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Hypophosphatemia in critically ill adults and children – a systematic review

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Abstract:	Background & aims Phosphate is the main intracellular anion essential for numerous biological processes. Symptoms of hypophosphatemia are non-specific, yet potentially life-threatening. This systematic review process was initiated to gain a global insight into hypophosphatemia, associated morbidity and treatments. Methods A systematic review was conducted (PROSPERO CRD42020163191). Nine clinically relevant questions were generated, seven for adult and two for paediatric critically ill patients, and prevalence of hypophosphatemia was assessed in both of these groups. We identified trials through systematic searches of Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, CINAHL, and Web of Science. Quality assessment was performed using the Cochrane risk of bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Results

	For all research questions, we identified 2727 titles in total, assessed 399 full texts, and retained 82 full texts for evidence synthesis, with 20 of them identified for several research questions. Only 3 randomized controlled trials were identified with two of them published only in abstract form, as well as 28 prospective and 31 retrospective studies, and 20 case reports. Relevant risk of bias regarding selection and comparability was identified for most of the studies. No meta-analysis could be performed. The prevalence of hypophosphatemia varied substantially in critically ill adults and children, but no study assessed consecutive admissions to intensive care. In both critically ill adults and children, several studies report that hypophosphatemia is associated with worse outcome (prolonged length of stay and the need for respiratory support, and higher mortality). However, there was insufficient evidence regarding the optimal threshold upon which hypophosphatemia becomes critical and requires treatment. We found no studies regarding the optimal frequency of phosphate measurements, and regarding the time window to correct hypophosphatemia. In adults, nutrient restriction on top of phosphate repletion in patients with refeeding syndrome may improve survival, although evidence is weak. Conclusions Evidence on the definition, outcome and treatment of clinically relevant hypophosphatemia in critically ill adults and children is scarce and does not allow answering clinically relevant questions. High quality clinical research is crucial for the development of respective guidelines.

Hypophosphatemia in critically ill adults and children – a systematic review

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Abbreviations

AKI	Acute Kidney Injury
ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	Adenosine Triphosphate
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRRT	Continuous Renal Replacement Therapy
ESICM	European Society of Intensive Care Medicine
HDU	High-Dependency Unit
HypoP	Hypophosphatemia
ICU	Intensive Care Unit
LOS	Length of Stay
MEN	Section of Metabolism, Endocrinology and Nutrition
MV	Mechanical Ventilation
NICE	National Institute for Health and Care Excellence
Pi	(inorganic) phosphate measured from serum/plasma
PICO	Population/Indicator/Comparator/Outcome
PICU	Pediatric Intensive Care Unit
Q	Question
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
SOFA	Sequential Organ Failure Assessment

Abstract

Background & aims: Phosphate is the main intracellular anion essential for numerous biological processes. Symptoms of hypophosphatemia are non-specific, yet potentially life-threatening. This systematic review process was initiated to gain a global insight into hypophosphatemia, associated morbidity and treatments.

Methods: A systematic review was conducted (PROSPERO CRD42020163191)**.** Nine clinically relevant questions were generated, seven for adult and two for pediatric critically ill patients, and prevalence of hypophosphatemia was assessed in both groups. We identified trials through systematic searches of Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, CINAHL, and Web of Science. Quality assessment was performed using the Cochrane risk of bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Results: For all research questions, we identified 2727 titles in total, assessed 399 full texts, and retained 82 full texts for evidence synthesis, with 20 of them identified for several research questions. Only 3 randomized controlled trials were identified with two of them published only in abstract form, as well as 28 prospective and 31 retrospective studies, and 20 case reports. Relevant risk of bias regarding selection and comparability was identified for most of the studies. No meta-analysis could be performed. The prevalence of hypophosphatemia varied substantially in critically ill adults and children, but no study assessed consecutive admissions to intensive care.

In both critically ill adults and children, several studies report that hypophosphatemia is associated with worse outcome (prolonged length of stay and the need for respiratory support, and higher mortality). However, there was insufficient evidence regarding the optimal threshold upon which hypophosphatemia becomes critical and

requires treatment. We found no studies regarding the optimal frequency of phosphate measurements, and regarding the time window to correct hypophosphatemia. In adults, nutrient restriction on top of phosphate repletion in patients with refeeding syndrome may improve survival, although evidence is weak.

Conclusions: Evidence on the definition, outcome and treatment of clinically relevant hypophosphatemia in critically ill adults and children is scarce and does not allow answering clinically relevant questions. High quality clinical research is crucial for the development of respective guidelines.

Key words: phosphate, hypophosphatemia, critical illness, refeeding syndrome, prevalence, outcome

Introduction

Phosphate is the main intracellular anion of the human body and it is indispensable for numerous essential biological processes. Indeed, energy derived from food or endogenous catabolism is stored as energy-rich phosphate bonds (e.g. adenosine triphosphate, creatine phosphate). Phosphate is an essential component of DNA and RNA, the cell membrane, signaling molecules, 2,3-diphosphoglycerate in red blood cells, and hydroxyapatite in the bone. Besides that, phosphorylation and dephosphorylation through the activities of numerous kinases, respectively phosphatases are important in regulating protein function, as well as in carbohydrate metabolism [1]. The kidney is a major regulator of phosphate homeostasis, normally 80-90% of filtered phosphorus is reabsorbed and the rest is excreted in the urine [2, 3].

Hypophosphatemia does not necessarily indicate phosphorus depletion [2] as only about 1% of phosphorus is present in the extracellular compartment, mainly in form of inorganic phosphate that can be measured from serum/plasma (Pi). However, hypophosphatemia often reflects a whole body deficiency and may mirror a dysfunction of homeostasis and thus potentially severe illness. Hypophosphatemia may result from decreased intake and absorption, increased losses, or transcellular redistribution caused by an increased cellular uptake of phosphate [4, 5]. Several risk factors for hypophosphatemia commonly occur in critically ill patients, including anorexia, feeding intolerance, pre-existing nutritional deficits, increased cellular phosphate uptake by refeeding, insulin therapy and acute respiratory alkalosis, and increased losses through diuretics, continuous renal replacement therapy [1, 4] and antacids. Symptoms of hypophosphatemia are non-specific, yet potentially life-threatening, and include muscle weakness, impaired myocardial contractility and

ventricular arrhythmias, respiratory failure, rhabdomyolysis, ileus, immune dysfunction, encephalopathy, and hypercalciuria [1, 5]. Despite the presumed importance of maintaining normal phosphate concentration in both health and disease states, and the common presence of risk factors of hypophosphatemia, several recent surveys have indicated that routine phosphate monitoring is not widespread in patients admitted to intensive care units (ICU) and that hypophosphatemia is often not corrected [6, 7].

In this context, there is an urgent need for a better understanding of the morbidity and treatment of hypophosphatemia. As a first step, we performed a systematic review. The aim was to summarize the existing evidence regarding hypophosphatemia, its association with outcome, as well as the clinical impact of correcting hypophosphatemia in critically ill adults and children.

Methods

The project was initiated by a group of intensivists within the Section of Metabolism, Endocrinology and Nutrition (MEN) of the European Society of Intensive Care Medicine (ESICM), and received ESICM endorsement. We registered the study protocol at PROSPERO (CRD42020163191). Our specific research questions (Q) in PICO (Population/Indicator/Comparator/Outcome) format are presented in **Table 1**.

Study selection

We identified studies through systematic searches of Medline, EMBASE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. The literature searches were updated in February 2020, for Q4 search strategy was adjusted after

initial assessment and the last search performed in June 2020. We did not impose restrictions on publication date, language or publication status. We included observational studies (both prospectively and retrospectively collected data; cohort studies; case-control studies), case reports, and randomized controlled trials (RCTs) in critically ill adults and children. We excluded non-clinical studies and studies not related to critical illness.

We imported citations from each database into the reference management software Endnote (Version X9) and removed duplicates. For each question, two authors independently screened the titles and abstracts and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. Thereafter, two authors independently screened the full text and identified studies for inclusion in evidence synthesis. In cases of disagreement, a third author arbitrated. We assessed reference lists of all studies and matching review articles and used the related articles feature of Medline to identify additional references. We completed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagrams for each research question (Supplement 1).

All identified papers were assessed for reporting of prevalence of hypophosphatemia.

Data extraction and management

Data extraction for all studies retrieved for full text assessment was performed by at least two authors for each research question. Studies relevant for evidence synthesis were selected during this process and the reason for exclusion documented for the remaining studies. Predefined outcomes of interest included mortality (ICU mortality, and at latest time-point reported), ICU-dependency, ICU length of stay, hospital

length of stay, duration of mechanical ventilation, frequency and type of arrhythmias, infections, acute kidney injury, renal replacement therapy, dynamic Sequential Organ Failure Assessment (SOFA) (sub)scores, rhabdomyolysis, muscle weakness and gastric residual volumes. Definitions for each outcome were assessed as reported by the study authors in the respective publications.

Risk of bias assessment

Quality assessment was performed using the Cochrane risk of bias tool for RCTs [8] and the Newcastle-Ottawa Scale for observational studies [9, 10]. Risk of bias assessment was performed only for cohort and case-control studies that included at least 10 patients.

Data analysis and report

Anticipating the underlying limited quality of the evidence, we did not intend to perform meta-analyses *a priori,* but assessed identified evidence for respective possibility. We summarized our results in form of a scoping review. Per research question, we reported the number of studies retrieved, the summary of the main findings in these studies, and a concise summary of the topic.

Results

Study selection

During the search process, we merged the initial questions regarding association of hypophosphatemia with impaired outcome and with organ failures (questions 1 and 2 addressing critically ill adults and questions 8 and 9 addressing critically ill children). The PRISMA flow diagrams are presented in Supplement 1. Aggregating all research

questions, we identified 82 papers used for evidence synthesis, with 20 of them selected for several questions. Studies addressing prevalence of hypophosphatemia in adults are presented in **Supplement Table S1** and are included for each research question separately (**Tables S2 to S6)**.

Risk of bias assessment

Of 82 papers selected for evidence synthesis, 24 included less than 10 patients. Accordingly, risk of bias assessment was performed for 58 studies, consisting of 3 RCTs, 24 prospective and 31 retrospective observational studies. Risk of bias evaluation for observational studies showed high risk of bias in all studies in comparability domain, resulting in overall rating as 'poor' according to AHRQ (Agency for Healthcare Research and Quality) standards. Rating in selection domain was ≥3 stars in 58%. In outcome/exposure domain 76% of studies were rated with three stars. The risk of bias assessment separated per research question is presented in Supplement 2.

General considerations

During the review process, it became obvious that there was no uniform definition of clinically relevant hypophosphatemia for ICU patients, whether adult or pediatric. Different authors have proposed to distinguish between moderate (serum/plasma phosphate level – Pi<0.65 mmol/l) and severe (Pi<0.32 mmol/l) hypophosphatemia [1]. However, these cut-offs are based on old studies in hospitalized patients, and not ion ICU patients [11, 12], or are defined by clinical chemistry laboratories [13]. In ICU patients, phosphate level might change faster than in non-ICU population, with consequences being potentially more severe. A recent point-prevalence survey in

ICU patients defined severe hypophosphatemia as Pi<0.65 mmol/l [14]. Hereafter, the values will be reported according to the authors' definitions in respective studies.

Prevalence of hypophosphatemia in adult critically ill patients

The majority of data on prevalence originate from prospective or retrospective observational small-size studies in specific pathologies. Variability is related to case-mix and to sampling time point. We did not identify any study evaluating consecutive ICU admissions (**Supplement, Table S1**). In one large retrospective cohort study covering a 4-years period and 2730 unselected ICU patients – 20% presented with at least one episode of hypophosphatemia (Pi<0.6 mmol/l) [15].

Hypophosphatemia in ICU results from phosphate internal redistribution and renal losses [1, 4]. Initiation of nutrition is only one of the causes of hypophosphatemia in critically ill patients. Not only the refeeding hypophosphatemia, but glucose-insulin therapy, respiratory alkalosis and catecholamines may cause cellular redistribution-related hypophosphatemia. Hypophosphatemia caused by renal losses occurs due to diuretics, corticosteroids and continuous renal replacement therapy (CRRT) [16]. In 290 mixed ICU patients – excluding patients on CRRT – the prevalence of all-cause hypophosphatemia, prospectively evaluated on Days (D) 1, 3, 5 and 7, was 24%, and 1.4% for severe hypophosphatemia [16], 80% being attributed to effluent losses. The prevalence of hypophosphatemia in patients with acute kidney injury (AKI) on RRT was highly variable from 11 to 85% in a recent review [4]. In a recent retrospective cohort-study hypophosphatemia occurred in 63% of patients within mean 34h after starting CRRT despite systematic phosphate administration [17].

The secondary analysis of an RCT comparing mortality in low-intensity versus a high-intensity CRRT in 1441 ICU patients [18] revealed that 32.1% (462 patients)

developed hypophosphatemia (Pi<0.6 mmol/L) with a peak on D3 and D4: 39% of patients presented more than one episode of hypophosphatemia. Among them, 3% presented with severe hypophosphatemia (Pi<0.2 mmol/L).

Some studies reported prevalence of hypophosphatemia up to 60% in unselected [19-21] and in selected cohorts (e.g. in severe brain injury [22] and post cardiac surgery [23]. At the opposite, a retrospective study identified hypophosphatemia 'only' in 16% of 68 critically ill patients with anorexia nervosa included from 11 ICUs out 30 participating ICUs [24]. A small prospective study including 41 patients with phosphate determination reported hypophosphatemia (Pi<0.8 mmol/l) on admission in 29%, with 33% of them presenting severe hypophosphatemia (Pi<0.3 mmol/l) [25].

Several studies have focused on the relationship between hypophosphatemia and nutrition support. In 109 adult ICU patients, not suffering renal failure, nor severe hypophosphatemia upon admission, staying at least 48 hours and receiving enteral nutrition, hypophosphatemia occurred in 40% of patients, with 4% qualified as severe. Yet, all patients received systematic daily intravenous phosphate complements [26]. Likewise, in medical ICU patients with multiple comorbidities, receiving nutritional support for ≥4 days, hypophosphatemia (Pi<0.77 mmol/l) occurred during the first 7 days in ICU in 53% of patients (10% with Pi<0.32 mmol/l), with no difference between those receiving enteral or parenteral nutrition [20]. Hypophosphatemia (Pi<0.7 mmol/l or a decrease ≥0.5 mmol/l from baseline) occurred in 31% of 926 adult general-ICU patients in a retrospective cohort, mostly within the first three ICU days [19]. In 213 surgical critically-ill patients receiving enteral nutrition for at least 72 hours, a prevalence of 59% hypophosphatemia (Pi<0.65 mmol/l) and 7% severe (Pi<0.3 mmol/l) was retrospectively observed [21]. In the retrospective study by Olthof et al

hypophosphatemia occurred in 37% of 337 patients (discussed in detail under Q5) [27].

In summary, data on the prevalence of hypophosphatemia in adult ICU patients are limited and reported very variable numbers. A recent review proposes that hypophosphatemia occurs in one third of ICU patients without new evidence [28], this appreciation being a recitation of several earlier narrative reviews [29, 30] and based on two studies from 1990s [31, 32]. Reports vary due to subjectively selected cohorts, different studied causes of hypophosphatemia, variability in phosphate supplementation and inconsistency in cut-off for defining hypophosphatemia. Nevertheless, hypophosphatemia appears a common complication occurring particularly during the first days of critical illness, occurring also in absence of artificial nutrition.

Individual research questions

Q1+2: Is hypophosphatemia associated with development of organ failures and impaired outcome in adult ICU patients?

We identified 810 records from the search and two additionally, of which 604 were excluded based on title and abstract (Supplement 1). During full text assessment, 173 records were excluded subsequently, finally resulting in 35 relevant publications, consisting of one RCT, two post-hoc analyses of RCTs and 32 observational studies (**Supplement, Table S2**).

In general, subjects with a more severe illness are more likely to present with hypophosphatemia at admission [19, 33]. However, hypophosphatemia at admission has also been shown to be an independent risk factor for 28-day mortality [34].

Similarly, it is commonly observed that postoperative hypophosphatemia after elective surgery is related to magnitude or difficulty of the surgical procedure, to comorbidities, and to severity of underlying disease [33, 35-37].

To evaluate the potential impact on outcome, it is important to know at what time point the sample was taken, and to describe the study group and corrective actions. Hypophosphatemia at admission or occurring independent of CRRT or nutrition is associated with a higher mortality risk in several retrospective series [19, 20, 38-40], although not in all [26, 27, 41-44]. In contrast, hypophosphatemia secondary to CRRT has limited clinical consequences in most retrospective studies [19, 45-48] (possibly related to “preventive” phosphate administration [49]), but not in all [34, 48, 50]. Associations have been observed between hypophosphatemia and respiratory failure, need of mechanical ventilation or failure of weaning [48, 51-55], circulatory failure [56], and neurological failure [57]. Moreover, phosphate repletion was associated with improved organ function and survival in several studies [32, 58, 59]. One study observed better outcome associated with phosphate repletion [60].

The picture for hypophosphatemia related to nutrition as a feature of the refeeding syndrome, is more complicated; the importance of nutrient restriction is addressed under Q5. Several observational reports, and one RCT, indicate refeeding hypophosphatemia as a mortality and morbidity risk [27, 31, 61]. In this perspective the aggressiveness of the nutritional start and hypophosphatemia occurring before or after initiation of feeding should be considered. Restoration of phosphate level might be sufficient to abolish a negative effect [21], but combination with a withholding of 50% of nutrition for 3-5 days was associated with improved survival and morbidity in a RCT [61].

In summary, it remains unanswered whether the association of hypophosphatemia with organ failure and mortality can be generalized, or is subgroup- or context-specific, and whether there is a causal relation, or a reflection of disease severity. Likewise, the pathophysiological mechanisms behind these phenomena remain to be clarified [15].

Q3: In adult ICU patients with hypophosphatemia, should we aim to normalize serum phosphate levels within 24 hours?

We identified 199 records (198 via direct search, and 1 additional during assessment of identified papers). We excluded 180 records based on title and abstract and assessed the full text of 19 papers. No comparative study evaluating phosphate repletion versus no (or insufficient) administration with relevant clinical outcomes could be identified (Supplement 1). Strikingly, several studies had been published as an abstract, but no full papers followed within the next 2-8 years. Consequently, there is no evidence to answer this study question.

One paper suggested for full text assessment did not fulfil the criteria (i.e. correction within 24hrs), but may be valuable for practice and needing integration in future RCTs [62]. This small (n=47) but well documented RCT, tested rapid (2-3 hours) versus gradual (4-6 hours) correction of moderate or severe hypophosphatemia. Both regimes showed to be effective and safe with regard to short-term adverse outcomes [62].

Q4: Is hypophosphatemia associated with muscle weakness in adult ICU patients?

We identified 835 records (826 from search and 9 additional), of which 781 were excluded based on title and abstract (Supplement 1). Subsequently, 19 records were excluded, finally resulting in 35 relevant publications, consisting of one RCT, one clinical experimental study, 17 observational studies, and 16 case reports (**Supplement, Table S3**).

All the studies on muscle weakness did not focus on skeletal muscle but rather on respiratory muscle weakness, estimated by weaning failure, duration of mechanical ventilation or change in trans-diaphragmatic pressure. None of the studies specifically investigated skeletal muscle weakness.

In a per protocol analysis of the only RCT addressing Q4, phosphate administration compared to none decreased the number of days on mechanical ventilation (19.5 vs. 15.9 days, $p<0.05$), decreased reintubation rate (10.5% vs 8.2%, $p<0.05$), and increased negative inspiratory force (16.5 vs 23.0 cm H_2O, $p<0.05$). This RCT (published only in abstract form), however, was limited due to 28.9% (n=44) of the 152 critically ill patients on mechanical ventilation being excluded from analysis [63].

Phosphate administration increased trans-diaphragmatic pressure upon phrenic stimulation in a small clinical experimental study in 8 hypophosphatemic mechanically ventilated critically ill patients [64].

Eight prospective and 8 retrospective observational studies included a median of 190 participants (range 60-2730) [15, 19, 31, 34, 36, 40, 48, 51-55, 65-68] . Source of bias (Supplement 2), other than retrospective design [15, 19, 34, 52, 54, 65, 68], included a selection bias due to the inclusion being based on availability of phosphate measurements [19, 34, 36, 54, 67, 68]. Hypophosphatemia as compared to normo-phosphatemia was associated with weaning failure in five [52, 53, 55, 65, 67] out of six studies in patients with AKI [67], exacerbation of COPD [52, 55, 65] and mixed ICU-populations [53, 54]. Association between hypophosphatemia and prolonged mechanical ventilation was shown in six out of eight studies [19, 31, 34, 36, 40, 48]. Duration of mechanical ventilation was longer in the normo-phosphatemic group in a study of septic patients [59], and one mixed-ICU study did not find an independent association of hypophosphatemia with mechanical-ventilation free days [15].

In a single-center, prospective, observational study of 100 patients with multiple trauma admitted to the ICU who needed mechanical ventilation the best cut-off point for serum phosphate to predict longer duration of mechanical ventilation was 0.99 mmol/L [51], being within the normal range. The last observational study described worsening of respiratory function in two patients due to severe hypophosphatemia and more frequent occurrence of increased muscle enzymes in the hypophosphatemic group [68].

Sixteen case reports reported symptoms of muscle weakness in hypophosphatemic patients. Serum phosphate levels varying between 0.1-0.6 mmol/l were associated with general weakness [69-73], decreased muscle tone and muscle strength [74, 75], paralysis [76], flaccid quadriparesis [77, 78], absent tendon reflexes [74, 76], rhabdomyolysis [79], ataxia [69], dyspnea [71, 80], decreased vital capacity [70] and

acute respiratory failure [69, 70, 72-79, 81-84] in 16 case reports in toto. Clinical improvement was related to phosphate repletion in all cases.

In summary, based on weak evidence, hypophosphatemia appears to be associated with muscle weakness in critically ill adult patients.

Q5: Should we aim to caloric restriction in adult ICU patients who develop hypophosphatemia after initiation of feeding?

We identified 288 records (279 directly via search and 9 additional from other research questions) of which 263 were excluded based on title and abstract. During full text assessment 22 were excluded (Supplement 1), finally resulting in 3 relevant publications (**Supplement**, **Table S4**).

In patients developing hypophosphatemia (Pi<0.65 mmol/l with change >0.16 mmol/l) within the first 3 days, nutrient restriction improved hospital, 60- and 90-day survival [61]. Nutrient restriction consisted in a decrease in caloric intake to 20 kcal/kg for two days followed by a progressive increase to target if there was no more need for additional phosphate. In case of new hypophosphatemia during the escalation of caloric intake, the protocol started again with two days of reduced caloric intake. Most of the increased mortality in the standard care group occurred after ICU discharge around day 10. Standard care increased glycemia and lactatemia and provoked excess pulmonary and overall infections rate. The RCT included 339 patients over a period of 3.5 years in 13 hospitals (7 patients per ICU year) in exclusively in Australia and New Zealand, cautioning external international validity. Nevertheless, one observational study in patients ventilated for >7 days found that a lower caloric intake during the first 3 days in ICU was associated with a better survival in the subgroup that developed hypophosphatemia [27]. This observation is remarkable because the

group with feeding-associated hypophosphatemia already had a trend for a lower caloric intake during the first 3 days [27]. Additionally, one RCT, published only in abstract form, observed more hypophosphatemia in isocaloric vs calorie-restricted group [85].

All reviews recommend a gradual increase in caloric intake in critically ill patients at risk for refeeding syndrome [86]. Most studies in a previous systematic review agree with the National Institute for Health and Care Excellence (NICE) criteria as risk factors, but the identification of this risk group does not appear to be very precise [87]. The ASPEN refeeding recommendations balances the concept of gradual increase in caloric intake against the desire to achieve a fast weight gain in anorexia nervosa patients [88]. This is certainly not applicable in ICU patients where rapid weight gain in not an objective.

In summary, prevention or attenuation of hypophosphatemia related to artificial nutrition is probably possible with a gradual increase in calories over the first days in ICU. In patients with Pi<0.65 mmol/l a decrease of caloric intake until phosphate level is normalized, appears to be associated with improved outcome.

Q6: Should we assess serum phosphate at least three times a week in adult ICU patients?

We identified 78 records, of which 70 were excluded based on title and abstract (Supplement 1). Remaining 8 references were excluded after full text assessment. In 4 references, the search question was not addressed. The other 4 appeared to be just a study protocol. Full text assessment did not reveal any additional references.

Accordingly, we could not identify any relevant paper addressing the sampling frequency and based on the current evidence, this question cannot be answered.

Q7: Should we target serum phosphate levels of 0.8 mmol/L versus lower in adult ICU patients?

We identified 351 records (336 via search directly and 15 additional titles during assessment of identified papers), of which 309 were excluded based on title and abstract (Supplement 1). During full text assessment, 27 records were excluded subsequently, finally resulting in 15 relevant publications, consisting of one RCT, 12 observational studies and 2 case reports.

Studies included relatively few patients (median 24, range 1-152), and were characterized by a substantial heterogeneity (**Supplement, Table S5**) and did not compare directly a phosphate target of 0.8 mmol/L versus a lower repletion target.

In a RCT (published only in abstract form, see details in Q4) in 152 critically ill patients, the intervention reportedly facilitated weaning from mechanical ventilation, with no difference in ICU length of stay [63].

We identified three observational studies in which a cohort with more intensive phosphate administration was compared to a historical control group with less or no phosphate administration. Two studies attributed clinical benefit to the phosphate repletion protocol, with less need for antiarrhythmic treatment [58], and fewer complications in ICU, defined as a combination of new infections, new-onset arrhythmias and myocardial infarction [89]. A third study did not attribute adverse reactions to phosphate repletion but did not report clinical outcomes in both groups

[90]. Several potential sources of bias are present in the three studies, including the retrospective design [89, 90], the use of a historical control group with potentially other changes in treatment over time [58, 89, 90], insufficient data regarding baseline risk factors [58, 89], inadequate phosphate repletion in a subset of patients [90], no data regarding achieved phosphate concentrations after repletion [58], and post hoc exclusion of potentially treated patients [58].

Nine observational studies and two case reports reported divergent clinical effects occurring after phosphate administration to patients [32, 56, 91-99]. Three observational studies and one case report found increased cardiac index and/or left ventricular stroke work (index) immediately after infusion of an intravenous phosphate supplement to patients with hypophosphatemia (with different cut-offs, albeit always <0.65 mmol/l) [32, 56, 95, 97]. A case report attributed resolution of hemolytic anemia and related encephalopathy to correction of extreme hypophosphatemia (Pi=0.03 mmol/l) [96]. Five observational studies reported no change in creatinine (clearance), urea concentrations, urinary output, or tendon reflexes 6 to 48 hours after infusion of a phosphate supplement for hypophosphatemia [91-93, 98, 99]. One observational study reported no arrhythmias during infusion of potassium phosphate to correct hypophosphatemia [94]. Numerous sources of bias include the short follow-up period in all studies, exclusion of potentially treated patients in retrospective studies [91, 92], uncertainty regarding adequacy of phosphate administration [56, 91-94, 96, 97, 99], selective reporting [98], potential selection bias [32], and the use of CRRT as confounder of spontaneous changes in urea and creatinine concentrations [99].

In summary, we found no studies investigating which phosphate repletion target would be optimal in adult ICU patients. We found several studies and case reports attributing clinical benefit to phosphate administration in patients developing hypophosphatemia, with varying targets and protocols for repletion. However, all studies were relatively small and suffered high risk of bias in several assessed components (Supplement 2).

Q8+Q9: Is hypophosphatemia associated with development of organ failures and impaired outcome in critically ill children?

We identified 164 records about hypophosphatemia in critically ill pediatric patients (149 directly via search and 15 additionally), of which 121 were excluded after abstracts reading. We assessed 43 full texts, and subsequently excluded 29 records, finally resulting in 14 relevant publications, consisting of 7 observational prospective studies, 5 retrospective studies and two case reports (**Supplement, Table S6**).

Definition of hypophosphatemia in children depends on age [100-110]. In a monocentric retrospective study including 235‘980 hospitalized children (6 months to 18 years old), severe hypophosphatemia was defined as a serum $Pi \leq 0.38$ mmol/l, based on need for transfer to pediatric high-dependency (HDU) or pediatric intensive care units (PICU) as a surrogate for adverse outcome [111]. Based on a more conservative cut-off of 0.8 mmol/l, hypophosphatemia on admission to PICU, would occur in 5% to 50% of admitted patients [100, 108, 109, 112-114], even in countries with low prevalence of malnourished children [115]. Moreover, hypophosphatemia occurs during the first 3 to 7 days in PICU in 30% to 76% of stays [102, 104, 105, 107, 113]. Risk factors on admission or during PICU-stay are: malnutrition like

kwashiorkor, rickets, anorexia nervosa [101, 108], refeeding syndrome [112], diabetic ketoacidosis [106], sepsis [100, 115], hemofiltration [116], and total parenteral nutrition [117].

Only a few studies have addressed the association of hypophosphatemia with duration of mechanical ventilation, length of stay and mortality in PICU [100, 101, 108, 110, 113-115, 118-120].

In Kenyan PICUs, hypophosphatemia was rare on admission (<7%) in a cohort of 346 patients admitted with severe malaria, but increased to 30% after 24 hours in 56 children with electrolytes determination [102]. In multivariate analysis, development of hypophosphatemia was not a risk factor of fatal outcome.

An Indian PICU-cohort including 162 critically ill children out of 369 admissions (exclusion of expected abnormality involving phosphate homeostasis) [108], hypophosphatemia occurred at least once during the first 10 days in 111 patients (72%): it was associated with prolonged PICU length of stay, but not with duration of mechanical ventilation and mortality. It is important to notice that the high overall mortality of 40% reported in this PICU could limit the external validity of the results.

The four retrospective studies conducted in Brazil, France and Turkey, reported 269 patients (range: 32-128) in total with hypophosphatemia from 851 children admitted to PICU (range: 42-613) with at least one measurement of serum phosphorus. Prevalence and association with clinical outcomes were highly variable between studies [100, 110, 112, 115].

Additionally, hypophosphatemia has been associated with gastro-intestinal complications [121], tonico-clonic seizures [122], muscle weakness, rhabdomyolysis and thrombocytopenia [123].

To summarize, hypophosphatemia is frequently reported in retrospective and cohort studies in critically ill children admitted to PICU, especially with malnutrition, diabetic ketoacidosis, or sepsis. In addition, hypophosphatemia may develop during the first days in PICU in case of severe burns, refeeding syndrome, hemofiltration, or total parenteral nutrition.

Hypophosphatemia appears to associate with the PICU length of stay, without modifying the duration of mechanical ventilation. Whether it could have impact on the mortality of critically ill pediatric patients remains unknown. Unfortunately, high level of evidence studying the impact of hypophosphatemia on clinical outcome of critically ill children is lacking.

Discussion

While the numerous studies showed that low phosphate values were frequent in critically ill adults and children, this systematic review also shows the paucity of solid evidence regarding hypophosphatemia. The prevalence varies depending on the case-mix, the timing, and treatments such as enteral/parenteral nutrition or CRRT.

While clinical chemistry laboratories propose clear reference ranges [13, 111], clinical relevant hypophosphatemia requiring treatment is a poorly defined entity, i.e. without a standardized definition or clear treatment goals. In addition, the optimal practices for measurement, and correction of hypophosphatemia remain unclear.

Case reports commonly describe fast development of hypophosphatemia in critically ill patients with harmful consequences [124], whereas larger studies do not seem to capture the most severe cases. Therefore, and because multiple factors contributing to hypophosphatemia are commonly present in critically ill, the rationale to

recommend measuring phosphate levels daily seems appropriate. However, strong supportive evidence is lacking. The limited number of prospective studies indicates that research is required to fill the evidence gaps demonstrated in this systematic review. Considering the severity of the reported manifestations, recommendations for systematic monitoring should be developed.

Currently it remains unclear whether hypophosphatemia caused by different mechanisms and developing with the different speed plays a role in determining the outcome: hypophosphatemia might just be a biomarker of the different diseases. Whether simply correcting serum phosphate levels solves the problem remains uncertain as large RCTs are lacking. In this regard, the mechanism causing hypophosphatemia is likely important as deducted from the available scarce evidence on refeeding hypophosphatemia.

The limitations of our systematic review are related to the studies that were included: scarce data, variable definitions and variable practices preclude objective comparisons and clear conclusions for our research questions. Furthermore, an important proportion of the reported information comes from retrospective reviews, observational studies and case reports. The overall sample size was small and two out of three identified RCTs were available only in abstract form. Targeted research is needed to identify the optimal strategy for phosphate monitoring and repletion.

Conclusions

Evidence to answer the pre-defined questions was insufficient. It is likely that hypophosphatemia affects several organ systems and impairs outcome in critically ill adults and children. However, the exact cut-off of serum/plasma phosphate level and

magnitude of the clinical impact remain unclear: the optimal frequency of measurements, target serum phosphate, and repletion strategy are also uncertain. When hypophosphatemia occurs in the context of refeeding syndrome, restriction of the caloric intake progression probably attenuates the magnitude of hypophosphatemia and may improve survival. Prospective interventional trials are required as are guidelines for management.

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Statement of Authorship

ARB, MMB and CI drafted the proposal of this systematic review, MC, JG, CB and ARB drafted the study protocol. JS and ARB drafted the study questions that were thereafter adjusted and agreed by all co-authors. CB and ARB defined search formulas. SF, OJB, JW, SJS and CI performed literature assessment of Q1+2, JS contributed as third reviewer to solve discrepancies. GB and MC performed literature assessment for Q3. QB and AdM performed literature assessment for Q4 and Q6. MH and MM performed literature assessment for Q5. JG and KT performed literature assessment for Q7. MAP and SD performed literature assessment for Q8+9, JS contributed as third reviewer. CI and SF performed literature assessment for prevalence. JG and ARB drafted the tables. ARB, CB, CI, JW, OJB, AdM, MC, MH, JG, KT, MHP and MMB drafted different parts of the manuscript. All authors revised the manuscript for intellectual content.

Conflict of Interest

None of the co-authors has any competing interest to declare regarding the present systematic review.

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Supplements

Supplement 1. PRISMA flow diagrams

This file presents flow diagrams for each research question.

Supplement 2. Risk of bias assessment

This file presents results of risk of bias assessment for research questions where the assessment was applicable.

Supplement 3. PRISMA checklist

This file includes PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) checklist.

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Table 1. Research questions and search formulas

1. Is hypophosphatemia associated with impaired outcome in adult ICU patients?				Search formula
PICO components				
Population	Indicator	Comparator	Outcome(s)	
Adult ICU patients *§	Hypophosphatemia in ICU, at least one measurement with Serum phosphate level <0.8 mmol/L	Serum phosphate level 0.8…1.3 mmol/L	Mortality Length of ICU stay New infections Duration of MV	#1 intensive care unit OR ICU OR critical care OR critical illness OR critically ill #2 hypophosphatemia OR hypophosphatemic OR hypophosphataemia OR serum phosphate* OR S phosphate OR S-phosphate #3 #1 AND #2
2. Is hypophosphatemia associated with development of organ failures in adult ICU patients?				
PICO components				
Population	Indicator	Comparator	Outcome(s)	
Adult ICU patients *§	Hypophosphatemia in ICU, at least one measurement with Serum phosphate level <0.8 mmol/l	Serum phosphate level 0.8…1.3 mmol/l	AKI stages, RRT, Dynamics in SOFA (sub)scores, Arrhythmias Rhabdomyolysis Gastric residual volumes	
3. In adult ICU patients with hypophosphatemia, should we aim to normalize serum phosphate levels within 24 hours?				
PICO components				Search formula
Population	Intervention	Comparator	Outcome(s)	#1 as above #2 as above #3 phosphate replacement OR phosphate* replace* OR phosphate substitution OR phosphate substitute* OR phosphate admission #4 #1 AND #2 AND #3
Adult ICU patients with hypophos-phatemia	Phosphate replacement (intravenous or enteral) aimed to Serum phosphate level ≥0.8 within 24 hours	No replacement, or ineffective replacement (Serum phosphate level <0.8 for next 24 hrs)	Mortality Length of ICU stay Muscle weakness New infections Duration of MV Dynamics in SOFA (sub)scores Arrhythmias	

4. Is hypophosphatemia associated with muscle weakness in adult ICU patients?

PICO components				Search formula
Population	Indicator	Comparator	Outcome(s)	#1 as above #2 as above #3 muscle weakness [MeSH Terms] OR Respiratory insufficiency [MeSH] #4 muscle weakness OR Respiratory failure OR respiratory weakness #5 #3 OR #4 #6 #1 AND #2 AND #5
Adult ICU patients in whom development of muscle weakness was assessed	Hypophosphatemia (Serum phosphate level <0.8)	No hypophosphatemia (Serum phosphate level ≥0.8)	Mortality Length of MV Successful weaning of MV Muscle weakness	

5. Should we aim at caloric restriction in adult ICU patients who develop hypophosphatemia after initiation of feeding?

PICO components				Search formula
Population	Intervention	Comparator	Outcome(s)	#1 as above #2 refeeding syndrome OR re-feeding syndrome OR refeeding #3 #1 AND #2
Adult ICU patients who develop hypo-phosphatemia after initiation of feeding (EN, PN or combined)	Caloric restriction additionally to phosphate substitution	No caloric restriction, just phosphate substitution	Mortality, Length of ICU stay Organ failures Infections Muscle weakness Arrhythmias	

6. Should we assess serum phosphate at least 3 times a week in adult ICU patients?

PICO components				Search formula
Population	Intervention	Comparator	Outcome(s)	#1 as above #2 serum phosphate assessment OR s phosphate assessment OR s-phosphate assessment OR serum phosphate* assessment* OR s phosphate* assessment OR s-phosphate* assessment #3 #1 AND #2
Adult ICU patients *§	Serum phosphate assessment at least 3 times a week	No serum phosphate assessment, or less than 3 times a week	Incidence of hypophosphatemia Incidence of hyperphosphatemia Mortality Length of ICU stay Organ failures Muscle weakness New infections	

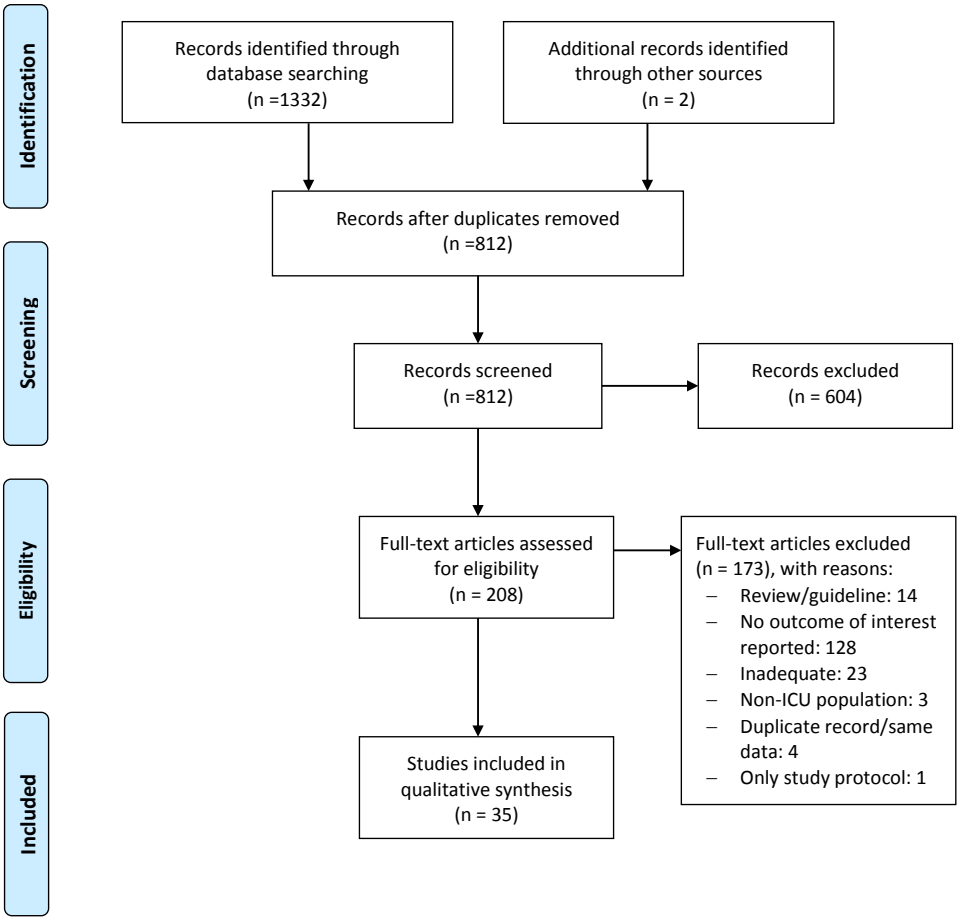
7. In adult ICU patients, should we target serum-P levels of 0.8 mmol/l vs. lower?				
PICO components				Search formula
Population	Intervention	Comparator	Outcome(s)	#1 as above #2 phosphate replacement OR phosphate* replace* OR phosphate substitution OR phosphate substitute* OR phosphate admission #3 #1 AND #2
Adult ICU patients *	Phosphate replacement with target of daily Serum phosphate level ≥0,8	No phosphate replacement, or target Serum phosphate level <0.8 mmol/l	Mortality Length of ICU stay Organ failures Muscle weakness Rhabdomyolysis New infections Arrhythmias	
QUESTIONS IN CHILDREN				
8. Is hypophosphatemia associated with impaired outcome in critically ill children?				Search formula
PICO components				
Population	Indicator	Comparator	Outcome(s)	#1 as above #2 hypophosphatemia OR hypophosphatemic OR hypophosphatemia OR serum phosphate* OR S phosphate OR S-phosphate #3 child [MeSH] #4 children OR child* OR child OR adolescent OR juvenile OR infant OR child, preschool #5 #3 OR #4 #6 #1 AND #2 AND #5
Critically ill children *§	Hypophosphatemia in ICU, at least one measurement with Serum phosphate level <0.8 mmol/l	Serum phosphate level 0.8…1.3 mmol/l	Mortality Length of ICU stay New infections Duration of MV	
9. Is hypophosphatemia associated with development of organ failures in critically ill children?				
PICO components				
Population	Indicator	Comparator	Outcome(s)	
Critically ill children *§	Hypophosphatemia in ICU, at least one measurement with Serum phosphate level <0.8 mmol/l	Serum phosphate level 0.8…1.3 mmol/l	AKI stages, renal replacement therapy Dynamics in SOFA (sub)scores Gastric residual volumes Arrhythmias	

Legend:
Predefined patient subgroups:
* Mechanical ventilation; Vasopressors; Sepsis; RRT; Parenteral nutrition only; EN only or combined with PN; Cardiac surgery.
§ Severity of hypophosphatemia (mild, moderate, severe).
≠ High vs low illness severity scores (APACHE II - Acute Physiology And Chronic Health Evaluation, SAPS II - Simplified Acute Physiology Score).
Abbreviations: AKI: acute kidney injury; EN: enteral nutrition; ICU: intensive care unit; MV: mechanical ventilation; PN: parenteral nutrition; RRT: renal replacement therapy; SOFA: Sequential Organ Failure Assessment

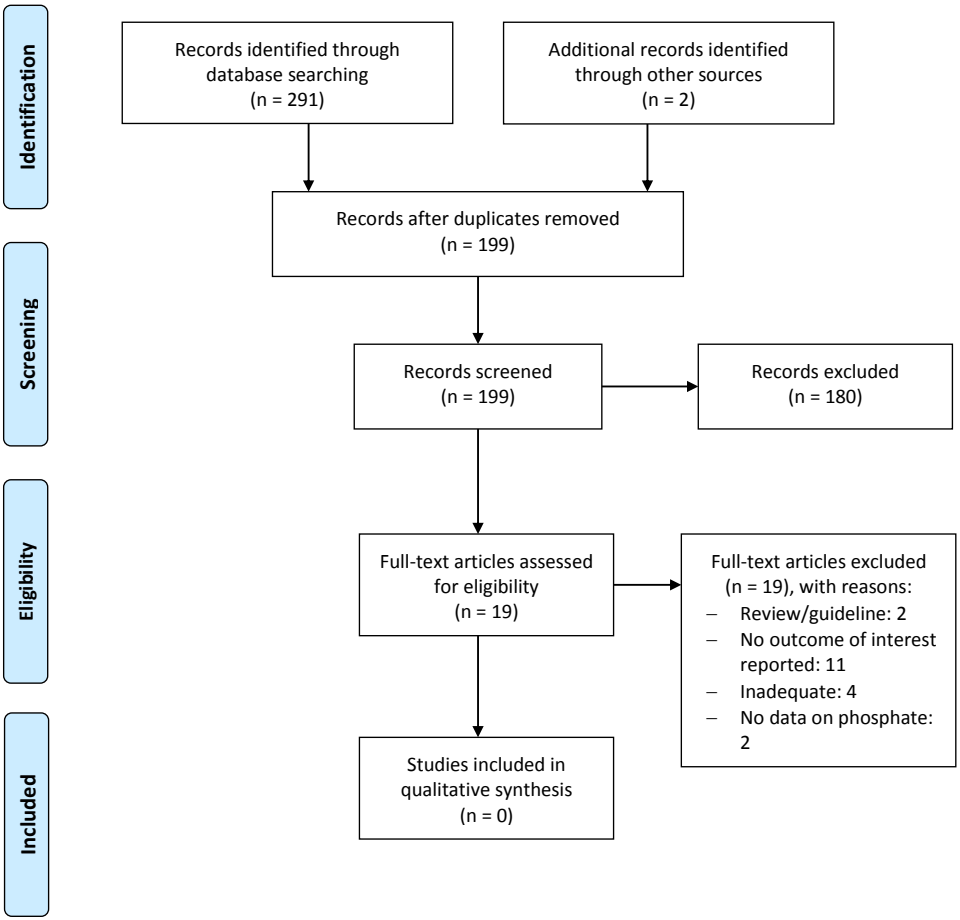
Figure (flow diagram)

Supplement 1. PRISMA flow diagrams

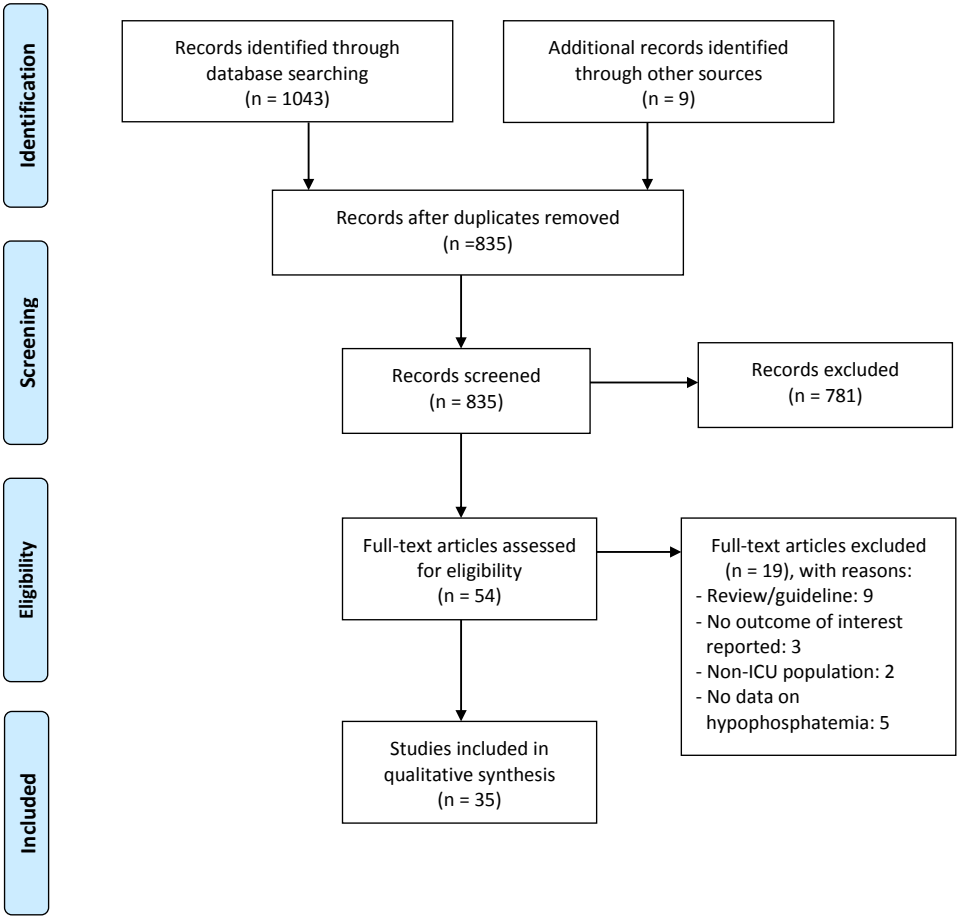
Flow diagram SQ 1,2: Is hypophosphatemia associate with impaired outcome in adult ICU patients?



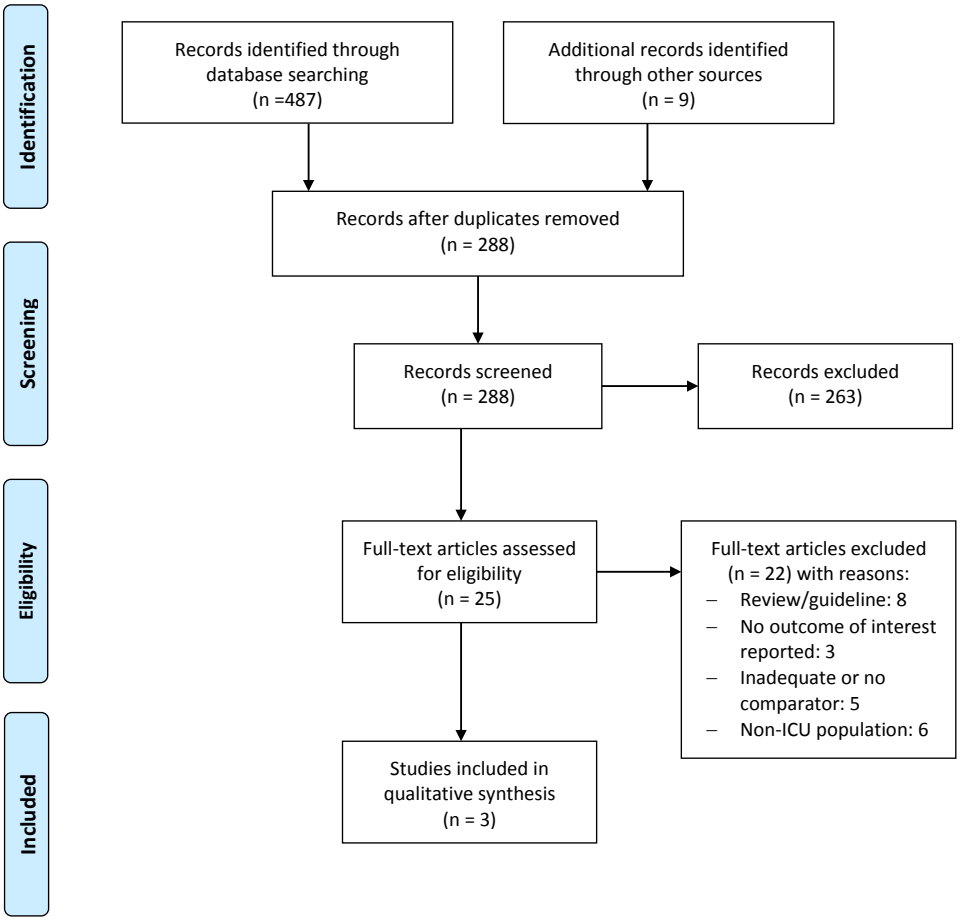
Flow diagram SQ 3: In adult ICU patients with hypophosphatemia, should we aim to normalize serum phosphate levels within 24 hours?



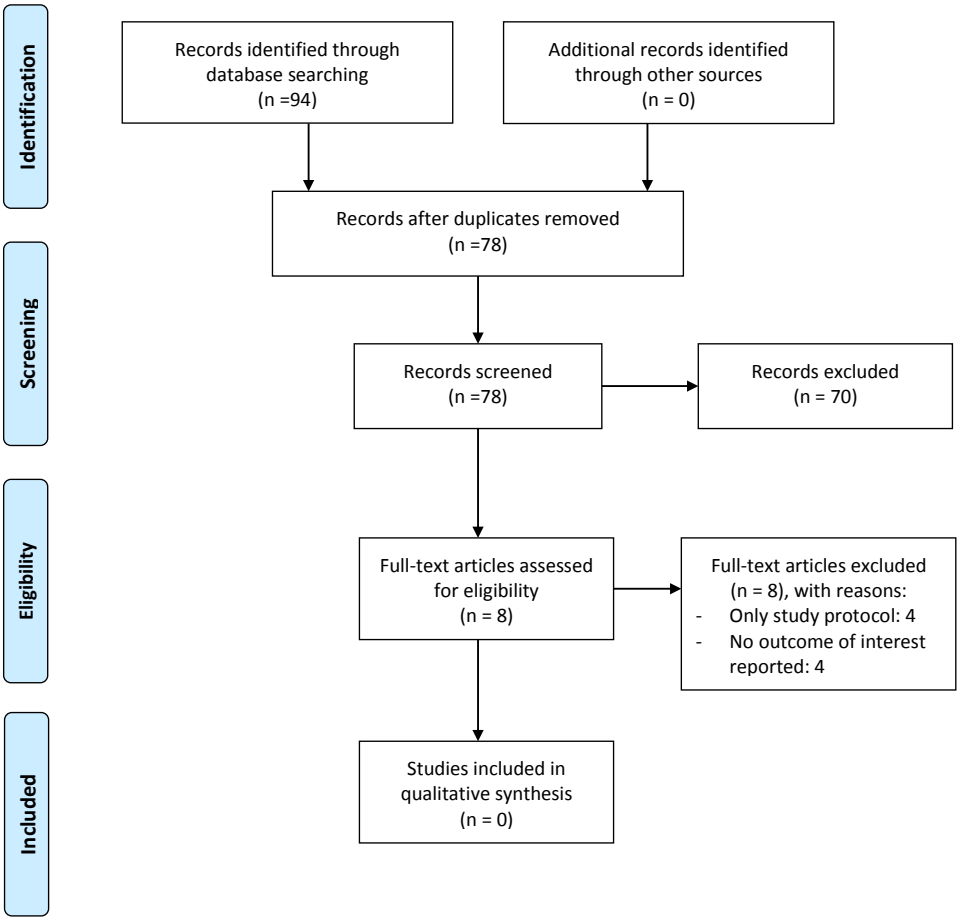
Flow diagram SQ 4: Is hypophosphatemia associated with muscle weakness in adult ICU patients?



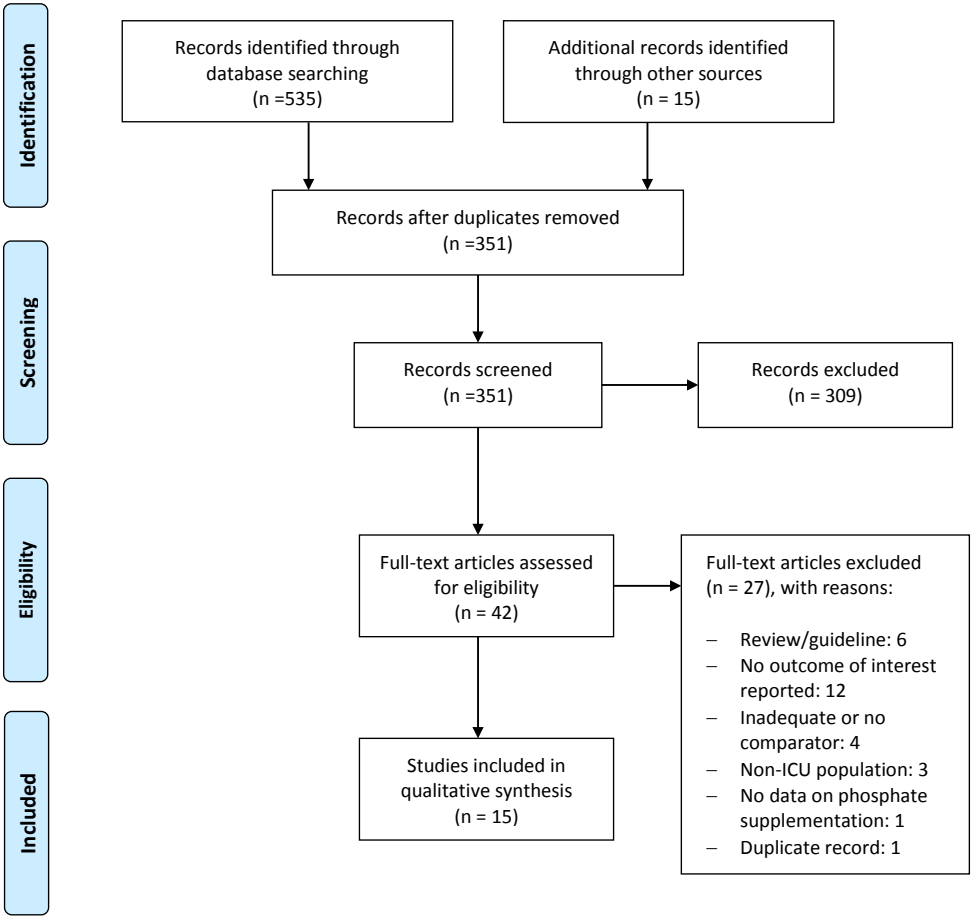
Flow diagram SQ 5: Should we aim at caloric restriction in adult ICU patients who develop hypophosphatemia after initiation of feeding?



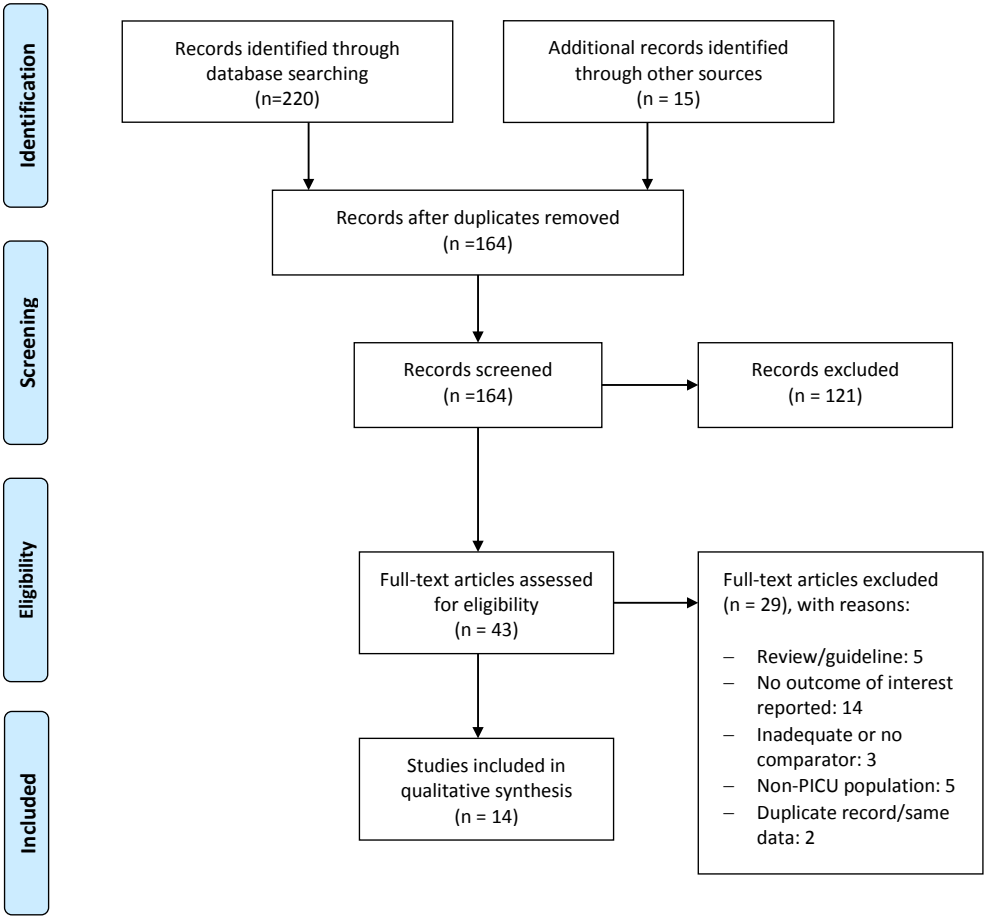
Flow diagram SQ 6: Should we assess serum phosphate at least 3 times a week in adult ICU patients?



Flow diagram SQ 7: In adult ICU patients, should we target serum-P levels of 0.8 mmol/l vs. lower?



Flow diagram SQ 8,9: Is hypophosphatemia associated with impaired outcome in critically ill children?



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Table 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Abstract; Page 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 8-9, Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Abstract; Page 9-10; Supplement
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplement: Tables S1 to S6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplement; Page 10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplement: Tables S1 to S6; Page 11-26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 11-26
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 25-26
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 27

PRISMA 2009 Checklist

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