Menoufia Medical Journal

PRINT ISSN: 1110-2098 - ONLINE ISSN: 2314-6788

journal hompage: www.menoufia-med-j.com

Volume 36 | Issue 3 Article 6

2023

Phosphorus: The Forgotten Electrolyte in The Paediatric Intensive Care Unit

Fady Mohamed ElGendy
Department of Pediatrics, Faculty of Medicine, Menoufia University, Menoufia, Egypt

Wafaa Abdelaziz Eladrosy
Department of Pediatrics, Faculty of Medicine, Menoufia University, Menoufia, Egypt,
drwafaaeladrosy22186@gmail.com

Muhammad Said El-Mekkawy
Department of Pediatrics, Faculty of Medicine, Menoufia University, Menoufia, Egypt

Recommended Citation

ElGendy, Fady Mohamed; Eladrosy, Wafaa Abdelaziz; and El-Mekkawy, Muhammad Said (2023) "Phosphorus: The Forgotten Electrolyte in The Paediatric Intensive Care Unit," *Menoufia Medical Journal*: Vol. 36: Iss. 3, Article 6.
DOI: https://doi.org/10.59204/2314-6788.1082

ORIGINAL STUDY

Phosphorus: The Forgotten Electrolyte in the Paediatric Intensive Care Unit

Fady M. ElGendy, Wafaa A. Eladrosy*, Muhammad S. El-Mekkawy

Department of Pediatrics, Faculty of Medicine, Menoufia University, Menoufia, Egypt

Abstract

Objective: **To evaluate prevalence of hypophosphatemia and hyperphosphatemia and their association with outcomes among critically ill children.**

Background: **Phosphorus is an essential element for various biological functions but data about serum phosphorus level abnormalities among critically ill children are limited.**

Patients and methods: **Prospective observational study including children admitted into Pediatric Intensive Care Unit (PICU). Serum phosphorus was measured on admission, 4, 8, and 12 day Pediatric Sequential Organ Failure Assessment (pSOFA) score was calculated on admission. Hypophosphatemia and hyperphosphatemia risk factors were determined. The primary outcome was PICU mortality.**

Results: **On admission, 37.8% of patients had hypophosphatemia and 6.6% had hyperphosphatemia. 52.2% and 12.2% of patients had greater than or equal to one episode of hypophosphatemia and hyperphosphatemia, respectively. Hypophosphatemia and hyperphosphatemia were generally nonsevere. Hypophosphatemic patients had higher frequency of sepsis on admission compared with normal phospatemic patients (36.2% vs. 12.5%, $P = 0.019$). Frequency of steroid use was higher among hypophosphatemic children (27.7% vs. 6.3%, $P = 0.017$). Hypophosphatemia was associated with longer PICU stay ($P = 0.028$) and hospital-acquired infections ($P = 0.022$). The pSOFA and frequencies of both sepsis and elevated serum creatinine were significantly higher among hyperphosphatemic patients compared with normophosphatemic patients. Hyperphosphatemia was associated with higher mechanical ventilation rate ($P = 0.018$). No significant difference in mortality rate was found between hypophosphatemic, hyperphosphatemic, and normophosphatemic patients. However, phosphorus level on day 8 was lower among nonsurvivors [median (interquartile range): 3.2 (2.3−4.7) vs. 3.9 (3.4−5.2), $P = 0.046$].**

Conclusion: **Phosphorus abnormalities, particularly hypophosphatemia, are common among critically ill children. Hyperphosphatemia was more likely to be found among patients with renal dysfunction, sepsis, and higher pSOFA score. Hypophosphatemia was associated with longer PICU stay, hospital-acquired infections, higher mechanical ventilation rate and pSOFA score.**

Keywords: Critically ill, Hyperphosphatemia, Hypophosphatemia, Paediatric, Phosphate, Phosphorus

1. Introduction

Critically ill children are liable to several electrolyte disturbances with potentially serious impacts on outcome. However, phosphorus has received little attention compared with other electrolytes like sodium, potassium, and calcium [1]. Phosphorus is the second most abundant mineral in the human body. It is a component of nucleic acids and is important for formation of teeth and bones as well as for bipolarity of lipid membranes and lipoproteins. Metabolically, phosphorus is essential for energy storage; regulation of gene expression; blood buffering; activation of enzymes; and signal transduction of regulatory pathways such as in the immune response [1].

Phosphorus is highly reactive, so it does not exist as a free element in nature but is typically present as 'phosphates' (compounds containing phosphate ion, $PO4^{3-}$) [2]. Phosphate exists predominantly in

Received 25 May 2023; revised 11 July 2023; accepted 16 July 2023.
Available online 20 September 2023

* Corresponding author at: Mansoura, Al Dakahlia, 05037, Egypt. Fax: 0502238450.
E-mail address: drwafaaeladrosy22186@gmail.com (W.A. Eladrosy).

https://doi.org/10.59204/2314-6788.1082

the intracellular space (intracellular to extracellular ratio is 100 : 1) [3] and it has two forms: organic and inorganic. Organic phosphate is the major form, and it exists as a complex with carbohydrates, proteins, and lipids (e.g., cell membranes). Inorganic phosphate mainly exists as free inorganic ions. Almost all the phosphorus in the extracellular space is in the form of inorganic phosphate. Although small, this fraction is readily measurable and gives a clue to the status of phosphorus stores [4].

Hyperphosphatemia is usually caused by renal dysfunction. Hypophosphatemia can be caused by decreased intake and intestinal absorption e.g., malnutrition and diarrhea. However, transcellular shift is the commonest cause. This includes respiratory alkalosis, glucose infusion, insulin therapy, refeeding, catecholamines, rapid cell proliferation in malignancy, and hungry bone syndrome. Increased renal loss of phosphorus is a frequent cause of hypophosphatemia e.g., metabolic acidosis, intravenous fluids, diuretics, and glucocorticoids. Hypophosphatemia can cause multiple organ system dysfunctions, manifesting as muscle weakness, rhabdomyolysis, respiratory failure, ileus, heart failure, arrhythmias, encephalopathy, seizures, immune dysfunctions, and decreased oxygen delivery to the tissues due to depletion of 2, 3-diphosphoglycerate [5–8]. Medications commonly used in intensive care unit (ICU) can cause hypophosphatemia. These include catecholamines, sodium bicarbonate, diuretics, and antacids [9].

Despite its critical importance, phosphorus level is not routinely monitored in ICUs. A survey conducted by the European Society of Intensive Care Medicine revealed that only 35.9% of participants perform daily measurements of phosphate [10]. Furthermore, pediatric studies investigating the role of phosphorus in critically ill children are few, small, and inconclusive. We, therefore, conducted the present study to evaluate the prevalence of serum phosphorus abnormalities and their association with mortality and morbidity among critically ill children.

2. Methods

This was a prospective observational study, conducted on critically ill children admitted to the Pediatric Intensive Care Unit (PICU) of Menoufia University Hospital from November 2020 to March 2022. Menoufia University Faculty of Medicine Research Ethics Committee approved the study protocol (IRB: 9/2020PEDI20). Written informed consents were obtained from parents. Critically ill children, aged 1 month to 16 years, were consecutively enrolled in the study. Exclusion criteria included primary genetic disease associated with abnormal phosphorus level such as X-linked hypophosphatemic rickets, McCune-Albright syndrome, hypoparathyroidism, hyperparathyroidism, and pseudohypoparathyroidism. On admission, patients were evaluated through history and clinical examination. Sepsis and severe sepsis were diagnosed according to international pediatric sepsis consensus conference guidelines [11]. Illness severity was determined by calculating the pediatric Sequential Organ Failure Assessment (pSOFA) score by the end of the first 24 h [12]. Serum phosphorus was measured within 24 h of PICU admission then repeated on the fourth, eighth, and 12th days. Hypophosphatemia and hyperphosphatemia were defined in relation to age-dependent pediatric norms: under 1 year: 4.8–8.4 mg/dl; from 1 year to less than 5 years: 4.3–6.8 mg/dl; from 5 years to less than 13 years: 4.1–5.9 mg/dl; from 13 years to less than 16 years (male): 3.5–6.2 mg/dl; from 13 years to <16 years (female): 3.2–5.5 mg/dl [13]. 'Severe hypophosphatemia' was defined as a serum phosphorus level less than 1.5 mg/dl while 'severe hyperphosphatemia' was defined as hyperphosphatemia associated with 'calcium x phosphorus product' greater than 70. Other laboratory investigations included blood gas analysis, serum electrolytes, complete blood count, serum creatinine, blood urea nitrogen, and liver function tests. Microbiological cultures were taken from blood, urine, cerebrospinal fluid, and pleural fluid as indicated. Patients were monitored until discharge from PICU. The primary outcome was all-cause PICU mortality. Secondary outcome measures included mechanical ventilation requirement, vasoactive medication requirement, hospital-acquired infections, mechanical ventilation duration, vasoactive infusion days, and length of PICU stay. Hospital-acquired infections included principally central line-associated bloodstream Infections (CLABSI) and ventilator-associated pneumonia (VAP) which were defined according to previous guidelines [14,15]. Serum Phosphorus level measurement was done on AU680 Beckmann autoanalyzer (Beckmann, Instrument Inc., Fullerton, CA 2634–3100, USA), using Beckman Coulter inorganic phosphorus kit. Phosphorus levels were given in mg/dl.

Data were statistically analyzed, using IBM Statistical Package for Social Sciences (SPSS) version 23 (Armnok, NY: IBM Corp). Quantitative data were presented in the form of mean ± standard deviation (for normally distributed variables) or median and interquartile range (for nonnormally distributed variables). Qualitative data were presented in the

form of numbers and percentages. Chi-square test (χ^2) used to determine the associations between qualitative variables. *t*-test used compare the means between two groups. Mann–Whitney *U* test used instead of *t*-test if the variable nonnormally distributed. Correlations between quantitative variables were assessed by Spearman correlation coefficient (r_s). Results were considered statistically significant if *P* value was less than 0.05.

3. Results

Ninety patients were enrolled. Their median age was 36 months (IQR: 5–99). 57.8% were males. 25.6% had malnutrition and the mortality rate was 24.4% (Table 1). The primary reasons for PICU admission were neurological (25.6%), respiratory (20%), cardiac (14.4%), surgical (7.8%), renal (6.7%), trauma (6.7%), metabolic (3.3%), endocrinal (3.3%), gastrointestinal (3.3%), sepsis without a focus (3.3%), toxicological (2.2%), malignant (1.1%), hematological (1.1%), and immunological (1.1%). Serum phosphorus was measured to 90 patients on day 1; 75 patients on the day 4; 37 patients on day 8; and 23 patients on day 12. On admission, 37.8% of patients had hypophosphatemia while 6.6% had hyperphosphatemia. During PICU stay, 52.2 and 12.2% of patients had one or more episodes of hypophosphatemia and hyperphosphatemia, respectively. 42.2% of patients had recurrent or persistent abnormal phosphorus level (Table 2).

Patients who developed one or more episodes of hypophosphatemia had significantly higher frequency of steroid use and sepsis/severe sepsis diagnosis on admission compared with normophosphatemic children. These hypophosphatemic children were more likely to develop hospital-acquired infections and need longer PICU stay (Table 3).

On admission, prevalence of sepsis/severe sepsis was higher among hypophosphatemic, compared with normophosphatemic, patients (38.2% vs. 18%, $P = 0.046$). The minimum phosphorus level during PICU stay was lower among patients who developed hospital-acquired infections compared with those who did not [median (IQR): 3.3 (2.4–4.0) vs. 4.2

Table 1. Baseline demographic, clinical, and laboratory data of patients.

Variable	All Patients ($n = 90$)
Age, m	36 (5–99)
Male sex	52 (57.8%)
Weight, Kg	12.5 (6–22)
Category	
Sepsis	15 (16.7%)
Severe sepsis	11 (12.2%)
Non-sepsis	64 (71%)
Complex chronic condition	21 (23.3%)
Malnutrition	23 (25.6%)
Steroids	21 (23.3%)
Diuretics	9 (10%)
Omeprazole	41 (45.6%)
Shock on admission	9 (10%)
pSOFA[a]	2 (1–4)
Mechanical ventilation	26 (28.9%)
Mechanical ventilation duration, days	1.5 (1–3)
Vasoactive medication use	12 (13.3%)
Vasoactive infusion days	0
Hospital-acquired infections	12 (13.3%)
PICU[b] stay, days	8 (5–15.5)
PICU mortality	22 (24.4%)
CRP[c], mg/dl	12 (2–30.8)
Hemoglobin, g/dl	10.6 ± 2.43
WBC[d], 1000/ul	11.5 (7–16.3)
Platelets, 1000/ul	280 (211.8–402.3)
Creatinine, mg/dl	0.49 (0.3–1)
ALT[e], U/L	27.5 (16–71)
Total bilirubin, mg/dl	0.8 (0.5–1.1)
Albumin, g/dl	3.3 (2.97–3.8)
Total calcium, mg/dl	8.89 ± 0.99
Hypocalcemia (on admission)	33 (36.7%)

Data is presented as median (interquartile range), mean ± SD, or number (%).

[a] Pediatric Sequential Organ Failure Assessment score.
[b] Pediatric Intensive Care Unit.
[c] C-reactive protein.
[d] White Blood Cell count.
[e] Alanine aminotransferase.

Table 2. Phosphorous status of patients.

Variable	Patients ($n = 90$)
Phosphorous status (on admission)	
Abnormal phosphorous	40 (44.4%)
Hypophosphatemia	34 (37.8%)
Hyperphosphatemia	6 (6.6%)
Normal phosphorous	50 (55.6%)
Phosphorous status (in the first 12 days)	
Abnormal phosphorous	58 (64.4%)
Hypophosphatemia	47 (52.2%)
Hyperphosphatemia	11 (12.2%)
Normal phosphorous	32 (35.6%)
Phosphorous status (persistent/recurrent)	
Single episode	20 (22.2%)
Hypophosphatemia	13 (14.4%)
Hyperphosphatemia	7 (7.8%)
Persistent/recurrent abnormality	38 (42.2%)
Hypophosphatemia	34 (37.8%)
Hyperphosphatemia	4 (4.4%)
Severity of phosphorus abnormalities	
Severe hypophosphatemia	2 (2.2%)
Severe hyperphosphatemia	2 (2.2%)
Mild/moderate hypophosphatemia	45 (50%)
Mild/moderate hyperphosphatemia	9 (10%)
Phosphorous, day 1, mg/dl ($n = 90$)	4.78 ± 1.53
Phosphorous, day 4, mg/dl ($n = 75$)	4.57 ± 1.42
Phosphorous, day 8, mg/dl ($n = 37$)	3.7 (3.1–4.9)
Phosphorous, day 12, mg/dl ($n = 23$)	4.1 (2.9–4.7)
Minimum phosphorous, mg/dl	3.98 ± 1.36
Maximum phosphorous, mg/dl	5.1 ± 1.63
Mean phosphorous, mg/dl	4.5 ± 1.41

Table 3. Comparison between patients with any episode of hypophosphatemia and those with normal phosphorus level.

Variable	Hypophosphatemia ($n = 47$)	Normophosphatemia ($n = 32$)	*P*-value
Age, m	24 (5–84)	29 (6.8–72)	0.50
Weight, kg	10 (6–20)	12 (5.9–23.1)	0.4
Category (on admission)			
Sepsis/severe sepsis ($n = 26$)	17 (36.2%)	4 (12.5%)	0.019[a]
Nonsepsis ($n = 64$)	30 (63.8%)	28 (87.5%)	
Complex chronic condition	14 (29.8%)	4 (12.5%)	0.072
Malnutrition	15 (31.9%)	6 (18.8%)	0.19
Furosemide intake	3 (6.4%)	5 (15.6%)	0.26
Omeprazole	20 (42.6%)	15 (46.9%)	0.70
Steroids	13 (27.7%)	2 (6.3%)	0.017[a]
Malignancy	1 (2.1%)	0	1
Mechanical ventilation	15 (31.9%)	5 (15.6%)	0.10
Mechanical ventilation duration, days	1 (1–3)	2 (1–4)	0.61
Hospital-acquired infections	11 (23.4%)	1 (3.1%)	0.022[a]
Vasoactive medication use	7 (14.9%)	3 (9.4%)	0.73
Vasoactive infusion days	0	0	0.47
pSOFA[b]	2 (1–4)	2 (1–3)	0.46
PICU[c] stay (among survivors), days	8 (6–13)	6 (3–9.5)	0.028[a]

Data is presented as median (interquartile range) or number (percent).
[a] Statistically significant.
[b] Pediatric Sequential Organ Failure Assessment score.
[c] Pediatric Intensive Care Unit.

(3.2–5), $P = 0.039$]. Among patients admitted without sepsis, five developed hospital-acquired infections, all had at least one episode of hypophosphatemia (three of them had hypophosphatemia on admission). No hospital-acquired infections developed among patients admitted without sepsis and with normal phosphorus level ($P = 0.052$). On admission, no significant difference was found between hypophosphatemic and normophosphatemic patients in serum albumin ($P = 0.48$), creatinine ($P = 0.58$), alanine transaminase (ALT) ($P = 0.79$), total bilirubin ($P = 0.65$), C-reactive protein (CRP) ($P = 0.52$), white blood cell (WBC) ($P = 0.62$), hemoglobin ($P = 0.55$), platelet count ($P = 0.88$), or bicarbonate level ($P = 0.16$). Children who developed at least one episode of hyperphosphatemia during PICU stay had significantly higher pSOFA score, mechanical ventilation rate, and sepsis/severe sepsis frequency on admission (Table 4). Eight of these hyperphosphatemic patients (72.7%) had elevated serum creatinine on admission, six of them had acute kidney injury and two had chronic kidney disease. On admission, frequency of sepsis/severe sepsis was higher among hyperphosphatemic, compared with

Table 4. Comparison between patients with any episode of hyperphosphatemia and those with normal phosphorous.

Variable	Hyperphosphatemia ($n = 11$)	Normophosphatemia ($n = 32$)	*P*-value
Category			
Sepsis/severe sepsis ($n = 26$)	5 (45.5%)	4 (12.5%)	0.034[a]
Non-sepsis ($n = 64$)	6 (54.5%)	28 (87.5%)	
Complex chronic condition	3 (7.3%)	4 (12.5%)	0.35
Malnutrition	2 (18.2%)	6 (18.8%)	1
pSOFA[c]	3 (2–9)	2 (1–3)	0.011[a]
Elevated creatinine on admission[b]	8 (72.7%)	10 (31.3%)	0.03[a]
Malignancy	0	0	1
Mechanical ventilation	6 (54.5%)	5 (15.6%)	0.018[a]
Mechanical ventilation duration, days	2.5 (1–4.5)	2 (1–4.5)	0.79
Hospital-acquired infections	0	1 (3.1%)	1
Vasoactive medications	2 (18.2%)	3 (9.4%)	0.59
Vasoactive infusion days	0	0	0.69
PICU[d] stay (among survivors), days	7 (6.5–17.8)	6 (3–9.5)	0.19

Data is presented as median (interquartile range) or number (percent).
[a] Statistically significant.
[b] Six patients had acute kidney injury and two patients had chronic kidney disease.
[c] Pediatric Sequential Organ Failure Assessment score.
[d] Pediatric Intensive Care Unit.

normophosphatemic, children (66.7% vs. 18%, $P = 0.022$) (Table 4).

Serum phosphorus on day 8 was significantly lower among nonsurvivors. No significant difference was found between survivors and nonsurvivors in the frequency of either hypophosphatemia or hyperphosphatemia on admission or during the first 12 days of PICU stay. Two patients had severe hypophosphatemia, and both survived. Two patients had severe hyperphosphatemia; one of them had calcium x phosphorus product of 70.6 and survived; the other patient had a product of 92.8 and died. First day phosphorus level was correlated with fourth day ($r_s = 0.73$, $P < 0.001$), eighth day ($r_s = 0.42$, $P = 0.009$), and 12th day ($r_s = 0.56$, $P = 0.006$) phosphorus levels. Mean phosphorus level was correlated with the admission serum creatinine ($r_s = 0.22$, $P = 0.049$). Serum potassium on day 1 was correlated with serum phosphorus on day 1 ($r_s = 0.23$, $P = 0.039$); day 4 ($r_s = 0.44$, $P < 0.001$); and day 8 ($r_s = 0.37$, $P = 0.027$); but not on day 12 ($r_s = 0.38$, $P = 0.09$). No correlation was found between phosphorus level on any day and the admission albumin, bilirubin, CRP, bicarbonate, platelet count, or pSOFA (Table 5).

4. Discussion

We have demonstrated that phosphorus abnormalities are common among critically ill children. 52.2% of our patients had one or more episodes of hypophosphatemia, replicating previous pediatric studies, with some reporting higher rates of 60.2–76% de Menezes and colleagues, Kilic and colleagues [16–20] while others reported lower rates of 27.2–47% Springer and colleagues, El Beleidy and colleagues [21,22]. Likewise, hypophosphatemia is common among critically ill adults, but at lower rates of 15.4-28% Suzuki and colleagues, Berger and colleagues [23–25].

Table 5. Relation of phosphorus and calcium status to mortality.

Variable	Survivors ($n = 68$)	Nonsurvivors ($n = 22$)	P value
Phosphorus status (on admission)			
Hypophosphatemia	27 (39.7%)	7 (31.8%)	0.79
Hyperphosphatemia	5 (7.4%)	1 (4.5%)	
Normophosphatemia	36 (52.9%)	14 (63.6%)	
Abnormal phosphorus	32 (47.1%)	8 (36.4%)	0.38
Normal phosphorous	36 (52.9%)	14 (63.6%)	
Severe hyperphosphatemia	1 (1.5%)	1 (4.5%)	0.43
Mild/moderate hyperphosphatemia	67 (98.5%)	21 (95.5%)	
Phosphorus status (in the first 12 days)			
Hypophosphatemia	35 (51.5%)	12 (54.5%)	
Hyperphosphatemia	7 (10.3%)	4 (18.2%)	0.49
Normophosphatemia	26 (38.2%)	6 (27.3%)	
Abnormal phosphorus	42 (61.8%)	16 (72.7%)	
Normal phosphorus	26 (38.2%)	6 (27.3%)	0.35
Severe hypophosphatemia (<1.5 mg/dl)	2 (2.9%)	0	1
Mild/moderate hypophosphatemia (≥1.5 mg/dl)	66 (97.1%)	22 (100%)	
Phosphorus status (persistent/recurrent)			
Hypophosphatemia (persistent/recurrent)	23 (33.8%)	11 (50%)	0.13
Hypophosphatemia (single episode)	12 (17.6%)	1 (4.5%)	
Hyperphosphatemia (persistent/recurrent)	3 (4.4%)	1 (4.5%)	1
Hyperphosphatemia (single episode)	4 (5.9%)	3 (13.6%)	
Abnormal phosphorus (persistent/recurrent)	26 (38.2%)	12 (54.5%)	0.26
Abnormal phosphorus (single episode)	16 (23.5%)	4 (18.2%)	
Normal phosphorus	26 (38.2%)	6 (27.3%)	
Minimum phosphorous, mg/dl	4 ± 1.27	3.9 ± 1.56	0.82
Maximum phosphorous, mg/dl	4.9 ± 1.51	5.5 ± 1.9	0.22
Mean phosphorous, mg/dl	4.45 ± 1.31	4.6 ± 1.67	0.67
Phosphorous, day 1, mg/dl	4.7 ± 1.45	4.99 ± 1.79	0.46
Phosphorous, day 4, mg/dl	4.49 ± 1.29	4.8 ± 1.75	0.40
Phosphorous, day 8, mg/dl	3.9 (3.4–5.2)	3.2 (2.3–4.7)	0.046[a]
Phosphorous, day 12, mg/dl	4.3 (3.6–6)	3.3 (2.4–2.4)	0.67
Hypocalcemia (first day)	22 (32.4%)	11 (50%)	0.06
Calcium (first day), mg/dl	8.95 ± 0.94	8.73 ± 1.12	0.38

Data is presented as mean ± SD, median (interquartile range), or number (percent).
[a] Statistically significant.

Factors underlying discrepancy in hypophosphatemia rates between pediatric and adult studies are not clear, but it should be noted that pediatric studies are small compared with adult studies. More importantly, the phosphorus cutoff used to define hypophosphatemia in children is higher, which automatically yields higher prevalence of hypophosphatemia. Anyhow, available evidence signifies that hypophosphatemia is not uncommon among critically ill children; so, it is prudent to adopt a policy of routine monitoring.

Among the factors previously implicated in hypophosphatemia etiology, we found only an association with corticosteroids, consistent with another pediatric study by Springer and colleagues Kilic and colleagues [20]. In line with a previous pediatric study by Santana and colleagues [18], we did not find an association of hypophosphatemia with furosemide while other pediatric studies did El Shazly and colleagues [17]. Additionally, hypophosphatemia was not associated with omeprazole, another study reported an association with H2-blockers Kilic and colleagues [20].

Catecholamines can cause hypophosphatemia through inducing parathyroid hormone release, Brown, and Greenwood [9], Brown and colleagues [26], Brown and colleagues [27]. Dopamine decreases renal tubular reabsorption of phosphate by decreasing abundance of sodium-dependent phosphate transporter 2a [28]. However, we did not detect significant difference in the frequency of vasoactive medication use or vasoactive infusion days between hypophosphatemic and normophosphatemic patients, which is consistent with a small pediatric study by El Beleidy and colleagues [22] and a multicenter adult study by Padelli and colleagues [24], although, a small pediatric study by Santana and colleagues [18], found that dopamine was independent risk factor of hypophosphatemia. These conflicting finding might be due to differences among studies in the types or doses of catecholamines.

Metabolic acidosis was also linked to hypophosphatemia as it stimulates phosphaturia Blaine and colleagues [3]. Nevertheless, consistent with a previous study by Padelli and colleagues [24], we noted no correlation between the admission bicarbonate level and phosphorus level on any day. Decreased bicarbonate levels usually result from metabolic acidosis and less frequently from respiratory alkalosis, and both can cause hypophosphatemia. However, metabolic acidosis is usually caused by shock which simultaneously causes renal dysfunction and phosphorus retention. Moreover, low bicarbonate level frequently rises in response to therapeutic interventions, aborting its effects on future phosphorus levels.

In contrast to other pediatric studies by de Menezes and colleagues [16], El Shazly and colleagues [17], Santana and colleagues [18], we found no association between hypophosphatemia and malnutrition. This can be understood because it is refeeding, rather than malnutrition, that causes hypophosphatemia and most PICU patients are not given enteral or total parenteral nutrition on admission. In fact, serum phosphorus is usually normal in cachectic patients before refeeding although total phosphorus stores are depleted. Even after refeeding, 2–5 days are needed before hypophosphatemia develops Worley and colleagues [29]. Noteworthy, we did not evaluate relation of refeeding to hypophosphatemia in the present study.

The correlation we found between potassium and phosphorus can be attributed to the inhibitory effect of hypokalemia on renal sodium phosphate cotransporter activity Blaine and colleagues [3]. Most importantly, factors that tend to reduce phosphorus level in critical illness are numerous and presence of one of them does not necessarily translate to hypophosphatemia since other factors may simultaneously operate to increase phosphorus level. For example, the presence of metabolic acidosis in the setting of acute kidney injury produces conflicting effects on phosphorus excretion.

A remarkable finding in the present study was the significantly higher prevalence of sepsis among hypophosphatemic children which is consistent with previous pediatrics study by Kilic and colleagues [20] and adult study by Miller and colleagues [30].

Interaction between phosphorus and sepsis might be mutual. On the one hand, sepsis can cause hypophosphatemia due to metabolic acidosis, and treatment with drugs like catecholamines. Phosphorus level was also shown to be inversely correlated with inflammatory cytokines. Moreover, injection of interleukin-6 (IL-6), tumor necrosis factor-α, and IL-1β in mice markedly decreased phosphate levels Barak and colleagues [31]. On the other hand, hypophosphatemia increases the liability for infection by affecting granulocyte count and phagocytic activity Eisenberg and colleagues [32]. All ATP-dependent functions in leukocytes, like chemotaxis and phagocytosis, are impaired in hypophosphatemia Craddock and colleagues [33]. Haglin and colleagues [34] suggested that hypophosphatemia is a risk factor for acquiring secondary bacterial infections like pneumonia and sepsis

among adults with influenza Haglin and colleagues [34]. In support of these findings, we observed a significantly lower minimum phosphorus level among children who developed hospital-acquired infections. Additionally, children who had one or more episodes of hypophosphatemia were more likely to acquire hospital-acquired infections. Importantly, among patients admitted without sepsis, hospital-acquired infections developed only among those who had one or more episodes of hypophosphatemia (most of them had hypophosphatemia on admission). Our findings suggest, but do not prove, causality since we did not record in some cases what came first: hypophosphatemia or hospital-acquired infections.

Overall, findings point to a role of hypophosphatemia in causing infections, but causality may also run in the opposite direction. In other words, sepsis can cause hypophosphatemia and hypophosphatemia can cause sepsis.

As regards clinical outcome, we found that phosphorus level on day 8 was significantly lower among nonsurvivors but no significant difference in mortality rate was found between hypophosphatemic and normophosphatemic children. Previous studies generally failed to find an association between hypophosphatemia and mortality among critically ill children by de Menezes and colleagues [16], El Shazly and colleagues [17], Shah and colleagues [19], Kilic and colleagues [20]. A meta-analysis of adult studies by Sin and colleagues [35] concluded that hypophosphatemia is not associated with mortality among ICU patients. In this context, most pediatric studies failed to detect association of hypophosphatemia with mortality predictive scores Santana and colleagues, Kilic and colleagues [15,18,20]. Similarly, we found no association between pSOFA and hypophosphatemia. It is possible that only the small subset of patients with severe hypophosphatemia are at a real risk of death, while most patients have mild hypophosphatemia that is well tolerated. This is corroborated by a study by Shor and colleagues [36] on adults with sepsis where severe hypophosphatemia increased mortality by 8 folds. In our study, only two patients had severe hypophosphatemia who were readily treated by phosphate-containing solutions, and both survived.

It has been proposed that prolonged mechanical ventilation is a potential consequence of hypophosphatemia due to respiratory muscle weakness which was confirmed by some pediatric studies by Shah and colleagues [19], and Kilic and colleagues [20]. However, we did not find an association between phosphorus status and mechanical ventilation rate or duration. This unexpected finding is, nonetheless, consistent with a small pediatric study by Kilic and colleagues [20] and a large retrospective adult study by Suzuki and colleagues [23]. It is possible that respiratory muscle weakness in hypophosphatemia plays a real role in the need for mechanical ventilation in some patients but in the majority other factors (like the pulmonary, cardiac, and neurological status) predominate, so larger studies are required to uncover the small effect of hypophosphatemia on mechanical ventilation. Interestingly, a multicenter study by Padelli and colleagues [24] on adults with bloodstream infections detected a significantly lower mechanical ventilation rate among patients with hypophosphatemia and another study by Miller and colleagues [30] of adults with severe sepsis and septic shock reported a shorter mechanical ventilation duration with hypophosphatemia. Consistent with previous pediatric studies by El Shazly and colleagues [17], Shah and colleagues [19], Kilic and colleagues [20], we found that hypophosphatemia was associated with significantly longer PICU stay. A meta-analysis of adult studies by Sin and colleagues [35] confirmed this finding.

In the present study, hyperphosphatemia was less common than hypophosphatemia, occurring in 12.2% of patients, while an adult study by Miller and colleagues [30] reported a higher rate of 21% among patients with severe sepsis and septic shock. Hyperphosphatemia in our study was mostly due to renal dysfunction, but the fact that one fourth of hyperphosphatemic patients did not have underlying renal causes suggests that phosphorus level should be monitored, and hyperphosphatemia should be expected even among critically ill children with normal renal function.

We also found that frequency of sepsis diagnosis on admission was significantly higher among hyperphosphatemic compared with normophosphatemic patients. It is likely that sepsis caused acute kidney injury, with consequent rise in serum phosphorus. Another finding was the significantly higher mechanical ventilation rate among our hyperphosphatemic patients, consistent with a previous study in adults with sepsis by Wang and colleagues [37].

Although hyperphosphatemia was not associated with mortality, it was associated with pSOFA score. The small sample size might be responsible for our failure to ascertain a significant association with mortality (type II error). It is also likely that mortality is associated only with severe hyperphosphatemia. Here, one of the two patients with severe hyperphosphatemia, who had the higher

calcium x phosphorus product, died. Unlike hypophosphatemia, hyperphosphatemia demonstrated more robust association with mortality in previous studies. Mortality rate and Pediatric Logistic Organ Dysfunction (PELOD) score were significantly higher among hyperphosphatemic critically ill children in one study by Akbas and colleagues [38]. Similar findings were reported by studies on adults with sepsis by Wang and colleagues [37] and burn by Kuo and colleagues [39].

At the molecular level, the detrimental effect of hyperphosphatemia might result from endothelial dysfunction caused by decreased nitric oxide and increased reactive oxygen species production. Apoptosis of endothelial cells also occurs through induction of the death-domain associated protein (DAXX) expression Wang and colleagues [40].

Limitations of the present study include the small sample size which precluded reliable subgroup analyses in case of hyperphosphatemia. Additionally, we did not evaluate some risk factors of hypophosphatemia like duration of starvation and refeeding. Finally, we did not document the temporal relation of hypophosphatemia to the onset of hospital-acquired infections in some patients.

4.1. Conclusion

Phosphorus abnormalities, particularly hypophosphatemia, are common among critically ill children. Risk factors for hypophosphatemia include sepsis and steroid treatment. Hyperphosphatemia was more likely to be found among patients with renal dysfunction, sepsis, and higher pSOFA score. Hypophosphatemia was associated with longer PICU stay and hospital-acquired infections. Hyperphosphatemia was associated with higher mechanical ventilation rate. Lower phosphorus level on eighth day was associated with mortality. Hyperphosphatemia was associated with pSOFA score but not with mortality. Large pediatric studies are needed to accurately determine prevalence, risk factors, and impact of phosphorus status on outcome.

Conflicts of interest

No conflict of interest.

References

[1] Calvo MS, Lamberg-Allardt CJ. Phosphorus. Adv Nutr 2015; 6:860–2.
[2] Iheagwara OS, Ing TS, Kjellstrand CM, Lew SQ. Phosphorus, phosphorous, and phosphate. Hemodial Int 2013;17:479–82.
[3] Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol 2015;10:1257–72.
[4] Bansal VK. Serum inorganic phosphorus. In: Walker HK, Hall WD, Hurst JW, editors. Clinical methods: the history, physical, and laboratory examinations. 3rd ed. Boston: Butterworths; 1990 [Chapter 198].
[5] Reintam Blaser A, Gunst J, Ichai C, Casaer MP, Benstoem C, Besch G, et al. Hypophosphatemia in critically ill adults and children. A systematic review. Clin Nutr 2021;40:1744–54.
[6] Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. Crit Care 2010;14:1–8.
[7] Choi HS, Kwon A, Chae HW, Suh J, Kim DH, Kim HS. Respiratory failure in a diabetic ketoacidosis patient with severe hypophosphatemia. Ann Pediatr Endocrinol Metab 2018;23:103–6.
[8] Singhal PC, Kumar A, Desroches L, Gibbons N, Mattana J. Prevalence, and predictors of rhabdomyolysis in patients with hypophosphatemia. Am J Med 1992;92:458–64.
[9] Brown GR, Greenwood JK. Drug- and nutrition-induced hypophosphatemia: mechanisms and relevance in the critically ill. Ann Pharmacother 1994;28:626–32.
[10] Vankrunkelsven W, Gunst J, Amrein K, Bear DE, Berger MM, Christopher KB, et al. Monitoring and parenteral administration of micronutrients, phosphate, and magnesium in critically ill patients: the VITA-TRACE survey. Clin Nutr 2021;40:590–9.
[11] Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.
[12] Matics TJ, Sanchez-Pinto LN. Adaptation, and validation of apediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically ill children. JAMA Pediatr 2017;171:e172352. 12.
[13] McDaniel L, Sokoll L, Thomas S. Blood chemistry and body fluids. In: Kleinman K, McDaniel L, Molloy M, editors. The harriet lane handbook the johns hopkins hospital. 22nd ed. Canada: Elsevier. Inc.; 2020. p. 646.
[14] O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis 2011;52:162–93.
[15] Smith H, Watkins J, Otis M, Hebden JN, Wright MO. Health care-associated infections studies project: an American journal of infection control and national healthcare safety network data quality collaboration case study-Chapter 2 Identifying Healthcare-associated Infections (HAI) for NHSN surveillance case study vignettes. Am J Infect Control 2022 Jun 1;50(6):695–8.
[16] de Menezes FS, Leite HP, Fernandez J, Benzecry SG, de Carvalho WB. Hypophosphatemia in children hospitalized within an intensive care unit. J Intensive Care Med 2006;21: 235–9.
[17] El Shazly AN, Soliman DR, Assar EH, Behiry EG, Gad Ahmed IA. Phosphate disturbance in critically ill children: incidence, associated risk factors and clinical outcomes. Ann Med Surg (Lond) 2017;21:118–23.
[18] Santana E, Meneses JF, Leite HP, de Carvalho WB, Lopes Jr E. Hypophosphatemia in critically ill children: prevalence and associated risk factors. Pediatr Crit Care Med 2009;10:234–8.
[19] Shah SK, Irshad M, Gupta N, Kabra SK, Lodha R. Hypophosphatemia in critically ill children: risk factors, outcome and mechanism. Indian J Pediatr 2016;83:1379–85.
[20] Kilic O, Demirkol D, Ucsel R, Citak A, Karabocuoglu M. Hypophosphatemia, and its clinical implications in critically ill children: a retrospective study. J Crit Care 2012;27:474–9.
[21] Springer AMM, Hortencio TDR, Melro EC, de Souza TH, Nogueira RJN. Hypophosphatemia in critically ill pediatric patients receiving enteral and oral nutrition. JPEN - J Parenter Enter Nutr 2022;46:842–9.
[22] El Beleidy A, El Sherbini SA, Elgebaly HF, Ahmed A. Calcium, magnesium, and phosphorus deficiency in critically ill children. Egypt Pediat Assoc Gazette 2017;65:60–4.

[23] Suzuki S, Egi M, Schneider AG, Bellomo R, Hart GK, Hegarty C. Hypophosphatemia in critically ill patients. J Crit Care 2013;28:5369−53619.
[24] Padelli M, Aubron C, Huet O, Héry-Arnaud G, Vermeersch V, Hoffmann C, et al. Is hypophosphataemia an independent predictor of mortality in critically ill patients with bloodstream infection? A multicenter retrospective cohort study. Aust Crit Care 2021;34:47−54.
[25] Berger MM, Appelberg O, Reintam-Blaser A, Ichai C, Joannes-Boyau O, Casaer M, et al. Prevalence of hypophosphatemia in the ICU - results of an international one-day point prevalence survey. Clin Nutr 2021;40:3615−21.
[26] Brown EM, Hurwitz S, Aurbach GD. Beta-adrenergic stimulation of cyclic AMP content and parathyroid hormone release from isolated bovine parathyroid cells. Endocrinology 1977;100:1696−702.
[27] Brown EM, Hurwitz SH, Aurbach GD. Alpha-Adrenergic inhibition of adenosine 3',5'-monophosphate accumulation and parathyroid hormone release from dispersed bovine parathyroid cells. Endocrinology 1978;103:893−9.
[28] Weinman EJ, Biswas R, Steplock D, Douglass TS, Cunningham R, Shenolikar S. Sodium-hydrogen exchanger regulatory factor 1 (NHERF-1) transduces signals that mediate dopamine inhibition of sodium-phosphate cotransport in mouse kidney. J Biol Chem 2010;285:13454−60.
[29] Worley G, Claerhout SJ, Combs SP. Hypophosphatemia in malnourished children during refeeding. Clin Pediatr 1998;37:347−52.
[30] Miller CJ, Doepker BA, Springer AN, Exline MC, Phillips G, Murphy CV. Impact of serum phosphate in mechanically ventilated patients with severe sepsis and septic shock. J Intensive Care Med 2020;35:485−93.
[31] Barak V, Schwartz A, Kalickman I, Nisman B, Gurman G, Shoenfeld Y. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. Am J Med 1998;104:40−7.
[32] Eisenberg SWF, Ravesloot L, Koets AP, Grünberg W. Effect of dietary phosphorus deprivation on leukocyte function in transition cows. J Dairy Sci 2019;102:1559−70.
[33] Craddock PR, Yawata Y, VanSanten L, Gilberstadt S, Silvis S, Jacob HS. Acquired phagocyte dysfunction. A complication of the hypophosphatemia of parenteral hyperalimentation. N Engl J Med 1974;290:1403−7.
[34] Håglin LM, Burman LA, Nilsson M. Predisposing chronic diseases and hypophosphatemia in patients with influenza. Arch Gerontol Geriatr 2010;51:26−30.
[35] Sin JCK, King L, Ballard E, Llewellyn S, Laupland KB, Tabah A. Hypophosphatemia and outcomes in ICU: a systematic review and meta-analysis. J Intensive Care Med 2021;36:1025−35.
[36] Shor R, Halabe A, Rishver S, Tilis Y, Matas Z, Fux A, et al. Severe hypophosphatemia in sepsis as a mortality predictor. Ann Clin Lab Sci 2006;36:67−72.
[37] Wang H, Zhang L, Liao W, Huang J, Xu J, Yang J, et al. Hyperphosphatemia rather than hypophosphatemia indicates a poor prognosis in patients with sepsis. Clin Biochem 2021;91:9−15.
[38] Akbaş Y, Koker A, Erkek N. Are we aware that hyperphosphatemia affects mortality and morbidity as much as hypophosphatemia in pediatric intensive care patients? Pediatr Endocrinol Rev 2019;17:35−40.
[39] Kuo G, Lee CC, Yang SY, Hsiao YC, Chuang SS, Chang SW, et al. Hyperphosphatemia is associated with high mortality in severe burns. PLoS One 2018;13:e0190978.
[40] Wang S, Wu M, Qin L, Song Y, Peng A. DAXX mediates high phosphate-induced endothelial cell apoptosis in vitro through activating ERK signaling. Peer J 2020;8:e9203.