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Protocol

Prospective multicenter study to describe the prevalence, outcomes, and management of phosphate disorders in intensive care patients: Study protocol for part B of the international GUTPHOS study

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ABSTRACT

Background: Aberrations in blood phosphate (Pi) levels, whether presenting as hypo- or hyperphosphatemia, appear to be associated with clinical complications and adverse outcomes in patients admitted to an intensive care unit (ICU). However, the prevalence of Pi disorders and the association with subsequent factors and organ failures leading to death in ICU patients are poorly described. Despite endeavors to understand the etiology and treatment of low Pi levels from systematic reviews and meta-analyses, the literature lacks comprehensive guidance for managing hypophosphatemia. Hyperphosphatemia, on the other hand, appears to be associated with higher mortality among critically ill patients, yet its prevalence among ICU patients, particularly following phosphate repletion, remains unknown. The present study aims to investigate the prevalence of Pi abnormalities upon ICU admission and their incidence during the first week of ICU stay, the factors associated with Pi alterations, and the effect of phosphate repletion on the normalization of Pi levels, and its associations with clinical outcomes.

Methods: This multicentre, prospective, non-interventional cohort study will include at least 1000 consecutive adult ICU patients (≥18 years) as part B of the GUTPHOS study. Sites are eligible if an anticipated minimal inclusion of 50 eligible patients during eight weeks from January 2024 until June 2024 and daily phosphate measurements during the first seven days of ICU stay are expected. All consecutive adult patients admitted to a participating ICU during the recruitment period, lasting up to eight weeks, or up to 120 patients if enrollment reaches that limit earlier, will be included. Study

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parameters include study site characteristics, patient demographics, daily assessment of Pi levels, Pi-related treatment, feeding details, renal replacement therapy details, the incidence of refeeding-associated hypophosphatemia and administered medication (during the first seven calendar days of ICU stay). There will be a follow-up period of a maximum of 90 days to document 28- and 90-day all-cause mortality as the primary outcome. Multiple logistic regression will be used to assess independent associations with mortality in addition to Receiver Operating Characteristics curves to identify cut-off Pi values associated with mortality and overcorrection. Linear mixed models will be conducted to assess Pi treatment effects. Subgroup analyses will be performed based on Pi abnormalities observed during ICU admission, categorized as normo-, hypo-, hyper-, or mixed, along with its severity (mild, moderate, or severe).

Discussion: The GUTPHOS study will be the first multicentre, prospective observational cohort study to investigate the prevalence, management practices, and consequent outcomes associated with Pi abnormalities during the first week of ICU admission. Its results may bridge the current evidence gap in repletion protocols while establishing the groundwork for a subsequent randomized controlled trial.

Clinical trial registry: NCT05909722.

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1. Background

Phosphate is a principal intracellular anion within the human body, playing an indispensable role in numerous fundamental metabolic processes [1]. The energy derived from dietary intake or endogenous catabolism is stored in energy-rich phosphate bonds, exemplified by adenosine triphosphate and creatine phosphate [1,2]. The human body tightly regulates the blood level of inorganic phosphate (Pi), with the kidneys predominantly reabsorbing 80–90% of filtered Pi while the remainder is excreted in urine [3]. However, this regulatory mechanism is significantly compromised in case of alteration of the renal function and when renal replacement therapy (RRT) is required [4]. Aberrations in blood Pi levels, whether presenting as hypo- or hyperphosphatemia, appear to be associated with clinical complications and adverse outcomes in patients admitted to an intensive care unit (ICU) [5,6]. Despite this association, the precise factors and organ failures that culminate in fatality remain inadequately characterized. In addition, the causal relationship between abnormal absolute Pi levels, relative changes, and life-threatening metabolic dysfunction remains unclear [7].

Blood Pi concentration is the primary indicator of Pi status in clinical practice. Nevertheless, it is imperative to note that hypophosphatemia does not invariably indicate depletion in total body phosphorus content, given that only 1% of phosphorus resides in the extracellular compartment, primarily measurable as Pi in serum [7]. Still, hypophosphatemia often mirrors systemic deficiency and may signify an underlying homeostatic disruption, potentially indicating severe illness [8]. Hypophosphatemia may be observed in critically ill patients due to the re-introduction of nutrition [9,10]. However, the pathophysiology and consequences of this refeeding-associated hypophosphatemia remain to be elucidated [11]. Despite endeavors to glean insight from systematic reviews and meta-analyses on best-practice hypophosphatemia treatment, the literature lacks comprehensive guidance for managing hypophosphatemia [7].

On the upper spectrum of blood Pi, acute or chronic hyperphosphatemia has been better described as a potential cause of mortality in patients with chronic renal failure [12]. Insufficient Pi clearance may be the result of acute kidney injury (AKI), which is frequently encountered in the critically ill [13]. Clinically, hyperphosphatemia can lead to life-threatening calcium-phosphate precipitation and acute hypocalcemia [14]. It has been associated with poor survival in critically ill patients in several retrospective observational studies [5,8,15].

Challenges persist in delineating severity thresholds, establishing treatment benchmarks, and comprehending Pi's dynamic response to interventions [16,17]. Additionally, empirical data regarding potential interactions between Pi and other electrolytes, such as potassium, magnesium, and calcium, are scarce. Studies examining the frequency and prevalence of hypo- and hyperphosphatemia within ICU settings are limited, particularly in establishing clear-cut severity thresholds or intervention criteria [7]. While renal replacement studies have provided some insights into the clinical relevance of hypophosphatemia, a comprehensive understanding of these electrolyte abnormalities during ICU admission remains lacking. As part B of the GUTPHOS study, this prospective multicenter study aims to investigate the prevalence of blood Pi abnormalities during the initial week of ICU admission in consecutive adult patients admitted to ICUs worldwide. In addition, factors associated with Pi alterations and the impact of treatment on normalizing Pi levels in critically ill patients will be investigated, and associations with 28- and 90-day mortality will be assessed.

2. Methods and analysis

2.1. Study design

The GUTPHOS study is an investigator-initiated collaboration between the steering committee members of the GUTPHOS investigators. The GUTPHOS investigators are active members of the Feeding, Rehabilitation, Endocrinology and Metabolism (FREM) section of the European Society of Intensive Care Medicine (ESICM). This study is part B of a combined multicenter prospective cohort, in which aside from the epidemiology, management, and outcomes of phosphate abnormalities, the validation of the Gastrointestinal Dysfunction Score (GIDS) is undertaken (part A). Part A of the GUTPHOS cohort will include at least 1400 subjects, while part B, a subset in which daily phosphate measurements are available, aims to include at least 1000 patients. Due to similarities in study protocols and common interest (both studies emerged from the FREM section of ESICM), these two studies are combined in one multicenter, prospective observational cohort study of consecutive adult ICU patients. The study is registered on ClinicalTrials.gov under the

clinical trial registry number NCT05909722 and is endorsed by the ESICM.

2.2. Setting

The GUTPHOS study aims to recruit at least 20 ICUs from the ESICM's global network, the FREM section, and the networks of individual investigators. ICUs are considered eligible if they expect to admit at least 50 eligible patients during eight weeks and provide daily Pi levels and repletion data during the patient's ICU stay for up to seven calendar days. Participating sites are free to choose the start of the eight-week study period within six months from the study start date of January 1, 2024. To prevent bias from variations in sample sizes across study sites, all participating sites will enroll all consecutive adult ICU patients, up to 120 patients, or a maximum recruitment period of 8 weeks, whichever occurs first.

2.3. Participants

All consecutive patients admitted to a participating ICU during the recruitment period of up to 8 weeks will be screened for eligibility. Irrespective of the predicted or expected duration of ICU stay or primary pathology, all patients who meet all inclusion criteria and none of the exclusion criteria will be deemed eligible and included in the study to reduce the risk of selection bias (Table 1).

2.4. Study procedures

A complete overview of study parameters is provided in the Appendix. Study parameters include study site characteristics, such as ICU size and type, average number of ICU admissions per year, type of hospital, and description of current practice regarding laboratory method for Pi assessment (including reference range). Baseline patient data will be collected (Table 2) on demographics, comorbidities, and ICU admission characteristics (admission diagnosis, principal pathology, time in hospital before ICU admission, do-not-resuscitate order, presence of AKI, disease severity expressed as the acute physiology and chronic health evaluation (APACHE II) score [18], modified nutritional risk (NUTRIC) score [19,20], and simplified acute physiology (SAPS II) score [21]. Daily assessments of the first seven calendar days of ICU stay are obtained or until ICU discharge, if earlier, including Pi concentrations up to three times daily and before and after repletion in case of phosphate repletion, other electrolytes, RRT, nutritional details, administered medication, the presence of sepsis or septic shock based on Sepsis-3 criteria [22] and sequential organ failure assessment (SOFA) scores [23]. In addition, the presence of refeeding-associated hypophosphatemia is evaluated, which is established when there is a decrease in Pi levels below 0.65 mmol/L within the first three ICU admission days of reintroduction of caloric intake, following a normal range (Pi > 0.81 mmol/L). This decrease should occur at a daily rate of at least 0.16 mmol/L without RRT support [9–11]. The follow-up period lasts until the 90th day following enrolment in which the medical research council (MRC) sum score on ICU and hospital discharge, ICU-, hospital- and 28- and 90-day all-cause mortality, hospital and ICU length of stay, and days alive and free of any modality of organ support by 28 days will be collected.

2.5. Study outcomes

The primary outcome of the study is 28- and 90-day all-cause mortality. Secondary outcomes include phosphate-related outcomes such as the prevalence of Pi abnormalities upon ICU admission, including its severity and duration during the initial week of ICU stay. The definition and severity grading of Pi abnormalities is described in Table 3. In addition, the incidence and severity of normo-, hypo-, hyperphosphatemia, or both during the first seven days of ICU stay is recorded. Furthermore, the biochemical response to treatment of hypophosphatemia, defined as the difference in serum phosphate following repletion, along with the incidence of overcorrection (defined as hyperphosphatemia or Pi $\geq$ 1.46 mmol/L) and other electrolyte disturbances (i.e., potassium, magnesium, calcium) following phosphate repletion will be assessed. Other secondary outcome parameters include days alive and free of organ support by day 28, ICU- and hospital mortality, ICU and hospital length of stay, and the prevalence of ICU-acquired weakness upon ICU discharge (defined as an MRC-sum score <48).

2.6. Ethical considerations

The University of Tartu Ethics Committee provided the primary ethical approval on May 29, 2023 (approval number 377/T-15). Each participating site will apply for local ethics Committee approval according to local site country and institutional regulations. If informed consent is deemed necessary for this observational study according to the approval of the local ethics, delayed informed consent is obtained from the patient or the patient's legal representative, next of kin, or proxy at the first possibility. If the patient's condition precludes personal consent to participate in this initial decision, but the legal representative, next of kin, or proxy agrees with participation, the patient will be asked secondarily during recovery. If the patient declines participation after being included in the study based on the consent by the patient's legal representative, next of kin, or proxy, already collected data will be handled according to local ethical rules at the site.

2.7. Data management

Patient data are collected as part of routine clinical care. National death registries, where available, or direct patient contact by site investigators will be used to obtain data on survival. All data will be recorded in an electronic case report form (eCRF) using Research Electronic Data Capture (REDCap) in a pseudonymized way. Patients are identifiable only at the site via coded patient logs, accessible only to the investigators at each site. The database will be kept until 15 years after the end of the study. Patient log sheets and

Table 1
In-and exclusion criteria for the study.

Inclusion criteria	Exclusion Criteria
- Admission to ICU during the study period - Age $\geq$18 years - Daily serum Pi measurements as part of the standard of care	- Restrictions of ICU-related care, including no intubation or no RRT on ICU admission, except for patients with a do-not resuscitate order only (i.e. without other restrictions) - Admitted to the ICU for treatment as a potential organ donor - Continuous chronic home ventilation (i.e. for neuromuscular disease) - Declined participation or informed consent - Readmission to the ICU during the study period

Table 2
Table of workflow and study-and outcome parameters obtained during the study.

	ICU Day 1	ICU Day 2	ICU Day 3	ICU Day 4	ICU Day 5	ICU Day 6	ICU Day 7	ICU discharge	Hospital discharge	Day 28	Day 90
Enrolment											
Screening	•										
Informed consent	•										
Baseline characteristics[a]	•										
Study period											
Serum phosphate	—	—	—	—	—	—	—				
Phosphate related treatment[b]	—	—	—	—	—	—	—				
Other electrolytes[c]	—	—	—	—	—	—	—				
Feeding details[d]	—	—	—	—	—	—	—				
RRT details[e]	—	—	—	—	—	—	—				
SOFA-score [23]	—	—	—	—	—	—	—				
Follow-up											
MRC-sum score [32] [f]								•	•		
Organ-free support days[g]										•	
All-cause mortality	—	—	—	—	—	—	—	—	—	—	—

Abbreviations: ICU = Intensive Care Unit; RRT = Renal Replacement Therapy; SOFA = Sequential Organ Failure Assessment; MRC = Medical Research Council.
[a] Includes demographics, ICU admission details, disease severity scores, and comorbidities. A full list of baseline characteristics is provided in the Appendix.
[b] Includes medication for hyperphosphatemia and phosphate repletion, including route, dosage and duration between two measurements.
[c] Includes potassium, magnesium, sodium, chloride, ionized calcium and bicarbonate.
[d] Includes the route of nutrition, total daily energy (nutritional and non-nutritional) and protein intake and additional administration of vitamins and trace elements.
[e] Includes modality, ultra-filtrate dosage, the composition of dialysate or substitution fluid, and usage of anticoagulation.
[f] If available.
[g] Total calendar days at 28 days during which the following organ support modalities were absent: ventilation, vasopressor, inotrope, RRT, ICU, or parenteral nutrition support.

Table 3
Definitions of hypo- and hyperphosphatemia (mmol/L or mg/dL) and their severity most commonly used in literature [3,12,13].

Definition	Mild	Moderate	Severe
Hypophosphatemia			
mmol/L	0.65–0.81	0.32–0.64	<0.32
mg/dL	1.98–2.51	0.99–1.98	<0.99
Hyperphosphatemia			
mmol/L	1.46–1.78	1.78–2.26	>2.26
mg/dL	4.5–5.5	5.5–7.0	>7.0

informed consent forms will be saved at least until the end of the study or according to local practice.

2.8. Sample size

Part A of the GUTPHOS was powered on 1400 inclusions for the validation of the GIDS score. Due to the study's observational nature, no formal power calculation was performed for part B of the GUTPHOS. As the number of patients to have significant hypophosphatemia is expected to be 20% based upon previous studies [7,8,15,24], and part of the study is to evaluate the effect of repletion of phosphate in these patients, a total number of 200 patients with significant hypophosphatemia likely to receive phosphate therapy are aimed to be included. Therefore, at least 1000 patients will be included in this study. The study anticipates an average number of 83 included patients per site and a drop-out rate of 10% (including missing relevant data). Therefore, at least 13 sites should participate in this study.

2.9. Statistical analysis

2.9.1. Epidemiology of hypo- and hyperphosphatemia

Descriptive statistics analyze patients' demographic and clinical data. Quantile–quantile plots visually assess continuous data normality, supported by the Kolmogorov–Smirnov test for inconclusive cases. Continuous values will be displayed as mean (95% confidence interval) or median [interquartile range], while discrete data will be shown as numbers (%). Subgroups will be formed based on Pi disorders observed upon ICU admission, categorized as normo-, hypo-, or hyperphosphatemia. Additional subgroups will encompass patients having and maintaining normal Pi levels-or having either hypo- or hyperphosphatemia or both (mixed) during the first seven days of ICU stay. Bivariate analyses will explore associations between Pi abnormalities and demographic and clinical characteristics to identify potential risk factors for hypo- and hyperphosphatemia. Subgroup differences are evaluated using an independent sample T-test for normally distributed data; otherwise, Mann–Whitney U tests will be applied. Patients having and maintaining normal Pi levels will be considered as the reference group. Non-dichotomous categorical data undergo analysis of variance. Normality assumptions and equal variances (via Levene's test) guide comparisons.

2.9.2. Outcome

For the primary endpoint mortality, survival curves for subgroups will be made using Kaplan–Meier curves and tested using a log-rank test. To test the association between Pi abnormalities in comparison to normal Pi levels and the primary outcome 28- and 90-day mortality, a proportional hazard regression model will be used. Linear regression models will be conducted to determine the association between Pi abnormalities and continuous outcome variables, including days alive and free of organ support at 28 days, as well as ICU and hospital length of stay. Additionally, the time to become free of organ support is compared between subgroups using a proportional hazard regression model. Lastly, logistic regression models for dichotomous outcome variables will be performed to evaluate the associations between hypophosphatemia in comparison to non-hypophosphatemia, the presence of ICU-acquired weakness, ICU- and hospital mortality. The models will be adjusted for significant variables in univariate analysis or those with univariate associations reflected by p-values

<0.10. Covariates suggestive of multicollinearity (e.g., Variance of Inflation factor >5.0) or violating the proportional hazard assumption will be excluded from the model.

2.9.3. Phosphate repletion

Receiver Operating Characteristics (ROC) curves will be drawn to identify cut-off values for Pi concentrations potentially associated with mortality and to identify amounts (mmol) of phosphate administration associated with overcorrection, defined as hyperphosphatemia (≥1.46 mmol/L) following repletion. A linear mixed model will estimate the treatment impact on mortality and the secondary endpoints days alive and free of organ support at 28 days and, in particular, ventilator-free days at 28 days, presence of ICU-acquired weakness, and ICU and hospital length of stay among patients undergoing Pi treatment. In addition, the effect of phosphate repletion on the dynamics of Pi and other electrolyte levels will be evaluated using linear mixed models. In the models, treatment will be integrated as a fixed effect. Moreover, patients will be added as a random effect due to multiple measurements clustered within individuals across time points. Time is introduced as a categorical variable, as interaction with treatment allows for exploring temporal treatment variations. Subsequently, these factors will be added to the mixed models to determine whether different factors influence this effect over time. Relevant covariates that may affect outcomes (i.e., univariate associations with p-values <0.10) will be included in the models.

IBM SPSS statistics 29.0 (I.B.M. Corp, Armonk, NY, USA; 2022) will be used for all analyses. Only two-sided analyses will be used, and *p*-values ≤0.05 will be considered statistically significant.

3. Discussion

This study will be the first multicentre, prospective observational cohort study to investigate the prevalence, management practices comprehensively, and consequent outcomes associated with Pi abnormalities during the first week of ICU admission.

3.1. Epidemiology and consequences of hypophosphatemia

While numerous prospective and retrospective observational studies report that hypophosphatemia is frequently observed in the critically ill, its prevalence exhibits variability related to the definition, sampling time point, pathology, medication, and ICU-related interventions such as enteral and parenteral nutrition, and RRT [8,16,24]. Direct effects of rapid blood phosphorus depletion, including respiratory failure, impaired myocardial contractility, and gastrointestinal symptoms, have been described in case reports [1,2], while harmful consequences of severe hypophosphatemia appear to be scarce in observational cohort studies in ICU patients [7]. Therefore, the clinical consequences of different degrees of hypophosphatemia regarding survival, length of admission, and organ support in ICU patients remain inconclusive. Nevertheless, daily monitoring of blood Pi is currently advised, but firm evidence is lacking. In addition, muscle weakness has been described in cases with severe hypophosphatemia, while to date, none of the previous cohort studies has specifically investigated its relationship with skeletal muscle weakness [7]. Critical illness-related skeletal muscle weakness results in long-term physical impairments in ICU survivors, which is a significant part of the Post Intensive Care Syndrome (PICS) [25,26]. Evaluation of muscle strength by assessing the MRC-sum score upon ICU discharge and its relation to hypophosphatemia is currently lacking. Therefore, this study may provide valuable and pivotal insights into the role of Pi abnormalities in ICU-acquired muscle weakness. In addition, although there is some evidence that Pi repletion may improve respiratory muscle strength [27,28], the association between hypophosphatemia and prolonged duration of mechanical ventilation in ICU patients remains inconclusive [6,7,29]. Elucidating the prevalence and clinical consequences of hypophosphatemia in adult ICU patients requires a large multicentre cohort, including consecutive critically ill patients with different entities and therapies, to ensure comprehensive analyses and subsequent subgroup analyses.

3.2. Phosphate repletion

A survey conducted across several ICUs globally indicates a deficiency of Pi repletion protocols in most participating centers [16]. The absence of a well-defined evidence-based threshold and target for repletion might underlie this gap in practice. Identifying substantially low Pi in this large multicentre cohort may help to establish a robust evidence-based foundation for defining clinically significant hypophosphatemia, potentially serving as a benchmark for determining phosphate repletion requirements. While Pi supplementation in ICU patients is considered safe [30], the efficacy of supplementation on Pi concentrations and the need for organ support remains largely understudied [17]. It may vary depending on the route of administration, severity, and entity of hypophosphatemia in ICU patients. The current study will identify severities and entities of hypophosphatemia in critically ill patients who could significantly benefit from supplementation. Therefore, this study may be a foundational framework for a subsequent, extensive, randomized controlled trial to assess the effect of hypophosphatemia treatment in critically ill patients.

3.3. Overcorrection of hypophosphatemia

Repletion of phosphate could lead to an excessive correction of Pi levels (≥1.46 mmol/L), yet the incidence rate, risk factors, and clinical consequences of iatrogenic hyperphosphatemia in the ICU remain undetermined. Elevated Pi levels can prompt an acute reduction in calcium levels and the development of nephrocalcinosis due to the deposition of calcium-phosphate crystals, which may contribute to morbidity in the critically ill [14]. Indeed, several retrospective studies highlight an association between hyperphosphatemia during critical illness and adverse outcomes [5,15,29], while some do not describe this association [31]. The etiology of hyperphosphatemia, such as AKI, trauma, rhabdomyolysis, or overcorrection, and its subsequent clinical management might influence the clinical outcomes of ICU patients but warrants further investigation.

3.4. Conclusions and future research

This prospective observational multicentre cohort study holds the potential to enhance understanding regarding the prevalence, management practices, and consequential outcomes associated with Pi abnormalities during the initial week of ICU admission. The study's global recruitment across diverse ICU settings worldwide, enrolling consecutive critically ill patients in a fixed time period, will minimize the chance of selection bias and, as a result, enhance the generalizability and understanding of trends across regions, ensuring broader applicability of findings than previous research.

Consequently, its results may bridge the current evidence gap in repletion protocols while establishing the groundwork for a subsequent randomized controlled trial.

Study status

The study's recruitment started in January 2024. Inclusion of the last patient is expected in June 2024.

Ethics approval

The medical ethics committee from the University of Tartu Ethics Committee has approved this study (number 3 77/T-15).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study will be made available upon reasonable request.

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Authors' contributions

MM drafted and revised the original manuscript. IWKK contributed to the conception of the research and revision of the final manuscript. ARHvZ contributed to the conception of the research, writing, and revision of the manuscript and has the principal investigator's role. ARB contributed to the conception of the research, writing, and revision of the manuscript and has the co-principal investigator's role. The steering committee members contributed to the conception of the research and revised and approved the final version of the manuscript.

Declaration of competing interest

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The other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.07.024.

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