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SPECIAL ARTICLE

Approach to hypophosphataemia in intensive care units – a nationwide survey

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ABSTRACT

Background: Evidence-based guidelines for monitoring of serum phosphate levels and for the treatment of hypophosphataemia in critically ill patients are lacking. The aim of this survey was to evaluate current practice with respect to diagnosis and treatment of hypophosphataemia in critically ill patients among intensive care unit (ICU) physicians in the Netherlands.

Methods: A survey was conducted among all hospitals with an ICU in the Netherlands. Paediatric ICUs were excluded from participation. A questionnaire was sent, with questions on practice regarding serum phosphate monitoring and treatment of hypophosphataemia. Respondents returned the questionnaire either by mail or through a web-based survey.

Results: A response was received from 67/89 ICUs (75%). Respondents mentioned renal replacement therapy, sepsis and malnutrition, as well as surgery involving cardiopulmonary bypass as the most important causes of hypophosphataemia in intensive care unit patients. Of all respondents, 46% reported to measure serum phosphate levels on a daily basis, whereas in 12% serum phosphate levels were measured only on clinical indication. Less than half of the respondents had some sort of guideline for correction of hypophosphataemia. In a vast majority (79%), correction of hypophosphataemia was reported to start with serum phosphate levels <0.60 mmol/l. Intravenous administration of phosphate was the preferred method of correction, with widely variable dosages and speeds of infusion. Complications of intravenous phosphate were reported to occur infrequently.

Conclusion: There is large variability in the way serum phosphate is monitored and hypophosphataemia is treated in critically ill patients in the Netherlands.

KEYWORDS

Hypophosphataemia, intensive care, monitoring, treatment, survey

INTRODUCTION

Intensive care unit (ICU) patients are at increased risk for developing hypophosphataemia due to the presence of multiple causal factors including – but not restricted to – volume expansion, diuretics, metabolic acidosis, respiratory alkalosis and the refeeding syndrome.[1] Reported incidences of hypophosphataemia, most frequently defined as a serum phosphate level <0.80 mmol/l, vary widely,[2,3] with highest incidences in patients with sepsis[4] and after hepatic[5] or cardiothoracic surgery.[6]

Hypophosphataemia may have serious consequences, such as respiratory failure and myocardial dysfunction. However, it is not known whether correction of hypophosphataemia affects the outcome of critically ill patients.[1] Notably, correction of hypophosphataemia by means of intravenous administration of phosphate concentrates may cause abnormalities of other electrolytes, Hyperkalaemia is of particular concern when sodium-potassium-phosphate solutions are used for correction, especially when administered at high speeds. Currently, no evidence-based guidelines exist for the monitoring of serum phosphate levels and treatment of hypophosphataemia in ICU patients. Consequently, suggested treatment regimens described in the literature are inconsistent.[7-12]

We hypothesised that the approach to hypophosphataemia in ICUs in the Netherlands would vary widely. The aim of this study was to evaluate current practice of monitoring

serum phosphate levels and treatment of hypophosphataemia in critically ill patients in the Netherlands. For this purpose, we sent a questionnaire to ICUs in the Netherlands.

METHODS

Design

We conducted a survey using a postal questionnaire among all hospitals with an ICU in the Netherlands. Paediatric ICUs were excluded from participation. The items in the questionnaire were selected on the basis of the current literature and professional experience. We chose to use only closed-ended questions as these enable comparison across respondents, require less time to complete than open-ended questions and are easy to code and process.[13] Approval by the Institutional Review Board was not deemed necessary since participation involved neither patients and experimental subjects nor patient data. Respondents were assured that confidentiality of individual and institutional response was protected. Completion and return of the questionnaire was considered equivalent to consent to participate in the study.

Questionnaire

The questionnaire consisted of 29 questions regarding causes of hypophosphataemia, frequency of serum phosphate measurements, triggers for correction and methods for correction of hypophosphataemia (the complete questionnaire is available online at http://home.kpn.nl/weae19qy/questionnaire.htm). To ensure clarity and consistency members of our local research group assessed the questionnaire for face and content validity before the final version was compounded and sent.

In November 2011, the questionnaire was sent by mail to all 89 ICUs. Respondents could either return the questionnaire by mail or complete the web-based version of the survey. Six weeks after sending the questionnaire, a reminder letter was sent. In addition, ICUs that did not respond were contacted by telephone one month after sending the reminder letter. Two months thereafter, the results were analysed.

For the purpose of the questionnaire, hypophosphataemia was defined as moderate or severe when the serum phosphate level was 0.32-0.65 mmol/l (1.0-2.0 mg/dl) or <0.32 mmol/l (<1.0 mg/dl), respectively, consistent with definitions in the international literature. The trigger for treatment of hypophosphataemia was expressed in decimals of the serum phosphate concentration in mmol/l (e.g. 0.30, 0.40 and 0.50 mmol/l), the preferred SI units used to report serum phosphate in hospitals in the Netherlands.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 19 (Chicago, IL, USA). Descriptive statistics of categorical variables are reported as total numbers and percentages. Continuous variables are reported as median and interquartile range. Pearson's chi-squared tests were used to evaluate the relationship between different categorical variables.

RESULTS

Survey response

Of the 89 questionnaires sent, 67 were returned (75%); 51 questionnaires by mail, 16 through the online survey; 39 (58%) respondents were internist-intensivists, and 22 (33%) were anaesthesiologist-intensivists. Characteristics of the responding ICUs are shown in *table 1*.

Table 1. *ICU characteristics*

		No. ICUs	
Type of hospital	Academic	8	(12%)
	Non-academic teaching hospital	37	(55%)
	Non-teaching hospital	21	(31%)
	Other	1	(2%)
Hospital size (beds)	<200	3	(4%)
	200-500	36	(54%)
	500-800	20	(30%)
	>800	8	(12%)
ICU size (ventilation beds)	<5	9	(13%)
	5-9	24	(36%)
	10-14	16	(24%)
	15-19	4	(6%)
	>20	14	(21%)
Number of ICU admissions per year	<500	10	(15%)
	500-1000	29	(45%)
	1000-1500	10	(15%)
	1500-2000	9	(14%)
	>2000	6	(11%)
Patient categories	Medical	67	(100%)
	General surgery	67	(100%)
	Major surgery*	45	(67%)
	Cardiothoracic surgery	10	(15%)
	Neurosurgery	15	(22%)
Number of full-time intensivists (median, IQR)		4.8	(3-7)
Number of full-time ICU nurses (median, IQR)		40	(26-75)

***Major surgery: major trauma, vascular, gastrointestinal and orthopaedic surgery; IQR = interquartile range.**

Causes of hypophosphataemia

Responses from academic, non-academic teaching and non-teaching hospitals were consistent regarding causes of hypophosphataemia. Particularly, renal replacement therapy was considered a risk factor for the development of hypophosphataemia (84%), as well as sepsis (84%) and malnutrition (79%). Respondents from ICUs where cardiac surgery patients were admitted, more frequently considered cardiopulmonary bypass during surgery to be an important cause of hypophosphataemia than respondents from other ICUs. Other assumed important causes of hypophosphataemia are displayed in *table 2*.

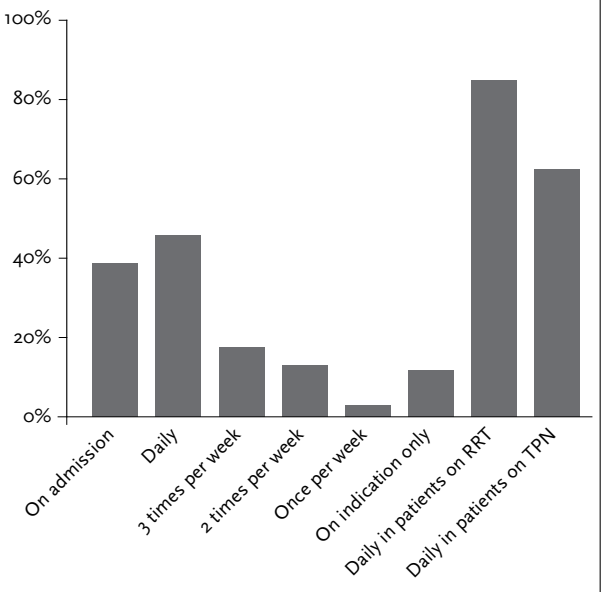
Monitoring of serum phosphate levels

Responses from academic, non-academic teaching and non-teaching hospitals were consistent, but varied more widely regarding policies of monitoring of serum phosphate levels. Of all respondents, 46% reported to measure serum phosphate levels every day in every patient; 12% measured serum phosphate levels only on indication (*figure 1*). Serum phosphate levels were routinely measured on admission to the ICU by 39% of the respondents. In patients receiving renal replacement therapy, serum phosphate levels were reported to be measured every day by 85%.

Incidence of hypophosphataemia

The estimated incidences of moderate and severe hypophosphataemia in the ICU are shown in *table 3*. Respondents from ICUs measuring serum phosphate levels every day in all patients estimated the frequency of moderate hypophosphataemia higher than those who performed phosphate measurements less frequently (median estimated incidence of moderate hypophosphataemia 25-40% versus 15-25%, p<0.05). The estimated incidence of severe hypophosphataemia was not different between respondents from ICUs where serum phosphate levels are measured every day in all patients and ICUs that perform phosphate measurements only on indication.

Figure 1. *Monitoring frequency of serum phosphate levels*



RRT = renal replacement therapy; TPN = total parenteral nutrition.

Table 3. *Estimated incidences of hypophosphataemia*

	Estimated incidence	% of respondents
Moderate hypophosphataemia (serum phosphate <0.65 mmol/l)	5-15%	27
	15-25%	33
	25-40%	25
	>40%	15
Severe hypophosphataemia (serum phosphate <0.32 mmol/l)	0-5%	71
	5–15%	19
	15–25%	7
	25–40%	3

Table 2. *Causes of hypophosphataemia*

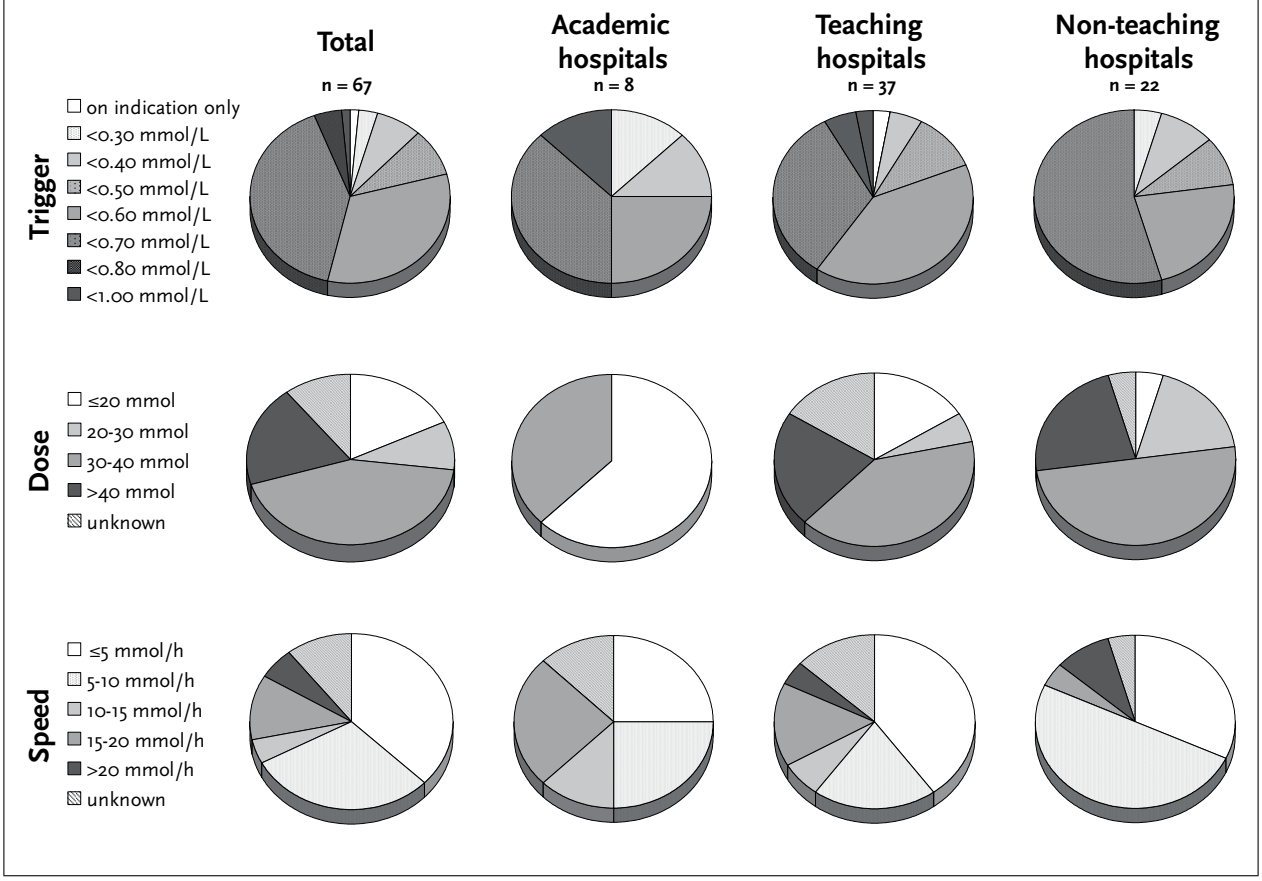
Risk factor	% of respondents
Renal replacement therapy	84
Sepsis	84
Malnutrition	79
Acid-base disorders	67
Diabetic ketoacidosis	61
Diuretic therapy	60
Major surgery	60
Diarrhoea	54
Increased risk for all ICU patients	46
Volume therapy	43
Inotropic/vasopressor therapy	21
Cardiopulmonary bypass	21
Mechanical ventilation	12

For every risk factor, the percentage of respondents considering this to be a risk factor for development of hypophosphataemia is reported.

Correction of hypophosphataemia

Fifty-three percent of respondents reported correction of hypophosphataemia to be guided by a local guideline. The trigger for correction of hypophosphataemia varied widely between responding ICUs, but was independent of the type of responding ICU. In the majority of ICUs (79%), intravenous infusion of phosphate is started if the serum phosphate is <0.60 mmol/l; in 13% hypophosphataemia is corrected only if the serum phosphate is <0.30 mmol (*figure 2*).

Figure 2. *Trigger, dose and speed of phosphate suppletion in different hospital categories*



Of all respondents, 87% reported phosphate to be exclusively administered intravenously. For intravenous correction, 69% reported using sodium-potassium-phosphate concentrates, 22% sodium-phosphate concentrates; 5% mentioned using both solutions; 5% mentioned using glycerophosphate. The maximum dose and rate of phosphate infusion varied widely, with phosphate dosages ranging from ≤20 mmol up to >40 mmol and speed of infusion ranging from ≤5 mmol up to >20 mmol per hour (*figure 2*); 43% reported using a dose of 30-40 mmol phosphate, and 37% reported using a speed of infusion of phosphate ≤5 mmol per hour. Differences between types of hospitals are shown in *figure 2*.

Complications of intravenous correction of hypophosphataemia

Of all respondents, 66% reported that complications of intravenous phosphate administration never occurred. Reporting of complications is neither dependent on the type of hospital nor on the reported phosphate infusion rates.

DISCUSSION

Dutch intensivists consider hypophosphataemia to be common in ICU patients. Consequently, serum phosphate levels are monitored frequently in those patients. To our knowledge, this is the first survey to investigate the approach to monitoring of serum phosphate levels and treatment of hypophosphataemia in critically ill patients. The results of this survey indicate that this approach varies considerably between hospitals.

In general, critically ill patients have multiple reasons for developing hypophosphataemia. Indeed, sepsis, trauma, major surgery, fluid therapy, acid-base disorders, refeeding and treatment with catecholamines or diuretics are all risk factors for the development of hypophosphataemia.[1] In addition, hypophosphataemia is considered to be not without consequences. Hypophosphataemia has been associated with respiratory muscle and myocardial dysfunction, cardiac arrhythmia, neuromuscular symptoms and leucocyte dysfunction,[1,14] and may therefore cause additional morbidity and maybe even mortality. Intravenous infusion of phosphate may not be without risk,

as it may induce hypocalcaemia, hyperphosphataemia and hyperkalaemia, depending on which type of solutions are used.[1,15] It would be appropriate to have a guideline for the frequency of monitoring of serum phosphate levels and for the correction of hypophosphataemia in the ICU setting, which may even be different for distinctive patient groups in the ICU.

Evidence from randomised controlled trials regarding correction of hypophosphataemia is lacking. Several case reports, though, show improvement of myocardial function after correction of severe hypophosphataemia.[16-18] Two small prospective studies report improvement of myocardial performance after correction of hypophosphataemia in patients with sepsis[8] and after cardiac surgery.[3]

The reported frequency of measuring serum phosphate levels and policies regarding correction of hypophosphataemia varied widely in this survey. Despite the high incidence of hypophosphataemia and its possible detrimental effects in critically ill patients, there seems to be no consensus on how frequently serum phosphate levels should be measured. The estimated incidence of hypophosphataemia by the respondents of this survey, however, is largely consistent with reported incidences in the literature.[1] Maybe not too surprisingly, the survey showed an association between awareness of a high incidence of hypophosphataemia and the frequency of monitoring of serum phosphate levels. Frequency of measurement ranged from daily measurements to those who measure phosphate on indication only. The literature lacks advice regarding the frequency with which serum phosphate should be measured in ICU patients. Because risk factors for hypophosphataemia are frequently present in almost all ICU patients, and also because hypophosphataemia may have therapeutic consequences, we consider it appropriate to measure serum phosphate levels frequently and routinely. It is unclear, though, how frequently serum phosphate levels are to be measured. Routine daily measurement of serum phosphate may be unnecessarily frequent, except for those at high risk for hypophosphataemia.

Patients with malnutrition in whom feeding is initiated represent one of those high-risk groups. The refeeding syndrome is almost universally associated with hypophosphataemia.[19] Patients who are at risk for this syndrome should be monitored frequently and should promptly receive phosphate-enriched feeding. Malnutrition was considered an important risk factor for the development of hypophosphataemia by the respondents. Early feeding in critically ill patients, either enterally through a nasogastric tube or parenterally, is common practice. Although the type of feeding administered to a patient may potentially influence the risk for the development of hypophosphataemia, this issue was not addressed in the current survey.

Our survey showed a large variability with regard to the trigger for correction of hypophosphataemia. Only half of the respondents reported to have a guideline for correction of hypophosphataemia. The literature advises to correct hypophosphataemia when it is symptomatic and/or when serum phosphate levels fall <0.32.[1,20-22] Whether also moderate hypophosphataemia should be corrected in critically ill patients is less clear, but correction is advised in patients on mechanical ventilation.[14] Improved myocardial function has been reported after treating patients with phosphate levels between 0.30 and 0.40 mmol/l.[3,8] It seems reasonable to correct hypophosphataemia in patients with serum phosphate <0.40 mmol/l. Over 95% of the respondents to our survey reported to use at least this trigger. More research is needed, however, to investigate whether correction of hypophosphataemia improves outcome.

Dose and speed of phosphate administration varies greatly among Dutch ICUs, which may not be too surprising as different treatment protocols are suggested in the literature. Advised doses of phosphate boluses in the literature range from ≤15 mmol[7,9] to 40 mmol.[10,23] Two recent studies report on body weight-dependant phosphate doses ranging from 0.4 to 1.0 mmol of phosphate per kilogram[11,12] with acceptable safety and efficacy. The most commonly reported dose of phosphate administration in our study was 30 to 40 mmol. Notably, the reported speed of phosphate administration was ≤5 mmol per hour in most respondents. This is lower than the administration speeds reported in the literature ranging from 5-7.5[7,9,12] to 20 mmol per hour,[8,23] with acceptable safety. Given the currently available evidence, administering a phosphate dose of 40 mmol or 0.5 mmol per kilogram seems a practical approach for patients with hypophosphataemia. Although there is no evidence for the superiority of a certain speed, it seems acceptable and more practical to use an administration rate between 10 and 20 mmol per hour. While intravenous administration of hypophosphataemia may lead to hyperphosphataemia, hyperkalaemia and hypocalcaemia, depending on the type of electrolyte concentrate used, respondents in this survey reported these to occur very seldom. The exact incidence of these complications is not reported in the literature. Frequent measurement of electrolytes and avoidance of potassium-containing formulas in the presence of hyperkalaemia is advised to prevent complications, in particular life-threatening arrhythmias.

There are some limitations to this survey. First, the questionnaire was only sent to ICUs in the Netherlands. Practice in the Netherlands may differ from that in other countries and the generalisability of the results

may be poor. In addition, only one physician filled in the questionnaire for each responding ICU. The answers given may not represent the opinion of the entire ICU staff. Although there was a good response rate, selection bias may have been introduced because the responding ICUs may be those where hypophosphataemia receives more attention than in the other ICUs. Finally, both web-based and surveys returned by regular mail were analysed as one group. The two questionnaires were exactly identical, but we cannot rule out a difference in way of responding to the questions in these different formats. However, results between both groups did not differ when analysed separately.

In conclusion, there is a large variability in the monitoring of serum phosphate and treatment of hypophosphataemia in critically ill patients in ICUs in the Netherlands. Pending studies necessary for evidence-based guidelines, we propose to monitor serum phosphate levels frequently in all critically ill patients, and to correct hypophosphataemia when serum phosphate levels are <0.40 mmol/l, administering a dose of 40 mmol in two to four hours.

REFERENCES

1. 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:R147.
2. Kruse JA, Al-Douahji M, Carlson RW. Hypophosphatemia in critically ill patients: incidence and associations. Crit Care Med. 1992;20:s107.
3. Zazzo JF, Troche G, Ruel P, Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. Intensive Care Med. 1995;21:826-31.
4. 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.
5. Salem RR, Tray K. Hepatic resection-related hypophosphatemia is of renal origin as manifested by isolated hyperphosphaturia. Ann Surg. 2005;241:343-8.
6. Goldstein J, Vincent JL, Leclerc JL, Vanderhoeft P, Kahn RJ. Hypophosphatemia after cardiothoracic surgery. Intensive Care Med. 1985;11:144-8.
7. Rosen GH, Boullata JI, O'Rangers EA, Enow NB, Shin B. Intravenous phosphate repletion regimen for critically ill patients with moderate hypophosphatemia. Crit Care Med. 1995;23:1204-10.
8. Bollaert PE, Levy B, Nace L, Laterre PF, Larcan A. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. Chest. 1995;107:1698-701.
9. Perreault MM, Ostrop NJ, Tierney MG. Efficacy and safety of intravenous phosphate replacement in critically ill patients. Ann Pharmacother. 1997;31:683-8.
10. Charron T, Bernard F, Skrobik Y, Simoneau N, Gagnon N, Leblanc M. Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. Intensive Care Med. 2003;29:1273-8.
11. Taylor BE, Huey WY, Buchman TG, Boyle WA, Coopersmith CM. Treatment of hypophosphatemia using a protocol based on patient weight and serum phosphorus level in a surgical intensive care unit. J Am Coll Surg. 2004;198:198-204.
12. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. JPEN J Parenter Enteral Nutr. 2006;30:209-14.
13. Meadows KA. So you want to do research? 5: Questionnaire design. Br J Community Nurs. 2003;8:562-70.
14. Amanzadeh J, Reilly RF, Jr. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. Nat Clin Pract Nephrol. 2006;2:136-48.
15. Bugg NC, Jones JA. Hypophosphataemia. Pathophysiology, effects and management on the intensive care unit. Anaesthesia. 1998;53:895-902.
16. Claudius I, Sachs C, Shamji T. Hypophosphatemia-induced heart failure. Am J Emerg Med. 2002;20:369-70.
17. Heames RM, Cope RA. Hypophosphataemia causing profound cardiac failure after cardiac surgery. Anaesthesia. 2006;61:1211-3.
18. Machiels JP, Dive A, Donckier J, Installe E. Reversible myocardial dysfunction in a patient with alcoholic ketoacidosis: a role for hypophosphatemia. Am J Emerg Med. 1998;16:371-3.
19. Marinella MA. The refeeding syndrome and hypophosphatemia. Nutr Rev. 2003;61:320-3.
20. Subramanian R, Khardori R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. Medicine (Baltimore). 2000;79:1-8.
21. McLean B, Zimmerman JL. Fundamental Critical Care Support Textbook. fourth ed: Society of Critical Care Medicine; 2007.
22. de Vries A, Gans R, Levi M. Acute boekje – Richtlijnen voor de diagnostiek en behandeling van aandoeningen op het gebied van inwendige specialismen. Vierde editie ed. Alphen a/d Rijn, the Netherlands: Van Zuiden Communications B.V.; 2009.
23. Kruse JA, Al-Douahji M, Carlson RW. Rapid intravenous phosphate replacement in critically ill patients. Crit Care Med. 1992;20:s107.