Journal of Critical Care (2013) **28**, 838–843

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Journal of Critical Care

# Hypophosphatemia on the intensive care unit: Individualized phosphate replacement based on serum levels and distribution volume☆,☆☆,★

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**Keywords:**
Hypophosphatemia;
ICU;
Phosphate replacement

**Abstract**

**Background:** Hypophosphatemia occurs in about 25% of patients admitted to the intensive care unit. To date, a safe and validated phosphate replacement protocol is not available.

**Objective:** To evaluate an individualized phosphate replacement regimen.

**Design:** Fifty consecutive intensive care unit patients with a serum phosphate level <0.6 mmol/L were treated with sodium-potassium-phosphate intravenously at a rate of 10 mmol/h. The dose was calculated according to the following equation: Phosphate dose in mmol = 0.5 × Body Weight × (1.25 – [serum Phosphate]). Phosphate levels were measured immediately upon completion of the infusion, as well as the next morning at 8 AM.

**Results:** Post-infusion phosphate levels were >0.6 mmol/L in 98% of the patients. Hyperphosphatemia, hyperkalemia or a decrease in serum calcium were not observed. In about a third of patients serum phosphate decreased to <0.6 mmol/L within the next 24 hours after infusion. The phosphate distribution volume calculated from the results of infusion and corrected for renal phosphate loss during the infusion period was 0.51 L/kg (95% CI 0.42–0.61 L/kg).

**Conclusion:** This study shows that phosphate replacement with dose calculation based on serum phosphate levels and a Vd of 0.5 L/kg is effective and safe.



## 1. Introduction

Hypophosphatemia, defined as a serum phosphate level <0.6 mmol/L, is a frequent finding in intensive care unit (ICU) patients. It may be caused by redistribution, gastrointestinal loss, or renal phosphate loss. The reported prevalence of ICU hypophosphatemia ranges from 10–80%, with a mean of about 25% [1]. Severe hypophosphatemia,

☆ Conception and design: AB, MB, DT, MR, HdB.
☆☆ Analysis and interpretation: AB, MR, MB, CM, HdB.
★ Important intellectual content: AB, MB, HdB.

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http://dx.doi.org/10.1016/j.jcrc.2013.03.002

defined as a level <0.3 mmol/L, can lead to respiratory insufficiency, heart failure, arythmias, rhabdomyolysis, neuropathy, and thrombocytopenia [2,3]. The clinical significance of moderate hypophosphatemia (serum phosphate 0.3-0.6 mmol/L) is currently not exactly known. However, it is common practice to correct phosphate levels <0.6 mmol/L in patients on the ICU because there is evidence to suggest that moderate hypophosphatemia may impair diaphragmatic contractility, reduce left ventricular stroke work and can lead to insulin resistance [4–7].

Several phosphate replacement schedules have been proposed [1,2,8–12]. Most are based on the use of fixed doses without adjustment for the degree of hypophosphatemia or body weight, and most studies included only small numbers of patients. To date, no uniform policy or protocol has emerged from these data. There is no international guideline for phosphate replacement on the ICU, and thus, much variability exists between countries and individual hospitals. Based on a pilot-study in 7 subjects, French et al have proposed a protocol with individualized dose-calculation derived from the actual serum phosphate level and an apparent phosphate distribution volume [13]. This approach is attractive because physiologically it is the most rational approach of all previously proposed regimens. We therefore decided to implement this protocol as standard practice in our ICU, to assess its effects on serum phosphate levels, and to evaluate its safety. The present report describes the results of this analysis.

## 2. Patients and methods

This study was performed in a 15 bed ICU of a large teaching hospital in the Netherlands. The ICU population mainly consisted of general medical and surgical patients. It did not include post-CABG (coronary artery bypass graft) or severe trauma patients. All patients admitted to this ICU are routinely screened for hypophosphatemia on day 1, 3, 5, and 7. The present study includes the first 50 patients who were found to have a serum phosphate level <0.60 mmol/L during their stay. Exclusion criteria were serum creatinine >150 μmol/L, urine production rate <300 ml/24 h, hemodialysis, serum total calcium >2.65 mmol/L, and serum potassium >4.5 mmol/L.

Calculation of the total phosphate replacement dose was based on the actual serum phosphate level in mmol/L, a target level of 1.25 mmol/L and a phosphate distribution volume of 0.5 L/kg body weight:

$$\text{Phosphate dose} = 0.5 \times (\text{Body Weight}) \times (1.25 - [\text{serum phosphate}]).$$

Body weight was expressed in kg, serum phosphate in mmol/L, and phosphate dose in mmol.

The distribution volume of 0.5 L/kg was based on the findings of French et al in 7 critically ill patients [13].

Phosphate replacement was performed with sodium-potassium-phosphate $Na_2K_5PO4_6$ (NaKP). This formulation is the only available phosphate replacement formulation available in the Netherlands (Fresenius Kabi, 's-Hertogenbosch). It was administered intravenously through a separate channel of a central venous catheter by infusion pump, using a 50-mL syringe. The 50-mL volume was obtained by adding 30 ml NaCl 0.9% to four 5-mL ampoules of NaKP (1.5 mmol phosphate/ml) and, thus, contained 30 mmol phosphate, 15 mmol sodium and 25 mmol potassium. The infusion rate was fixed at 17 mL/h, that is, equivalent to a phosphate infusion rate of 10 mmol/h and a potassium infusion rate of 8.5 mmol/h. With a fixed infusion rate the total time of infusion will vary in proportion to the magnitude of the calculated dose. Serum phosphate, potassium, calcium, and albumin were measured at baseline (T-0), immediately after the completion of infusion (T-1), and also the next morning at 08.00h (T-2). The study was performed according to the regulations of the local medical ethical committee.

### 2.1. Assays

Serum total calcium, phosphate and potassium were measured by routine clinical chemistry laboratory assays. The normal range for total calcium is 2.10 to 2.55 mmol/L, for ionized calcium 1.10 to 1.32 mmol/L, for phosphate 0.87 to 1.45 mmol/L and for potassium 3.60 to 4.80 mmol/L. Total calcium was measured with a *o*-cresolphthaleine complexone method. Inorganic phosphate was measured with an ammonium molybdate method. Potassium was measured with an ion selective electrode method (all methods: Roche Diagnostics, Almere, The Netherlands). All calcium levels shown represent total calcium levels corrected for albumin according to the equation: total calcium = calcium + [0.025 × (40-albumin)]. TmP/gfr (tubular maximum phosphate reabsorption per glomerular filtration rate), a method to assess the renal threshold for phosphate re-absorption, was calculated according to the method of Bijvoet et al [14]. TmP/gfr normal range is 0.7–1.4 mmol/L). A level less than 0.7 mmol/L indicates a reduced renal threshold and excessive renal phosphate loss.

### 2.2. Statistics

Results are shown as mean values ± SEM. For data with a normal distribution the changes induced by treatment were analyzed by paired *t* test. Data with a non-normal distribution were compared by Wilcoxon signed-ranks test. A $P < .05$ was considered to reflect statistical significance.

## 3. Results

Baseline characteristics such as age, gender, weight, APACHE score, and ICU admission diagnosis are summarized in Table 1.