



Refeeding Syndrome in the First Seventy-Two Hours: Risk Stratification and the Limits of Phosphate Monitoring

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Abstract

Refeeding syndrome is anticipated by stratifying patients before feeding starts and monitoring phosphate afterwards. Neither step performs as well as its use implies. In a cohort of 149 patients receiving parenteral nutrition, the proportion developing refeeding hypophosphataemia was between 23 and 48 per cent depending only on which diagnostic criterion was applied, and the guideline risk criteria discriminated poorly across all of them, with areas under the curve of 0.43 to 0.53. A model built from critical illness, diuretic use and pre-existing hypomagnesaemia reached 0.74 but awaits validation. A randomised trial in intensive care found no difference in electrolyte decrement, corrected QT abnormality, infection or length of stay between moderate-risk and high-risk groups. The consensus definition requires falls in phosphorus, potassium or magnesium and describes its own severity thresholds as arbitrary. What is supported by randomised evidence is calorie restriction once hypophosphataemia appears.

Keywords: Refeeding syndrome; Hypophosphataemia; Risk stratification; Parenteral nutrition; Electrolytes

Introduction

Reintroducing nutrition to a depleted patient shifts glucose, phosphate, potassium and magnesium into cells as insulin secretion resumes, and in susceptible people the resulting electrolyte falls produce cardiac, respiratory and neurological disturbance [1,2,3]. The syndrome was described in prisoners of war and has been recognised in clinical nutrition for decades [4,5,19,20]. Reviews of the condition and of its management in medical inpatients have appeared repeatedly since [19,24,26], and it has been described as serious but neglected [26,27].

Practice rests on two steps. Patients are stratified before feeding begins, most often using national guideline criteria, and phosphate is monitored afterwards, with the first seventy-two hours treated as the period of greatest risk [6,7]. Both steps are widely implemented and neither is well validated. Rates of energy initiation and their relation to outcome have themselves been systematically reviewed [29].

This review examines how far the incidence of the syndrome depends on its definition, how well the stratification criteria predict who develops it, and what the randomised evidence supports.

Objective

The purpose of this review is to establish three things from the published literature. First, what proportion of at-risk patients develop refeeding hypophosphataemia, and how far that proportion is a property of the definition rather than of the patients. Second, how well the risk criteria in routine use discriminate between those who will and will not develop it. And third, which management step is supported by randomised rather than observational evidence.

Literature Review

The definitions: Early work defined refeeding hypophosphataemia as a fall in serum phosphorus to below 0.65 mmol/L within seventy-two hours of starting nutrition [8,9]. Criteria proposed at King's College Hospital in 2012 added electrolyte decrements alongside circulatory problems or organ dysfunction, but have rarely been used because of low sensitivity [10,11].

The consensus definition: In 2020 an interprofessional task force proposed a definition stratifying severity by proportional decrement in any one, two or three of serum phosphorus, potassium and magnesium: a fall of 10 to 20 per cent is mild, 20 to 30 per cent moderate, and above 30 per cent, or organ dysfunction resulting from such a fall or from thiamine deficiency, is severe, occurring within five days of reinitiating or substantially increasing energy provision (Figures 3 and 4) [12]. The authors state that the criteria for severity stratification are arbitrary, chosen to align with published stratifications for electrolyte decrements [12].

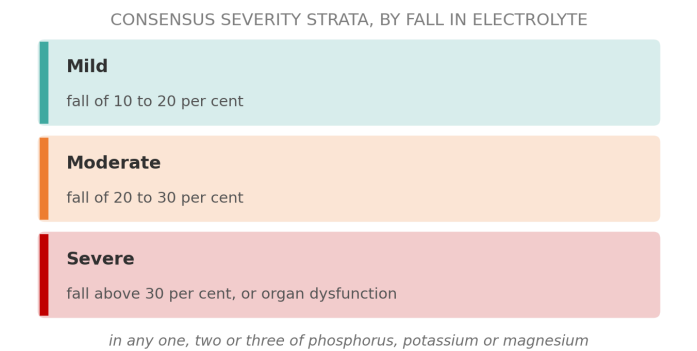


Figure 3: Consensus severity strata, by proportional fall in electrolyte [12]

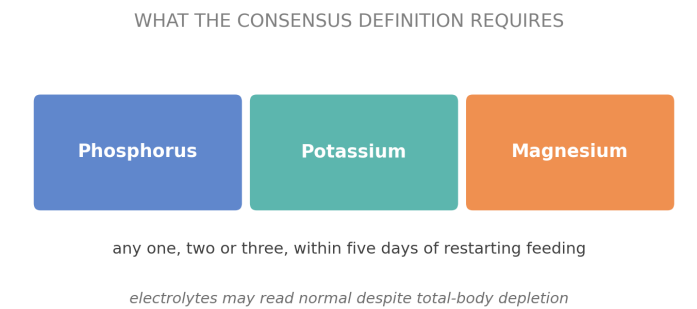


Figure 4: What the consensus definition requires [12]

Incidence depends on the definition: A prospective study of 149 patients receiving parenteral nutrition found that between 23 and 48 per cent, or 35 to 72 of the 149, developed refeeding hypophosphataemia depending on which diagnostic criterion was applied (Figure 1) [13]. The variation is not between populations but within one cohort, and it means that any reported incidence figure is uninterpretable without its definition attached.

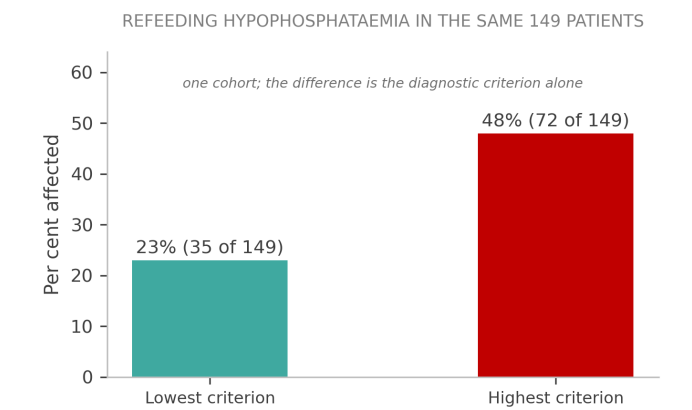


Figure 1: Refeeding hypophosphataemia in the same 149 patients, by criterion [13]

Table 1: Definitions of refeeding syndrome in current use, as published

Definition	Basis	Note
Early criterion	Phosphate below 0.65 mmol/L within 72 hours	Widely used [8,9]
King's College 2012	Electrolytes plus organ dysfunction	Low sensitivity [10,11]
Consensus 2020	Proportional fall in one to three electrolytes	Thresholds described as arbitrary [12]

How well the risk criteria predict: In the same cohort, the national guideline criteria demonstrated poor discrimination across all diagnostic definitions, with areas under the receiver operating characteristic curve of 0.43 to 0.53 (Figure 2). Critical illness, use of diuretics and hypomagnesaemia before parenteral nutrition were each independently associated with the outcome, and a model built from those three achieved an area under the curve of 0.74 (95% CI 0.66 to 0.82). The investigators concluded that the current guideline criteria poorly predict the occurrence of refeeding hypophosphataemia and that the derived model requires further validation [13].

Table 2: Performance of risk stratification as reported by the original investigators

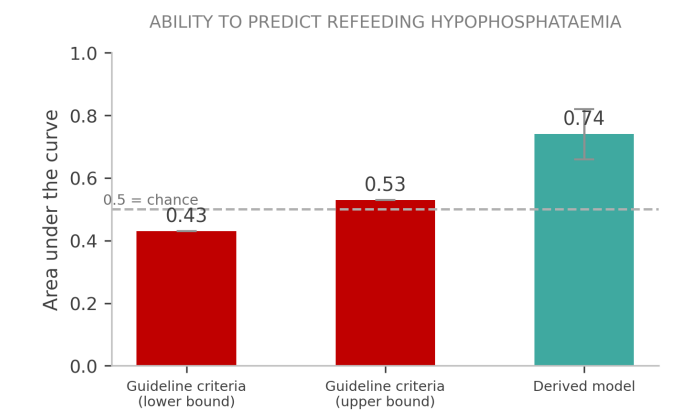


Figure 2: Ability to predict refeeding hypophosphataemia [13]

Whether stratification separates outcomes: A randomised controlled trial conducted in intensive care patients classified at risk by guideline criteria reported no differences between moderate-risk and high-risk groups in decrement of serum

electrolytes, corrected QT abnormalities, infection or length of hospital stay [11,14]. Modified criteria have added a very high-risk category, and the consensus recommendations propose more specific stratification of caloric intake, subcutaneous fat and muscle mass, but these and the malnutrition criteria proposed for the same purpose still lack wide validation across populations and have not been studied for their predictive value (Figure 6) [11,15,16].

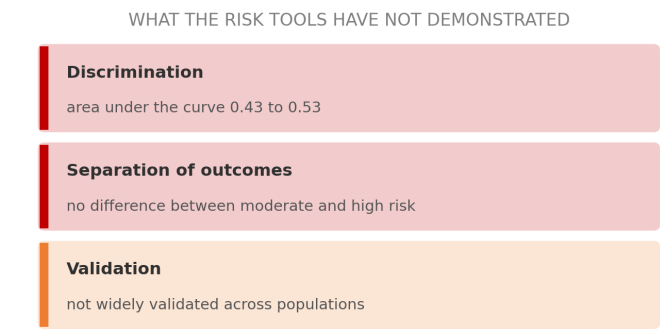


Figure 6: What the risk stratification tools have not demonstrated [11,13,15,16]

Property	Reported finding
Discrimination of guideline criteria	Area under the curve 0.43 to 0.53 [13]
Discrimination of derived model	0.74 (95% CI 0.66 to 0.82) [13]
Separation of clinical outcomes	None between moderate and high risk [11,14]
Validation across populations	Not established for modified criteria [15,16]

What the randomised evidence supports: A randomised trial in critically ill patients who developed new-onset hypophosphataemia within seventy-two hours of starting nutrition compared restricted with standard calorie provision. The restricted group received under 50 per cent of goal calories for the first three days, increasing by 25 per cent of target per day thereafter, while the control group received above 50 per cent of goal from the outset. The trial enrolled 339 patients whose phosphate fell below 0.65 mmol/L within seventy-two hours, and reported improved survival at sixty days in the restricted group (Figure 5) [12,17].

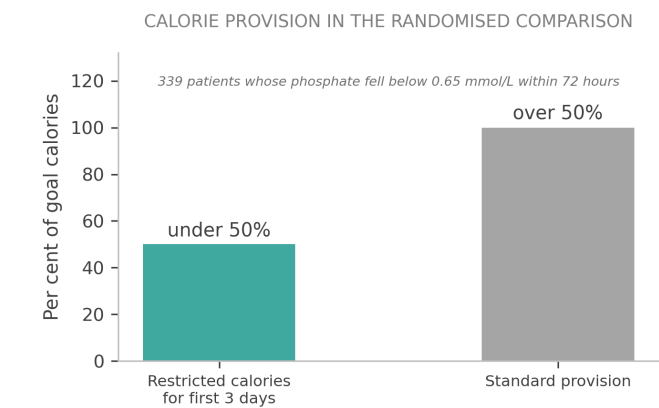


Figure 5: Calorie provision in the randomised comparison [12,17]

Applying the criteria in specific populations: The consensus definition has been applied retrospectively in burn patients receiving enteral feeding for at least seventy-two hours, in critically ill patients with coronavirus disease, and in neurocritical care, where several instruments were compared for their ability to identify those at high risk [16,18,19]. Reported incidence differs substantially between these settings, which is consistent with the definitional variation described above rather than necessarily with differences in underlying risk [12,13]. Systematic review and meta-analysis of reported incidence reached the same conclusion about definitional heterogeneity [25,32], and the condition has been examined separately in older hospitalised patients, in the frail elderly and in paediatric as well as adult intensive care [23,28,33].

Whether the syndrome matters to outcome: Retrospective comparison of critically ill patients with and without refeeding syndrome examined the effect of caloric intake in each group [21], and a cohort study related a newer risk classification to mortality [30]. Whether the electrolyte disturbance itself drives the excess risk, or marks a population already more severely ill, is not resolved by observational data, and the composition of the feed itself has been argued to bear on the question [31]. That uncertainty is not resolved by observational data, and the question has been raised directly in the critical care literature [34].

Who is at risk before feeding begins: Prevalence of the recognised risk factors has been measured directly in older hospitalised patients, where a substantial proportion met one or more criterion before any feeding decision was taken [23]. In the frail elderly the same factors cluster with the comorbidity that prompts admission, which is part of why the criteria identify large groups without separating them [23,28]. Management algorithms developed by consensus attempt to bridge that gap for medical inpatients [7,24].

The route of feeding matters: Refeeding hypophosphataemia has been reported as more common with enteral than with parenteral feeding in adult inpatients [9], while the predictive analysis reviewed above was conducted entirely in patients receiving parenteral nutrition [13]. Whether the discrimination figures

transfer to enterally fed patients has not been established, and prospective cohort data in patients started on artificial nutrition support of either kind report occurrence rates that again depend on the definition applied [10,25].

Method

Search strategy: PubMed and the archives of the major clinical nutrition, intensive care and general medical journals were searched for studies of refeeding syndrome and refeeding hypophosphataemia. Search terms combined refeeding syndrome with hypophosphataemia, risk stratification, incidence, guideline criteria and parenteral nutrition. Reference lists of the consensus recommendations [12] and a recent narrative review [11] were screened by hand for primary sources.

Eligibility: Studies were included if they reported incidence of refeeding syndrome or refeeding hypophosphataemia in a defined population, evaluated the predictive performance of risk criteria, or tested a management strategy. Consensus and guideline documents are cited for the definitions and recommendations they contain and are identified as such.

Data extraction and handling: Population, feeding route, the diagnostic definition applied and the reported estimate were extracted as published. The definition is stated alongside every incidence figure, because the same cohort yields figures differing twofold depending on the criterion applied, and that variation is the central point of this review. This article reports published findings and does not constitute guidance on the feeding, monitoring or electrolyte management of any individual patient, all of which are matters for the treating team. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis of published literature and was not registered as a systematic review.

Concluding Remarks

Two steps structure the management of this condition and the evidence for each is weaker than its adoption suggests. Stratifying patients before feeding is meant to identify who needs cautious reintroduction. In the one cohort where the guideline criteria were tested against outcome, they returned areas under the curve of 0.43 to 0.53 [13]. A value of 0.5 is chance, and part of that range sits below it. That is not a tool performing modestly; it is a tool not discriminating.

The randomised comparison points the same way from a different angle. Patients classified as moderate risk and high risk by those criteria did not differ in electrolyte decrement, corrected QT abnormality, infection or length of stay [11,14]. If the two strata do not separate on outcome, the stratification is not identifying distinct groups, whatever its face validity.

The incidence figures compound the difficulty rather than resolving it. Twenty-three per cent and 48 per cent of the same 149 patients met criteria for the condition, depending on the definition chosen [13]. Every prevalence estimate in this literature therefore carries its definition as a hidden parameter, and comparisons between studies using different criteria are comparisons of criteria.

Phosphate monitoring deserves the qualification in the title of this review. Phosphate is the hallmark and it is not sufficient: the consensus definition requires falls in phosphorus, potassium or magnesium, singly or together, and notes that electrolytes may read normal despite total-body depletion [12]. A protocol built on serial phosphate alone will miss the patient whose potassium or magnesium falls, and will be falsely reassured by a normal value in a depleted patient [12,22]. Refeeding hypophosphataemia has been reported as more common with enteral than parenteral feeding, so the route also bears on where monitoring is directed [9].

What is supported is narrower and more useful than the stratification apparatus around it. In the one randomised trial, restricting calories to under half of goal for the first three days after hypophosphataemia appeared improved survival at sixty days [12,17]. That is a response to a measured event rather than to a predicted one, and it does not depend on the risk criteria performing well. Whether a patient identified as high risk before feeding benefits from pre-emptive restriction has not been demonstrated [11,14,21]. Retrospective comparison of caloric intake in critically ill patients with and without the syndrome points the same way without settling it [21,34].

Two limitations belong with these conclusions. The predictive analysis derives from 149 patients at a single centre receiving parenteral nutrition, and the derived model has not been externally validated [13]. And no trial has randomised patients to management guided by one set of risk criteria against another with clinical outcomes as the primary endpoint, so the comparison this review implies has not been made directly [11,12,15].

A note on where the seventy-two hour window in the title comes from. The earliest definition set it as the interval within which phosphate had to fall for the event to count [8], and the randomised trial recruited on exactly that basis [12,17]. The 2020 consensus widened the window to five days [12]. The two are not interchangeable: a protocol monitoring for three days will not detect an event the consensus definition would count on day four, which is a further reason incidence figures diverge between studies [12,13,25].

Finally, the practical position this leaves. Stratification before feeding has not been shown to discriminate, and pre-emptive restriction on the basis of it has not been tested [11,13,14]. Monitoring after feeding starts detects a real event, and restricting calories once that event appears is supported by

randomised evidence [12,17]. On the published data the second is the better founded of the two activities, though it requires the monitoring to cover potassium and magnesium as well as phosphate [12].

A word on why the definitional problem persists. The consensus authors were explicit that a standard definition was absent and that its absence impedes accurate incidence estimation and complicates trial design [12]. Their own thresholds were chosen to align with existing stratifications for electrolyte decrements rather than derived from outcome data, and they say so [12]. A definition adopted for coherence rather than for prognostic performance will produce consistent reporting without necessarily identifying the patients who come to harm [12,25].

That is the gap a future study could close. Systematic review and meta-analysis of reported incidence has already shown how much of the variation is definitional [25,32]. What has not been done is to apply competing definitions to one prospective cohort and test each against clinical outcome rather than against electrolyte thresholds, which would establish which decrement actually marks the patient at risk [13,30]. Until that exists, the sensible reading is that the monitoring detects something real and the stratification preceding it does not yet identify who needs it [11,13,14].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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