [55]	2014	56	patients having a high risk for RFS according to NICE guidelines admitted for RF	shifts in electrolyte and clinical symptoms	20%	NR
	Vignaud, M. [30]	2010	68	AN patients	all adverse events occurring during nutritional rehabilitation of malnourished patients or having undergone a prolonged fast	10%	NR
	Fan, C.G. [56]	2004	15	patients with gastrointestinal fistula	shifts in electrolytes and clinical symptoms	9.4%	within 24h
	Saito, S. [57]	2014	111	AN patients	cardiovascular, respiratory, neurological or psychological changes with HP during RF	3.6%	NR
	Eichelberger, M. [24]	2014	37	hungerstrike patients	electrolyte disturbances (K <2.5mmol/l, PO4 <0.32mmol/l, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	3%	NR
	Rio, A. [22]	2013	243	patients on artificial nutrition support	electrolyte disturbances (K <2.5mmol/l, PO4 <0.32mmol/l, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	2%	NR
	Heimbürger, D.C. [42]	2010	142	HIV infected patients	HP and clinical symptoms	0.7%	NR
	Herranz, A. [58]	2013	312	patients receiving PN	shifts in electrolytes (PO4, K, Mg) AND edema AND impaired carbohydrate metabolism during PN	0%	NR
	Faintuch, J. [59]	2001	8	hungerstrike patients	relevant shifts in electrolytes and clinical symptoms	0%	NR
	Elnenaï, M.O. [60]	2011	35	patients admitted for PN	clinical features	0%	NR
	Leclerc, A. [61]	2013	29	AN patients	signs and symptoms of shifts in fluid and electrolytes (particularly phosphate)	0%	NR
	Gentile, M.G. [62]	2010	33	Very severe AN patients	clinical signs and symptoms of water retention, HP or of depletion of other electrolytes or the thiamine co-factor of glycolysis	0%	NR
	Hofer, M. [23]	2014	65	AN patients	electrolyte disturbances (K <2.5mmol/l, PO4 <0.32mmol/l, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	0%	NR
	Golden, N.H. [63]	2013	310	AN patients	HP associated with possible hypomagnesaemia and hypokalemia and clinical features	0%	NR
	Raj, K.S. [64]	2012	541	AN patients	metabolic and clinical changes under RF	NR	4.9 +/- 5.5 days
	Garber, A.K. [65]	2011	40	AN patients	NR	0%	NR
	Hoffmann, M. [66]	2008	621	Patients with moderate or severe HP	NR	10%	NR
NR = not reported AN = anorexic Not-AN = not anorexic HP = hypophosphatemia PO4 = phosphate K = potassium Na = sodium Mg = magnesium EN = enteral nutrition PN = parenteral nutrition RF = refeeding							

Table 2 – Adverse outcome of RFS

	Firstauthor	Y	N=	Population	Definition of RFS	Mortality rate	Association with RFS	Other Adverse Outcome
HYPOPHOSPHATEMIA	Zeki, S. [35]	2011	321	patients receiving PN or EN	PO4 < 0.6mmol/L	NR	death within 7 days and HP were not associated	NR
	Lubart, E. [47]	2009	40	frail elderly patients with feeding problems >72h	PO4 < 0.52mmol/L	6%	No correlation in 1st week and 1st month	NR
	Goyale, A. [34]	2015	52	patients receiving PN or EN	PO4 drop of >30% during the first 36h of PN administration	0%	NR	NR
	Kagansky, N. [51]	2005	325	patients >65yrs with at least one episode of HP compared with patients without HP	PO4 < 0.77mmol/L	threefold increased mortality rates	not an independent predictor for mortality	Longer LOS
	Coskun, R. [43]	2014	117	ICU patients receiving EN or PN	PO4 ≤ 0.78 mmol/L	NR	NR	ICU LOS longer
SHIFT IN ELECTROLYTE	Hernandez-Aranda, J.C. [52]	1997	50	patients with mild and severe malnutrition receiving EN or PN >7 days	drop of any electrolyte value under the reference range	29%	NR	Longer LOS
	Marik, P. E. [25]	1996	62	ICU patients starved for at least 48h	drop of PO4 by > 0.16mmol/L to below 0.65mmol/L accompanied by possible other electrolyte disturbances	NR	NR	Longer LOS
CLINICAL SYMPTOMS	Eichelberger, M. [24]	2014	37	hungerstrike patients	electrolyte disturbances (K <2.5, PO4 <0.32, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	0%	NR	NR
	Rio, A. [22]	2013	243	patients on artificial nutrition support	electrolyte disturbances (K <2.5, PO4 <0.32, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	0%	NR	NR
	Vignaud, M. [30]	2010	68	AN patients	all adverse events occurring during nutritional rehabilitation of malnourished patients or having undergone a prolonged fast	71%	NR	NR
	Heimbürger, D.C. [42]	2010	142	HIV infected patients	HP and clinical symptoms	lower survival probability at 12 weeks	NR	NR
NR = not reported AN = anorexic Not-AN = not anorexic HP = hypophosphatemia PO4 = phosphate K = potassium Na = sodium Mg = magnesium EN = enteral nutrition PN = parenteral nutrition RF = refeeding LOS = length of stay								

Table 3 – Risk factors of RFS

	Firstauthor	Y	N=	Definition of RFS	Risk Factors
HYPOPHOSPHATEMIA as definition criteria	Terlevich, A. [38]	2003	30	PO4 < 0.50 mmol/L	alcoholism, malignancy, anorexia nervosa, Crohn's disease, recurrent small bowel obstruction, pneumonia, dysphagia
	Marvin, V. [28]	2007	250	PO4 drop of ≥ 0.15 mmol/L to < 0.80mmol/L from baseline in the first 7 days of PN in patients with a period of > 48h without food	cancer patients
	Marvin, V. [27]	2008	140	PO4 drop of ≥ 0.15 mmol/L to < 0.80mmol/L from baseline in the first 7 days of PN in patients with a period of > 48h without food	high NRS ≥ 3 , lower Mg, age, <12mmol PO4 in first day's PN regimen
	Brown, CA. [46]	2015	123	PO4 < 0.87mmol/L	low BMI, low K, low prealbumin and high hemoglobin concentration
	Gaudiani, L. [45]	2014	132	hypophosphatemia	low prealbumin concentration
	Coskun, R. [43]	2014	117	PO4 ≤ 0.78 mmol/L	EN with energy provided in a short time
	Gonzalez Avila, G. [32]	1996	106	PO4 < 0.81mmol/L	age > 60yrs and moderate or severe malnutrition
	Goyale, A. [34]	2015	52	PO4 drop of >30% during the first 36h of PN administration	IGF-1 <63.7 ug/l
	Kagansky, N. [51]	2005	651	PO4 < 0.77mmol/L	infusion of glucose solutions, EN, weight loss, fever, high WBC count and creatinine kinase, low baseline concentration of PO4 and hypoalbuminaemia
	Zeki, S. [35]	2011	321	PO4 < 0.6mmol/L	enteral tube feeding
SHIFT IN ELECTROLYTE	Gaudiani, L. [44]	2012	25	PO4 < 0.87mmol/L	no risk factors found
	Redgrave, G.W. [53]	2015	461	shifts in electrolytes	lower admission BMI
	Whitelaw, M. [36]	2010	46	electrolyte and fluid shifts during RF	malnourished with % IBW <68
	Grasso, S. [49]	2013	34	HP and/or other shifts in electrolytes during RF	hypokalemia
	Marik, P. E. [25]	1996	62	drop of PO4 by > 0.16mmol/L to below 0.65mmol/L accompanied by possible other electrolyte disturbances	poor caloric intake for as short as 48hours and low prealbumin concentration
CLINICAL SYMPTOMS	Hofer, M. [23]	2014	65	electrolyte disturbances (K <2.5, PO4 <0.32, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	NICE
	Raj, K.S. [64]	2012	541	metabolic and clinical changes under RF	NICE
	Vignaud, M. [30]	2010	68	all adverse events occurring during nutritional rehabilitation of malnourished patients or having undergone a prolonged fast	poor caloric intake, NICE and higher nutritional intake during RF
	Eichelberger, M. [24]	2014	37	electrolyte disturbances (K <2.5, PO4 <0.32, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	NICE
	Chen, L. [55]	2014	56	shifts in electrolyte and clinical symptoms	NICE and EN in nursing homes
	Rio, A. [22]	2013	243	electrolyte disturbances (K <2.5, PO4 <0.32, Mg <0.5 mmol/L) AND clinical symptoms (peripheral edema or acute circulatory fluid overload) AND disturbance to organ function (respiratory failure, cardiac failure or pulmonary edema)	weight loss, poor caloric intake, NICE and low serum Mg concentration
	Gentile, M.G. [62]	2010	33	clinical signs and symptoms of water retention, HP or of depletion of other electrolytes or the thiamine co-factor of glycolysis	weight loss
	Golden, N.H. [63]	2013	310	HP associated with possible hypomagnesaemia and hypokalemia and clinical features	poor caloric intake and degree of malnutrition
	Flesher, M.E. [29]	2005	51	shifts in electrolytes associated with complications during early EN	malnourished patients
	Fan, C.G. [56]	2004	15	shifts in electrolytes and clinical symptoms	nutrition support suddenly introduced at full strength and patients with GI-fistula
	Elnenaie, M.O. [60]	2011	35	Clinical features	no risk factors found
	Charles, E.J. [67]	2014	83	NR	history of significant alcohol abuse, 5% weight loss in the preceding 30 d or 10% loss in the preceding 6 months, or poor caloric intake for at least 7 days
	Henderson, S. [68]	2010	43	NR	no risk factors found
	NR = not reported AN = anorexic Not-AN = not anorexic HP = hypophosphatemia PO4 = phosphate K = potassium Na = sodium Mg = magnesium EN = enteral nutrition PN = parenteral nutrition RF = refeeding				

Table 3a – Risk factors of RFS

Risk Factor	No of Studies	Studies and Firstauthors	No of patients included
poor caloric intake / malnutrition	8	Vignaud, M. [30], Rio, A. [22], Charles, E.J. [67], Golden, N.H. [63], Flesher, M.E. [29], Gonzalez Avila, G. [32], Marik, P. E. [25], Whitelaw, M. [36]	969
NICE	6	Hofer, M. [23], Raj, K.S. [64], Vignaud, M. [30], Eichelberger, M. [24], Chen, L. [55], Rio, A. [22]	1000
low electrolyte concentrations	5	Rio, A. [22], Marvin, V. [27], Brown, CA. [46], Grasso, S. [49], Kagansky, N. [51]	1191
weight loss	4	Rio, A. [22], Charles, E.J. [67], Gentile, M.G. [62], Kagansky, N. [51]	1010
low prealbumin / albumin concentration	4	Gaudiani, L. [45], Brown, CA. [46], Marik, P. E. [25], Kagansky, N. [51]	977
enteral nutrition	3	Chen, L. [55], Zeki, S. [35], Kagansky, N. [51]	707
no risk factors found	3	Elnenaï, M.O. [60], Henderson, S. [68], Gaudiani, L. [45]	103
higher or faster nutritional intake during RF	3	Vignaud, M. [30], Coskun, R. [43], Fan, C.G. [56]	200
low admission weight / BMI / AN patients	3	Terlevich, A. [38], Redgrave, G.W. [53], Brown, CA. [46]	614
alcohol abuse	2	Charles, E.J. [67], Terlevich, A. [38]	113
age	2	Marvin, V. [27], Gonzalez Avila, G. [32]	246
malignancy	2	Terlevich, A. [38], Marvin, V. [28]	280
IGF-1 <63.7 ug/l	1	Goyale, A. [34]	52
high NRS ≥3	1	Marvin, V. [27]	140
high hemoglobin concentration	1	Brown, CA. [46]	123
AN = anorexic EN = enteral nutrition RF = refeeding			

Table 4 – Preventive and therapeutic measurements

	Firstauthor	Y	N=	Preventive Medication	Therapeutic Medication	Effective?
HYPOPHOSPHATEMIA as definition criteria	Terlevich, A. [38]	2003	30	NR	50mmol PO4 over 24 h	yes
	Gonzalez Avila, G. [32]	1996	106	PO4 supplementation	NR	yes
	Marvin, V. [27]	2008	140	during the first 24h slow PN regimen providing <70% of protein and calories but > 12mmol PO4	NR	yes
	Garber, A.K. [65]	2011	40	no effective preventive measures found	NR	no
	Coskun, R. [43]	2014	117	lower energy intake	NR	no
	Doig, G. [26]	2015	339	NR	lower caloric intake	yes
SHIFT IN ELECTROLYTE	Whitelaw, M. [36]	2010	46	prophylactic administration of PO4		no
				lower initial energy intake, monitoring of PO4	supplementation of phosphate	yes
	Luque, S. [54]	2007	11	PO4 supplementation, thiamine 3.51mg/day	NR	yes
	Manning, S. [37]	2014	36	repeated electrolyte testing	NR	no
CLINICAL SYMPTOMS	Fan, C.G. [56]	2004	158	PO4 supplementation	NR	yes if phosphate < 0.30
	Gentile, M.G. [62]	2010	33	prophylactic administration of PO4 and K, cautious nutritional rehabilitation	NR	yes
	Vignaud, M. [30]	2010	68	for patients at risk initial nutritional support 10kcal/kg/d falling to as low as 5kcal/kg/d	NR	yes
	Chen, L. [55]	2014	56	thiamine and multivitamin supplementation, 15kcal/kg/day	NR	yes
	Golden, N.H. [63]	2013	310	lower caloric intake	NR	no
	Leclerc, A. [61]	2013	29	hypocaloric feeding	NR	no
	Flesher, M.E. [29]	2005	51	thiamine supplementation, cautious feeding	NR	no
	Rio, A. [22]	2013	243	hypocaloric feeding	NR	no
	NR = not reported AN = anorexic Not-AN = not anorexic HP = hypophosphatemia PO4 = phosphate K = potassium Na = sodium Mg = magnesium EN = enteral nutrition PN = parenteral nutrition RF = refeeding					

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