Guideline

Arch Pediatr Urug 2025; 96(2): e807
doi: 10.31134/AP.96.36

Correction guideline for severe hypophosphatemia in critically ill patients

Pauta. Corrección de hipofosfatemia grave en pacientes críticos

Diretrizes de correção para hipofosfatemia grave em pacientes gravemente enfermos

Andrea Rodríguez[1], Lucía del Puerto[2], Héctor Telechea[3]

Introduction

Acute and severe hypophosphatemia in critical care may be associated with multiple organ dysfunction. There are few reports on its prevalence, although it is estimated to be frequent[1].

In the Pediatric Intensive Care Unit of the *Centro Hospitalario Pereira Rossell* (PICU-CHPR), a prevalence of 33% was observed in patients at risk of refeeding syndrome, which may represent one of its possible etiologies[2]. In 2020, a cross-sectional prevalence survey conducted by the European Society of Intensive Care Medicine (ESICM), involving 60 intensive care units (ICUs) from 22 countries, showed a 15.4% prevalence and found that 60% of the participating units did not have treatment protocols[1]. Several studies report that hypophosphatemia is associated with poorer outcomes, increasing ICU stay, and longer duration of mechanical ventilation (MV)[1-4]. These complications are more prevalent in malnourished patients and are associated with the use of furosemide, dopamine, steroids, and beta-2 adrenergic agonists[4]. Low-energy intake and disease severity are related to hypophosphatemia, where inflammation in critically ill patients is an important factor in its development. In particular, patients with risk factors for refeeding syndrome may be predisposed to developing it[5]. Despite the association between hypophosphatemia and poorer clinical outcomes, the optimal threshold at which hypophosphatemia becomes critical and requires treatment, as well as the time frame for its correction, has not yet been determined[6]. Further studies are needed to determine its impact on mortality, as the published data to date are inconclusive[6]. There is greater consensus on its correction when it is acute, severe, or symptomatic[7]. Phosphorus is an electrolyte that accounts for 1% of total body weight, with approximately 85% of its reserves stored in bone tissue. The rest is distributed in muscles and soft tissues, and less than 1% is present in extracellular fluid[8]. The main source of phosphorus comes from the diet, being more available in foods of animal origin, followed by dairy products, especially in low-fat ones, legumes, and cereals[8].

Plasma phosphate levels are maintained within narrow ranges linked to changes in intestinal absorption, tubular reabsorption, and redistribution between intracellular and extracellular compartments, as well as bone reserves[8]. Tubular reabsorption is the main determinant[8].

Table 1 lists the main causes of hypophosphatemia in the three categories mentioned above.

Plasma phosphate levels depend on age, being higher in young children and adolescents. In adults, they range from 2.5 to 4.5 mg/dL (0.81-1.45 mmol/L)[8]. Hypoalbuminemia decreases plasma levels. Table 2 details reference ranges in pediatrics, although it is recommended to use reference tables specific to each hospital laboratory[9].

It is involved in oxidative phosphorylation, glycolysis, and enzymatic processes with protein phosphorylation[10].

1. Assistant, Pediatric Intensive Care Unit. CHPR. ASSE.
2. Pharmaceutical chemist. Pharmacy Department. CHPR. ASSE.
3. Prof. Pediatric Intensive Care Unit. CHPR. ASSE.
Pediatric Intensive Care Unit. CHPR. ASSE.
Neonatology Academic Unit. CHPR. Faculty of Medicine. UDELAR.
Unpublished work.
We declare that we have no conflicts of interest.
This work has been unanimously approved by the Editorial Committee.
Date received: February 24, 2025.
Date approved: May 22, 2025.

Table 1. Main causes of hypophosphatemia

Decreased intestinal absorption	Severe malnutrition with lack of nutrients and minerals Vitamin D deficiency. Antacids or chelating agents Intestinal malabsorption. Alcoholism
Increased renal losses	Hyperparathyroidism. Severe tubular diseases Genetic hypophosphatemic rickets. Diabetic ketoacidosis Severe acidosis Drugs (diuretics, steroids, anticonvulsants, chemotherapeutics, antiretrovirals) Postoperative renal transplant. Post-dialysis complications
Intracellular redistribution, transmembrane movements	Respiratory alkalosis. Lymphoma or acute leukemia Hypothermia Refeeding syndrome. Insulin use Postoperative thyroid or parathyroid surgery Critical patient (severe sepsis, severe burns)

Table 2. Reference values for plasma phosphate by age

Age	Plasma phosphate
Newborn	4,8 - 8,2 mg/dL
1 to 3 years	3,8 - 6,5 mg/dL
4 to 11 years	3,7 - 5,6 mg/dL
12 to 15 years	2,9 - 5,4 mg/dL
16 to 19 years	2,7 - 4,7 mg/dL

Table 3. Signs and symptoms associated with hypophosphatemia classified by system

System	Signs and symptoms
Cardiovascular manifestations	Alterations in cardiac contractility Ventricular arrhythmias
Pulmonary manifestations	Respiratory muscle weakness Acute respiratory failure with tissue hypoxia
CNS manifestations	Irritability Paresthesia Encephalopathy Delirium Seizures Coma Tetany Areflexic paralysis
Skeletal and smooth muscle manifestations	Proximal myopathy Dysphagia Ileus
Hematological manifestations	Hemolysis Impaired leukocyte function Thrombocytopenia
Effects on mineral metabolism	Hypercalciuria

Deficiency may lead to cardiorespiratory dysfunction and arrhythmias, as well as a decrease in diphosphoglycerate, which increases hemoglobin's affinity for oxygen, thereby promoting tissue hypoxia[10]. Acute hypophosphatemia without prior chronic phosphate depletion is not usually symptomatic[8]. Table 3 details the main symptoms attributable to severe hypophosphatemia, organized by system[11].

Indications for hypophosphatemia correction

Based on the review, it is suggested to correct hypophosphatemia when it is acute and severe or symptomatic[7-12].

It is considered severe when levels are below 2 mg/dL[12].

In cases of moderate hypophosphatemia, oral supplementation may be considered.

Phosphate replacement can be administered enterally, by enema, or intravenously.

Oral phosphate supplementation

The formulation we suggest for oral administration is used in our setting for patients with renal failure who require external phosphate supplementation. It is known as *Jolie's solution*, a compounded preparation made upon request[13].

This solution contains, per ml: 1 mmol of phosphate and 1 mEq of sodium[13].

Its composition is as follows:

- Orthophosphoric acid 85% - 5.45 g.
- Disodium phosphate (12H2O) - 18.75 g.
- Preserved water without propylene glycol q.s. to 100 mL.

Adverse effects of oral phosphate administration include diarrhea, nausea, vomiting, and abdominal pain[13]. In case of overdose, it may cause hyperphosphatemia, hypocalcemia, hypokalemia, hypernatre-

mia, and acute kidney injury[13].

The suggested oral supplementation is 2-3 times the normal dietary intake, depending on tolerance, divided into 2 to 3 doses. A table is attached showing the recommended dietary intake by age, according to the World Health Organization (WHO), and it varies depending on the age of the child.

According to other authors, 2-3 mmol/kg/day may also be considered.

Table 4 shows the recommended dietary phosphorus intake by age, expressed in mg and mmol per day.

It should be noted that active vitamin D is required for intestinal phosphate absorption[14].

Commercial phosphate formulations are available for use as oral laxatives or enemas. Some studies have shown a safe increase in phosphate levels in the ICU setting[16].

In our sphere, this oral solution contains disodium phosphate 900 mg/5 mL (180 mg/mL) and monosodium phosphate 2.4 g/5 mL (0.48 mg/mL). Since it acts as a laxative, it can cause the previously mentioned gastrointestinal complications; therefore, we recommended not administering more than 5 mL of the solution for the correction of hypophosphatemia and monitoring for the appearance of adverse symptoms.

Intravenous phosphate supplementation

Vials for intravenous use are available for cases that are severe and/or symptomatic, or in specific situations where there is poor tolerance to oral or enteral phosphate.

The vial contains 20 ml of sodium glycerophosphate (Glycophos); each ml provides 1 mmol of phosphate and 2 mmol of sodium[1]. Glycerophosphate requires hepatic hydrolysis and normal alkaline phosphatase levels[17].

Compatible solvents include normal saline and 5% dextrose. The solution should be diluted to reach the maximum suggested concentration, which varies according to the available venous access. The maximum concentration is 0.12 mmol/ml for central lines and 0.05 mmol/ml for peripheral lines[12-18]. It is recommended to administer it over 6 hours, not exceeding an infusion rate of 0.6 mmol/kg/hour.

Table 5 shows the suggested phosphate doses (in mmol) according to the degree of plasma phosphate depletion in children[12-19].

In adults, the approximate correction is 10 to 20 mmol/dose (half a vial or one vial), which is the maximum dose, regardless of weight.

Some authors suggest subsequent intravenous maintenance when hypophosphatemia is severe. The suggested maintenance doses are as follows[12]:

- Neonates 0.8-1.5 mmol/kg/day.
- Infants and children 0.5-1.5 mmol/kg/day.
- Adults 50 mmol/day.

Keep in mind that hypophosphatemia may occur with low, moderate, or even high phosphate stores, since the decrease in plasma phosphate levels can result from a transmembrane shift of phosphate. For this reason, phosphate maintenance should be individualized. For instance, in a severely malnourished patient with refeeding syndrome, where phosphate stores are presumed to be depleted, supplementation may be incorporated into the patient's parenteral nutrition if applicable.

As a practical example, consider a 1-year-old child weighing 10 kg who presents with severe symptomatic hypophosphatemia and a plasma phosphate level of 1 mg/dl. As mentioned earlier, the recommended correction is 0.16 mmol/kg, which, when multiplied by the child's weight, results in a total dose of 1.6 mmol to be administered.

As previously mentioned, 1 ml of sodium glycerophosphate (Glycophos) contains 1 mmol of phosphate and 2 mmol of sodium. Therefore, to correct 1.6 mmol, we would draw 1.6 mL from the vial and dilute it according to the available venous access.

Table 4. Recommended dietary phosphorus intake according to the World Health Organization

Age group	Requirement (mg/day)	Requirement (mmol/day)
Infants (0-6 months)	100 mg	3,2 mmol
Infants (7-12 months)	275 mg	8,9 mmol
Young children (1-3 years)	460 mg	14,8 mmol
Children (4-8 years)	500 mg	16,1 mmol
Children (9-13 years)	1250 mg	40,3 mmol
Adolescents (14-18 years)	1250 mg	40,3 mmol

Table 5. Severity levels of hypophosphatemia and suggested doses (mmol) for intravenous correction

Phosphatemia	Mmol of phosphate to be corrected
2 to 1 mg/dL	0.08 mmol/kg or 2.5 mg/kg over 6 hours
1 to 0.5 mg/dL	0.16-0.24 mmol/kg or 5-7.5 mg/kg over 6 hours
< 0.5 mg/dL	0.36 mmol/kg or 10 mg/kg over 6 hours

If a central venous line is available (maximum concentration 0.12 mmol/mL), the dilution would be as follows: 1.6 mL of sodium glycerophosphate should brought up to 15 mL with normal saline and administered over 6 hours at a 2.5 mL/hour rate.

The dilution mentioned above represents the maximum concentration allowed based on osmolarity. If deemed appropriate, it may be further diluted in a larger volume of saline.

If peripheral venous line is available (maximum concentration 0.05 mmol/ml), the dilution would be as follows: 1.6 mL of sodium glycerophosphate should brought up to 35 mL with normal saline and administered over 6 hours at a 5.8 mL/hour rate.

The same considerations regarding dilution as in the previous case apply.

Complications

As complications of intravenous infusion, it should be noted that phosphate can precipitate with calcium; they are incompatible.

High doses of phosphate in the absence of true depletion may lead to hyperphosphatemia, hypomagnesemia, hypocalcemia, and hypotension[7,18].

Monitoring

It is recommended to monitor blood pressure during phosphate infusion and measure serum levels every 12 hours when the risk of hypophosphatemia is significant.

In cases of refeeding syndrome, it should be remembered that correcting phosphate alone is not sufficient; it is also necessary to reduce the patient's energy intake in order to avoid perpetuating hypophosphatemia, as well as to administer intravenous thiamine[11,12].

Bibliographic references

1. Berger M, Appelberg O, Reintam A, Ichai C, Joannes O, Casaer M, et al. Prevalence of hypophosphatemia in the ICU: results of an international one-day point prevalence survey. Clin Nutr 2021; 40(5):3615-21. doi: 10.1016/j.clnu.2020.12.017.
2. Martínez A, Rodríguez A, Telechea H. Prevalencia del síndrome de realimentación en una unidad de cuidados intensivos pediátricos. Mayo-julio 2023. Arch Pediatr Urug 2024; 95(S1):e309. Disponible en: http://www.scielo.edu.uy/scielo.php?script=sci_arttext&pid=S1688-12492024000201309. [Consulta: 1 enero 2025].
3. Lusteau A, Valla F, Javouhey E, Baudin F. Hypophosphatemia in infants with severe bronchiolitis and association with length of mechanical ventilation. Pediatr Pulmonol 2023; 58(9):2513-9. doi: 10.1002/ppul.26538.
4. El Shazly A, Soliman D, Assar E, Behiry E, Gad I. Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes. Ann Med Surg (Lond) 2017; 21:118-23. doi: 10.1016/j.amsu.2017.07.079.
5. Springer A, Hortencio T, Melro E, de Souza T, Nogueira R. Hypophosphatemia in critically ill pediatric patients receiving enteral and oral nutrition. JPEN J Parenter Enteral Nutr 2022; 46(4):842-9. doi: 10.1002/jpen.2235.
6. Reintam A, Gunst J, Ichai C, Casaer M, Benstoem C, Besch G, et al. Hypophosphatemia in critically ill adults and children: a systematic review. Clin Nutr 2021; 40(4):1744-54. doi: 10.1016/j.clnu.2020.09.045.
7. Geerse D, Bindels A, Kuiper M, Roos A, Spronk P, Schultz M. Treatment of hypophosphatemia in the intensive care unit: a review. Crit Care 2010; 14(4):R147. doi: 10.1186/cc9215.
8. García A, Varsavsky M, Cortés M, Ávila V, Alhambra M, Novo C, et al. Phosphate disorders and clinical management of hypophosphatemia and hyperphosphatemia. Endocrinol Diabetes Nutr (Engl Ed) 2020; 67(3):205-15. doi: 10.1016/j.endinu.2019.06.004.
9. Sociedad Española de Endocrinología Pediátrica. Raquitismo de causa genética. Rev Esp Endocrinol Pediatr 2018;9(Suppl 25):1385-A458. Disponible en: https://www.endocrinologiapediatrica.org/revistas/P1-E25/P1-E25-S1385-A458.pdf
10. Zimmerman J, Rotta A. Fuhrman and Zimmerman's pediatric critical care. 6 ed. Philadelphia: Elsevier, 2022.
11. da Silva J, Seres D, Sabino K, Adams S, Berdahl G, Citty S, et al. ASPEN consensus recommendations for refeeding syndrome. Nutr Clin Pract 2020; 35(2):178-95. doi: 10.1002/ncp.10474.
12. Agustinho A, Bazo M, Krochik G, Vezzani C. GAP 2018 Manejo del Síndrome de Realimentación. BuenosAires: Hospital de Pediatría Garrahan, 2018. Disponible en: https://www.garrahan.gov.ar/images/intranet/guias_atencion/GAP_2018_-_MANEJO_SINDROME_DE_REALIMENTACION.pdf. [Consulta: 1 enero 2025].
13. Sociedad Española de Farmacia Hospitalaria. FOSFATO 1mmol/ml SOLUCIÓN ORAL (SOLUCIÓN DE JOULIE). Disponible en: https://gruposdetrabajo.sefh.es/farmacotecnia/images/stories/PN_Formulas/F/FOSFATO_1mmol_ml_SOL_HIP.pdf. [Consulta: 1 enero 2025].
14. García M, López M, Molina J. Manual para el diagnóstico y tratamiento de la deshidratación y de los trastornos hidroelectrolíticos en urgencias de pediatría. Madrid: Ergon, 2018.
15. Wolrd Health Organization. Food and Agricultura Organization of the United Nations. Vitamin and mineral requirements in human nutrition: report of a joint FAO/WHO expert

consultation, Bangkok, Thailand, 21–30 September 1998. 2 ed. Geneva: WHO, 2004. Disponible en: https://www.who.int/publications/i/item/9241546123. [Consulta: 1 enero 2025].
16. Ahmed A, Ullah R, Haque A, Rahman F, Mirza S, Jurair H. Efficacy and safety of phosphate enema as a therapeutic agent in hypophosphatemia in critically ill children. J Coll Physicians Surg Pak 2021; 31(3):356-8. doi: 10.29271/jcpsp.2021.03.356.
17. Agencia Española de Medicamentos y Productos Sanitarios. Glycophos 216 mg/ml concentrado para solución para perfusión Glicerofosfato de sodio. Disponible desde: https://cima.aemps.es/cima/pdfs/es/p/64328/64328_p.pdf. [Consulta: 1 enero 2025].
18. Taketomo C, Hodding J, Kraus D. Pediatric and Neonatal Dosage Handbook. 16 ed. Hudson, OH: Lexi-Comp, 2009.
19. Hospital de Pediatría Garrahan. Centro de Información sobre Medicamentos. Electrolitos (actualización 2022). Disponible en: https://www.garrahan.gov.ar/images/PDFS/MaterialEducativo/Equipo/El ectrolitos_2022.pdf. [Consulta: 1 enero 2025].

Correspondence: Dr. Andrea Rodríguez.
Email: andrea.med09@gmail.com

Data availability
The dataset supporting the results of this study is NOT available in open-access repositories.

Authors' contribution
All authors of this manuscript contributed to the conception and critical review and approved the final version for publication.

Andrea Rodríguez, ORCID 0000-0001-8913-3085.
Lucía del Puerto, ORCID 0009-0002-8629-0282.
Héctor Telechea, ORCID 0000-0001-8173-0117.