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Original article

Monitoring and parenteral administration of micronutrients, phosphate and magnesium in critically ill patients: The VITA-TRACE survey

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SUMMARY

Background & aims: Despite the presumed importance of preventing and treating micronutrient and mineral deficiencies, it is still not clear how to optimize measurement and administration in critically ill patients. In order to design future comparative trials aimed at optimizing micronutrient and mineral management, an important first step is to gain insight in the current practice of micronutrient, phosphate and magnesium monitoring and administration.

Methods: Within the metabolism-endocrinology-nutrition (MEN) section of the European Society of Intensive Care Medicine (ESICM), the micronutrient working group designed a survey addressing current practice in parenteral micronutrient and mineral administration and monitoring. Invitations were sent by the ESICM research department to all ESICM members and past members.

Results: Three hundred thirty-four respondents completed the survey, predominantly consisting of physicians (321 [96.1%]) and participants working in Europe (262 [78.4%]). Eighty-one (24.3%)

Abbreviations: EN, Enteral nutrition; ESICM, European Society of Intensive Care Medicine; ICU, Intensive care unit; MEN, Metabolism-Endocrinology-Nutrition; PN, Parenteral nutrition; RCT, Randomized controlled trial.

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respondents reported to monitor micronutrient deficiencies through clinical signs and/or laboratory abnormalities, and 148 (44.3%) reportedly measure blood micronutrient concentrations on a routine basis. Two hundred ninety-two (87.4%) participants provided specific data on parenteral micronutrient supplementation, of whom 150 (51.4%) reported early administration of combined multivitamin and trace element preparations at least in selected patients. Among specific parenteral micronutrient preparations, thiamine (146 [50.0%]) was reported to be the most frequently administered micronutrient, followed by vitamin B complex (104 [35.6%]) and folic acid (86 [29.5%]). One hundred twenty (35.9%) and 113 (33.8%) participants reported to perform daily measurements of phosphate and magnesium, respectively, whereas 173 (59.2%) and 185 (63.4%) reported to routinely supplement these minerals parenterally.

Conclusion: The survey revealed a wide variation in current practices of micronutrient, phosphate and magnesium measurement and parenteral administration, suggesting a risk of insufficient prevention, diagnosis and treatment of deficiencies. These results provide the context for future comparative studies, and identify areas for knowledge translation and recommendations.

1. Introduction

Micronutrients, consisting of vitamins and trace elements, are essential substances needed in minuscule amounts to ensure proper functioning of crucial physiological and metabolic processes [1–3]. In addition, phosphate and magnesium –although generally not labelled as micronutrient given their daily-required doses exceeding 100 mg– are two essential minerals [2,3]. Given their important role in maintaining homeostasis, severe deficiencies of micronutrients, phosphate and magnesium are potentially life-threatening [2,4,5]. Critically ill patients are at increased risk of developing such deficiencies due to illness-induced decreased intake, increased losses, drug interactions and potentially higher needs (Table 1) [1,2,4,6–8]. Moreover, the risk of developing a deficiency may be increased by the recent shift in feeding practices. Indeed, feeding guidelines based on recent large randomized controlled trials (RCTs) no longer support high-dose macronutrient feeding in the early phase of critical illness [9]. This delayed macronutrient administration may unintentionally reduce micronutrient, phosphate and magnesium provision in the early phase, potentially inducing or aggravating deficiencies. Since symptoms of micronutrient deficiencies, as well as of hypophosphatemia and hypomagnesemia are non-specific in the context of critical illness (Table 2), deficiencies can easily be overlooked [4,6]. Additionally, initiation of artificial feeding may render pre-existing deficiencies symptomatic. Indeed, refeeding acutely increases the need for certain minerals and micronutrients such as phosphate and thiamine, whereby rapid initiation of artificial feeding may lead to a potentially lethal refeeding syndrome [3]. Clinical signs of refeeding syndrome include cardiac arrhythmias, cardiogenic shock, muscle weakness and lactic acidosis. New-onset hypophosphatemia has been put forward as predominant biochemical feature of refeeding syndrome [10,11].

Despite the presumed importance of preventing and treating micronutrient and mineral deficiencies, it is still not clear how to optimize measurement and administration in critically ill patients, since large observational and interventional studies are lacking [1]. Blood micronutrient and mineral concentrations may be affected by exogenous infusion and redistribution, particularly related to inflammation [12], and thus not necessarily reflect tissue levels [8]. The need to separately administer micronutrients depends in part on the route of feeding [6]. Indeed, commercially available enteral nutrition formulations contain micronutrients, whereby their provision depends on the energy intake achieved [13]. In contrast, commercially available parenteral nutrition solutions –not containing any micronutrients due to instabilities– necessitate separate supplementation in patients receiving exclusive parenteral nutrition [9]. The optimal speed of parenteral micronutrient infusion is also a matter of debate. Direct sunlight and certain trace elements may degrade vitamins, particularly A, C and E [14,15]. A more rapid infusion of micronutrients could be an approach to overcome such degradation, but may transiently expose patients to supraphysiological concentrations and consequently enhance urinary loss of water-soluble micronutrients, which is concentration-dependent [16,17].

To gain more insight in the current practice regarding micronutrient, phosphate and magnesium monitoring and parenteral administration, the micronutrient working group within the Metabolism-Endocrinology-Nutrition (MEN) section of the European Society of Intensive Care Medicine (ESICM) designed a survey. The results will inform the design of comparative studies and may reveal discrepancies with existing guidelines.

2. Materials and methods

Nutritional experts with a special interest for micronutrients were invited to join the micronutrient working group. During an initial face-to-face meeting, the working group defined the scope of the survey and the target audience. Thereafter, the questionnaire was constructed, followed by adjustments through email communication until consensus was reached, optimizing content validity. Technical issues and timing were discussed during a final plenary meeting. The questionnaire was converted into an online survey with the web application Limesurvey (version 2.00, Hamburg, Germany) on a KU Leuven server. Only the principal investigators could make changes to the survey. To optimize face validity and unambiguous interpretation, the survey was tested by a focus group, consisting of intensive care specialists ($n = 10$), after which final adjustments were made. Subsequently, the survey was sent to the expert group for final approval and discussion on which questions should be mandatory.

The full questionnaire is available as online supplement (see additional file 1). The survey consisted of two main sections. The first section addressed respondent's characteristics including their working environment and general nutritional and metabolic management. The second section comprised specific questions about routine monitoring and parenteral administration of micronutrients, phosphate and magnesium. All fields were mandatory, except for ancillary questions regarding specific details on individual micronutrients (see additional file 1). When inquiring timing

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Table 1
Risk factors for developing a micronutrient, phosphate and/or magnesium deficiency.

Inadequate intake or uptake	Increased losses and consumption	Drug interaction (with single micronutrients)
- Prolonged starvation - Unbalanced diet - Bariatric surgery - Malabsorption syndromes (celiac disease, inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, short bowel) - Alcoholism - Chronic liver disease - Kidney dysfunction/failure - Drugs (proton pump inhibitors, H2-receptor antagonists, cholestyramine, broad spectrum antibiotics, metformin, thyroxin, ….)	- Large burn wounds - Meno(metro)rrhagia - Prolonged inflammation and oxidative stress - Increased urinary loss (diuretics, hyperparathyroidism, tubular dysfunction) - Continuous renal replacement therapy - Gastrointestinal fistula, chylous leak	- Isoniazid - Phenobarbital - Phenytoin - Penicillamine - Theophylline - Tricyclic antidepressants

Table 2
Clinical and laboratory signs of a micronutrient, phosphate and/or magnesium deficiency.

Anemia and other cytopenias
Hypokalemia
Hypocalcemia
Metabolic disturbances (lactic acidosis, hyperlipidemia, hyperglycemia)
Neurological and cognitive deficits
Cardiac dysfunction
Muscle weakness and myopathy
Osteoporosis/bone pain
Rickets and osteomalacia
Immune dysfunction
Skin lesions and delayed wound healing
Glossitis and (angular) cheilitis
Growth and developmental disorders

of particular events, day 1 was defined as the day of intensive care unit (ICU) admission.

The survey was active from October 1, 2018 until December 10, 2018. The invitation was sent by the ESICM research department to all ESICM members and past members on October 1, 2018. Respondents could only access the survey with the use of a unique token, preventing double participation. Non-respondents received a reminder on November 7 and November 26, 2018. The list of recipients and allocated tokens was not available to the researchers and was destroyed after completion of the survey. Participants had the possibility to save partially completed surveys and resume later. However, only fully completed surveys were available to the researchers and were included in the analyses. No personal data were saved and the answers could not be linked to the token used to access the survey, ensuring anonymity. The survey was endorsed by ESICM.

The Ethical Committee Research UZ/KU Leuven provided a favorable advice for the survey (S61822). The information provided in the survey was collected anonymously and did not contain personal data, hence falling outside the scope of the General Data Protection Regulation.

Data are presented as numbers and percentages, or as median (interquartile range). Percentages are expressed relative to the total number of respondents, unless indicated otherwise. Analyses were performed in JMP (version 14, SAS, Cary, North Carolina).

Table 3
Demographic characteristics of the respondents.

	n (%)
Profession	
Physician	321 (96.1%)
Nutritionist	7 (2.1%)
Nurse	5 (1.5%)
Clinical pharmacist	1 (0.3%)
Type of hospital	
Academic	208 (62.3%)
Non-academic	126 (37.7%)
Type of ICU	
Surgical	35 (10.5%)
Medical	27 (8.1%)
Mixed	267 (79.9%)
Burn/trauma	5 (1.5%)
ICU population	
Adults	292 (87.4%)
Children	16 (4.8%)
Mixed	26 (7.8%)

3. Results

3.1. General characteristics of the respondents

Three hundred thirty-four respondents completed the survey of whom 321 (96.1%) were physicians, 7 (2.1%) nutritionists, 5 (1.5%) nurses and 1 (0.3%) clinical pharmacist (Table 3). The reported working environment was predominantly European (262 [78.4%]), academic (208 [62.3%]), mixed surgical/medical ICU (267 [79.9%]), and only treating adult patients (292 [87.4%]) (Table 3 + Fig. 1A). Within Europe, most countries were represented, with eleven countries having more than ten respondents (Fig. 1B).

Two hundred twenty-seven (68.0%) participants reported to have access to sources documenting the presumed requirements of trace elements and vitamins in critically ill patients. The most commonly reported sources were guidelines (N = 170/227 [74.9%]) and analysis of the literature (N = 48/227 [21.1%]). One hundred sixty-eight (50.3%) respondents reported to have access to sources documenting the normal range of blood concentrations of trace elements and vitamins. The most commonly reported sources were guidelines (N = 87/168 [51.8%]) and analysis of the literature (N = 36/168 [21.4%]).

3.2. General nutritional and metabolic management

Full enteral nutrition was reported to be reached in the average patient after a median of 3 (2–4) days, with a range from 1 to 10 days (Fig. 2). When less than 60% of caloric intake is provided by enteral nutrition, parenteral nutrition was reported to be initiated median at day 5 (3–7; total range 1–21). Three hundred nine (92.5%) participants reported to have a protocol for blood glucose control, with varying targets (Fig. 3). Parenteral micronutrient supplementation in patients receiving no or insufficient artificial nutrition is initiated median at day 3

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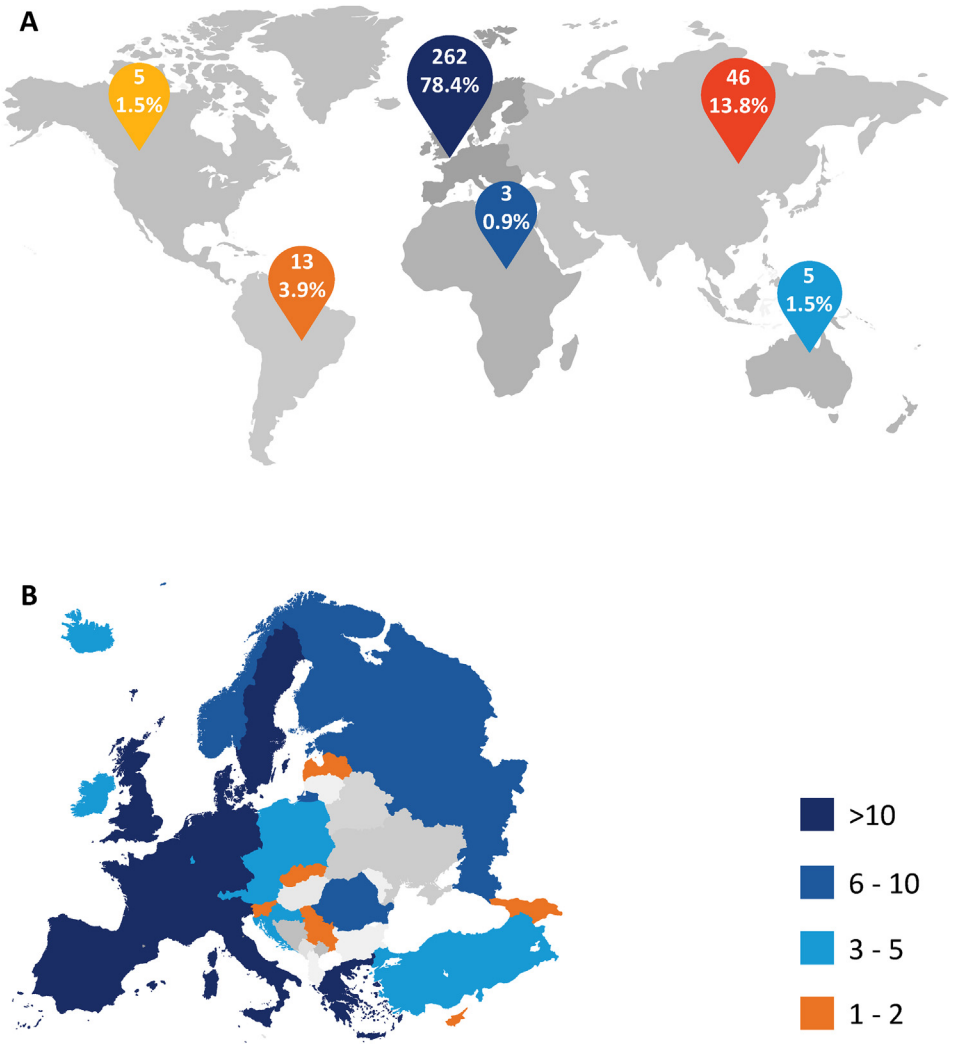

Fig. 1. Geographical location of the respondents. Continent (A) and European country (B) where respondents reported their intensive care unit is located.

(1–5; total range 1–999) for mixtures of water-soluble vitamins, day 3 (2–6; total range 1–999) for mixtures of lipid-soluble vitamins and day 3 (2–7; total range 1–999) for trace element preparations.

3.3. Micronutrient monitoring

Eighty-one (24.3%) respondents reported to monitor micronutrient deficiencies through clinical signs and/or laboratory abnormalities. The most frequently monitored laboratory abnormalities were anemia with or without other cytopenia (24 [7.2%]), followed by metabolic acidosis (13 [3.9%]). Among the clinical signs, skin lesions (46 [13.8%]), neurological signs (43 [12.9%]), decreased wellbeing and weakness (40 [12.0%]), and cardiac signs (32 [9.6%]) were most frequently monitored (Table 4). One hundred forty-eight (44.3%) respondents reported to routinely measure the blood concentrations of selected micronutrients to detect deficiencies. The 10 most frequently reported routine measurements and their respective measurement frequencies are depicted in Fig. 4. The three most frequently reported measurements were iron (97 [29.0%]), folate (65 [19.5%]) and vitamin B12 (58 [17.4%]).

3.4. Parenteral micronutrient administration

Two hundred ninety-two (87.4%) participants provided data on specific micronutrient supplementation, of whom 150 (51.4%) reportedly provided early parenteral combined multivitamin and trace element preparations at least in selected patients. Seventy-eight (26.7%) respondents reported to parenterally supplement all patients and 63 (21.6%) reported to only supplement selected patients (Table 5). Within the specific parenteral micronutrient preparations, thiamine was reported as most frequently supplemented (146 [50.0%]), followed by vitamin B complex (104 [35.6%]), folic acid (86 [29.5%]), vitamin B12 (85 [29.1%]), vitamin C (83 [28.4%]) and iron (68 [23.3%]) (Fig. 5). Respondents supplementing specific parenteral micronutrient preparations most often did so in selected patients. The modality of parenteral administration of both combined and specific micronutrient preparations was highly variable (Table 6).

3.5. Phosphate and magnesium monitoring and administration

One hundred twenty (35.9%) and 113 (33.8%) respondents reported to daily measure phosphate and magnesium, respectively, whereas 75 (22.5%) and 85 (25.4%) reported not to routinely

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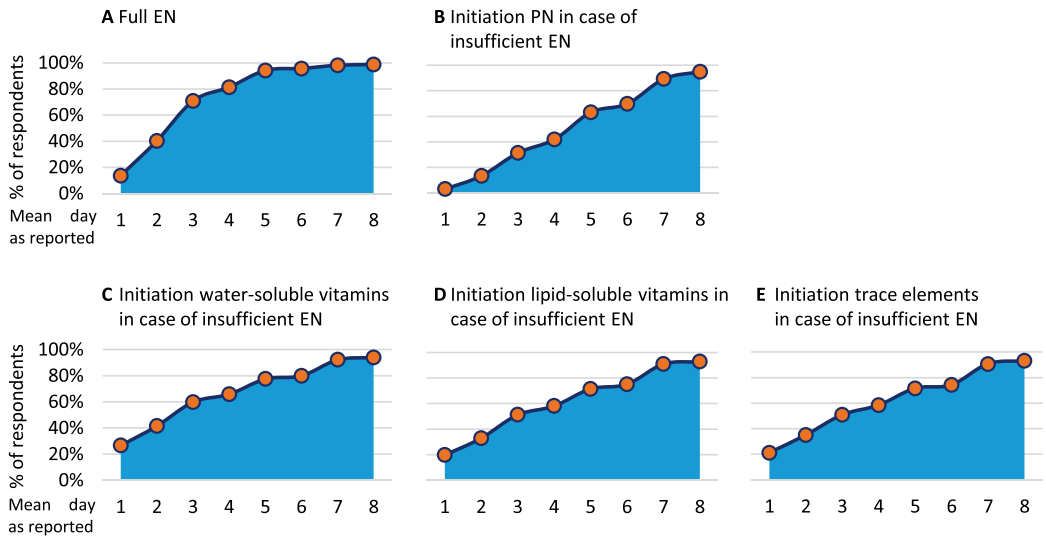

Fig. 2. Timing of enteral and parenteral nutrition, and parenteral micronutrient administration. (A) Average day in the intensive care unit (ICU) at which a respondent reported to reach full enteral nutrition (EN). (B) Average day at which a respondent reported to initiate parenteral nutrition (PN) if EN is insufficient (<60% of target caloric intake). (C–E) Average day at which a respondent reported to initiate parenteral water-soluble vitamins (C), lipid-soluble vitamins (D) or trace elements (E) in patients receiving insufficient enteral nutrition and no parenteral nutrition. Data presented as cumulative number of respondents. ICU day 1 represents the day of ICU admission.

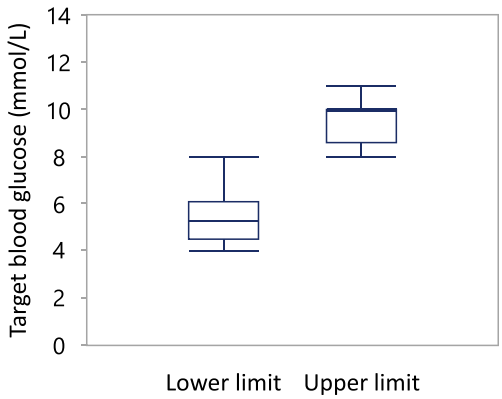

Fig. 3. Blood glucose control. Upper and lower blood glucose target. Boxes indicate median and interquartile range, whiskers 10th and 90th percentile.

measure phosphate and magnesium, or to measure not more than once a week (Table 7). Of the 292 respondents providing data on parenteral micronutrient and mineral supplementation, 173 (59.2%) and 185 (63.4%) reported to regularly supplement phosphate and magnesium, respectively. The modality of parenteral phosphate and magnesium administration considerably differed among respondents (Table 7).

3.6. Practical aspects and protocols regarding micronutrient management

Most of the respondents (276 [82.6%]) reported that the attending intensivist is in charge for the prescription of parenteral micronutrients, followed by a dedicated internal nutritional team (n = 27, [8.1%]) and a dedicated intensivist with extra expertise (n = 17, [5.1%]) (Table 8). One hundred nineteen (35.6%) respondents reported to have a protocol for the administration of parenteral micronutrients. Of these protocols, 66 (55.5%) are designed to prevent inactivation of selected vitamins by daylight, and 58 (48.8%) take incompatibilities between some micronutrients into account. Seventy-six (22.8%) respondents reported to have a protocol to prevent omission of micronutrients in parenteral nutrition. One hundred seventy (50.9%) reported to prescribe enteral or parenteral micronutrients on top of full enteral nutrition in some occasions.

4. Discussion

The VITA-TRACE survey inquired current practices regarding monitoring and parenteral administration of micronutrients and minerals in the critically ill. The results suggest a wide variation in clinical practice. Indeed, while some respondents reported to not routinely measure blood micronutrient, phosphate and magnesium concentrations, others reported to perform selective measurements on a daily basis and to have structured protocols. Similarly, the timing and indication of parenteral micronutrient, phosphate and magnesium supplementation differed considerably, and the presence and content of protocols for micronutrient administration varied. Most respondents reported not aiming to reach the full caloric target in the first days of critical illness and avoiding early parenteral nutrition. The vast majority of participants were physicians with more than 10 years of expertise, mainly working in mixed ICUs and treating only adult critically ill patients. Most participants resided in Europe, and most European countries were sufficiently represented in the survey. Hence, the results appear generalizable and reflective for real-life practices in Europe.

The results provide the basis for future comparative studies, as planned by the micronutrient working group of ESICM. Indeed, since there are only limited data on the daily requirements of micronutrients, phosphate and magnesium in general ICU patients, future studies should investigate existing practices from a pharmacological perspective, and study effects on patient-centered and health-economic endpoints [1]. The variability in micronutrient measurements could be partially related to an uncertainty to what extent decreases in selected micronutrient concentrations are related to inflammation-induced redistribution, and whether this requires treatment or not. Apart from studying this topic, future studies should examine how individual micronutrient and mineral administration can be optimized, in order to prevent potential inactivation of certain micronutrients by slow administration and long storage, and potential rapid renal losses associated with bolus

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Table 4
Monitored clinical signs and laboratory abnormalities of micronutrient, phosphate and magnesium deficiencies.

Symptom	n (%)
Laboratory abnormalities	49 (14.7%)
Anemia and/or other cytopenia	24 (7.2%)
Metabolic acidosis	13 (3.9%)
Other (altered liver enzymes or function, hypoalbuminemia, renal impairment, hypertriglyceridemia, increased INR, hyperammonemia, thyroid hormone, uremia)	12 (3.6%)
Skin lesions (dermatitis, dry, fragile skin; delayed wound healing; decubitus)	46 (13.8%)
Neurological signs	43 (12.9%)
Peripheral symptoms (muscle cramps, abnormal reflexes, paresthesia, …)	20 (6.0%)
Central nervous system (delirium, altered consciousness, convulsions, ataxia)	14 (4.2%)
Undefined	9 (2.7%)
Decreased general wellbeing and weakness	40 (12.0%)
Cardiac signs (arrhythmias, cardiac failure, edema)	32 (9.6%)
Mucosal lesions (mucositis, glossitis, angular cheilitis)	18 (5.4%)
Hair and nail lesions	17 (5.1%)
Bleeding diathesis	12 (3.6%)
Gastrointestinal disorders (diarrhea, vomiting, ileus)	9 (2.7%)
Ocular abnormalities (keratitis, Bitot's spots, night blindness, xerophthalmia)	7 (2.1%)
Osteoporosis	2 (0.6%)

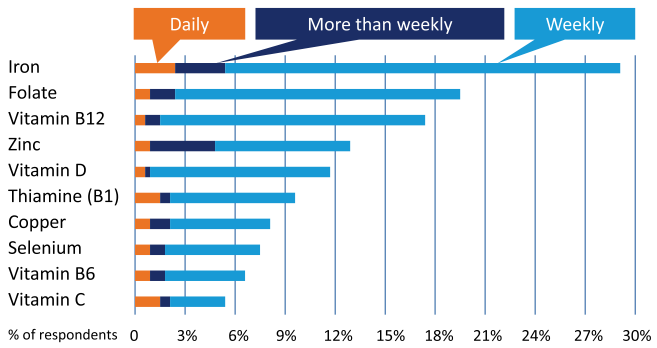

Fig. 4. Top ten most frequent micronutrient measurements. Percentage of respondents and the frequency at which they reported to measure selected micronutrients. Only the 10 most frequent measurements are displayed. Percentages are expressed relative to the total number of respondents.

infusions [14–17]. In addition, the optimal frequency of selected micronutrient measurements remains to be established, taking into consideration cost-effectiveness, and blood losses due to frequent blood sampling.

Iron, folate and vitamin B12 were the three micronutrients reported to be most frequently measured. Although speculative, this could be explained by the high frequency of anemia in critically ill patients [18]. Diagnosing iron deficiency is complex in critically ill patients, however, and we did not inquire whether additional measurements regarding iron status were performed concomitantly [19]. Not surprisingly, iron, folic acid and vitamin B12 were among the six most often parenterally supplemented micronutrients, mostly in selected patients. Vitamin B complex, thiamine and vitamin C completed the top six of most parenterally supplemented micronutrients. Thiamine administration is likely used in patients at risk to prevent Wernicke encephalopathy and cardiac failure [20]. Selective administration of vitamin C and thiamine

Table 5
Parenteral supplementation of mixed vitamins and trace elements.

		n (%)
Early mixed vitamin supplementation[a]		209 (71.6%)
of which[b]	in all patients	118 (40.4%)
	in selected patients	85 (29.1%)
No early mixed vitamins supplementation		83 (28.4%)
Early trace elements supplementation		168 (57.5%)
of which[c]	in all patients	89 (30.5%)
	in selected patients	70 (24.0%)
No early trace element supplementation		124 (42.5%)
Early mixed vitamins + trace elements supplementation		150 (51.4%)
of which[d]	in all patients	78 (26.7%)
	in selected patients	63 (21.6%)
No early mixed vitamins + trace elements supplementation		142 (48.6%)

Percentages were calculated relative to the number of participants providing data on supplementation (292/334, 87.4%).
[a] Mixed vitamins = mixed vitamins preparation, or combination of mixed water-soluble and lipid-soluble vitamin preparations, or vitamin A + vitamin B mixture + vitamin C + vitamin D + vitamin E.
[b] Data missing in 6 respondents.
[c] Data missing in 9 respondents.
[d] Data missing in 9 respondent.

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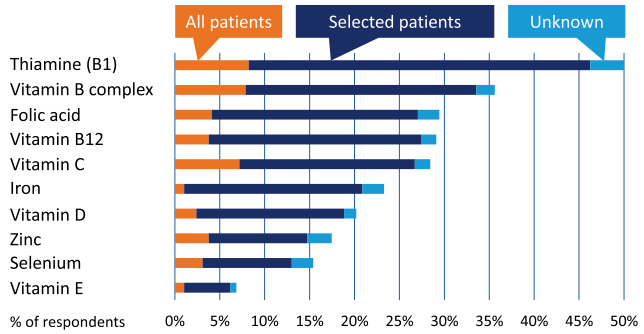

Fig. 5. Top ten most frequent specific parenteral micronutrient supplements. Percentage of respondents parenterally supplementing specific micronutrient formulations. Only the 10 most supplemented preparations are displayed. Percentages are expressed relative to the number of respondents providing data on parenteral micronutrient supplementation (N = 292).

regularly monitor neither parenterally administer micronutrients, phosphate and magnesium. Furthermore, the reported global practice of tolerating a macronutrient deficit in the first days of critical illness, in line with recent feeding guidelines [9], may provoke or aggravate a deficit when micronutrients, phosphate and magnesium are not monitored or are equally restricted. This constellation is potentially dangerous, since symptoms of micronutrient deficiencies, hypophosphatemia, hypomagnesemia and refeeding syndrome are non-specific and potentially life-threatening when left untreated [4]. In this regard, in critically ill patients developing refeeding syndrome, as defined by new-onset hypophosphatemia after initiation of artificial nutrition, a large RCT has found that temporarily restricting macronutrient intake while correcting micronutrient deficiencies and hypophosphatemia improved survival as compared to continuing and increasing macronutrient intake [10]. When phosphate is not measured, however, it is unlikely

Table 6
Method of parenteral micronutrient supplementation.

	Added to IV fluid bag, n (%)[a]	Separate bolus, n (%)[a]	Separate continuous infusion, n (%)[a]	Unknown, n (%)[a]
Combined water- and lipid-soluble vitamin preparations (N = 144)	69 (47.9%)	34 (23.6%)	17 (11.8%)	24 (16.7%)
Combined water-soluble vitamin preparations (N = 137)	73 (53.3%)	26 (19.0%)	19 (13.9%)	19 (13.9%)
Combined lipid-soluble vitamin preparations (N = 107)	60 (56.1%)	15 (14.0%)	17 (15.9%)	15 (14.0%)
Combined trace element preparations (N = 168)	99 (58.9%)	26 (15.5%)	19 (11.3%)	24 (14.3%)
Thiamine (B1) (N = 146)	23 (15.8%)	90 (61.6%)	9 (6.2%)	24 (16.4%)
Vitamin B complex (N = 104)	23 (22.1%)	51 (49.0%)	8 (7.7%)	22 (21.2%)
Folic acid (N = 86)	5 (5.8%)	54 (62.8%)	5 (5.8%)	22 (25.6%)
Vitamin B12 (N = 85)	5 (5.9%)	58 (68.2%)	7 (8.2%)	15 (17.6%)
Vitamin C (N = 83)	16 (19.3%)	43 (51.8%)	10 (12.0%)	14 (16.9%)
Iron (N = 68)	5 (7.4%)	37 (54.4%)	8 (11.8%)	18 (26.5%)
Vitamin D (N = 59)	2 (3.4%)	40 (67.8%)	3 (5.1%)	14 (23.7%)
Zinc (N = 51)	16 (31.4%)	12 (23.5%)	8 (15.7%)	15 (29.4%)
Selenium (N = 45)	12 (26.7%)	11 (24.4%)	6 (13.3%)	16 (35.6%)
Vitamin E (N = 20)	2 (10.0%)	9 (45.0%)	1 (5.0%)	8 (40.0%)

IV: intravenous.
[a] Percentage calculated relative to the number of respondents supplementing the respective micronutrient.

Table 7
Phosphate and magnesium.

	n (%)	n (%)
	Phosphate	Magnesium
Measurement blood concentration		
Never	22 (6.6%)	32 (9.6%)
Once a week	53 (15.9%)	53 (15.9%)
2 or 3 times a week	96 (28.7%)	98 (29.3%)
More than 3 times a week	43 (12.9%)	38 (11.4%)
Once a day	118 (35.3%)	111 (33.2%)
More than once a day	2 (0.6%)	2 (0.6%)
Regular parenteral supplementation of phosphate and magnesium[a]	173 (59.2%)	185 (63.4%)
All patients	38 (13.0%)	55 (18.8%)
Specific indications	127 (43.5%)	120 (41.1%)
Unknown	8 (2.7%)	10 (3.4%)
Method of parenteral administration[b]		
Separate continuous infusion	61 (35.3%)	45 (24.3%)
Separate bolus	57 (32.9%)	71 (38.4%)
Added to IV-fluid bag	33 (19.1%)	42 (22.7%)
Unknown	22 (12.7%)	27 (14.6%)

[a] Percentage calculated relative to the number of respondents providing data on micronutrient supplementation.
[b] Percentage calculated relative to the number of respondents supplementing phosphate or magnesium respectively.

might also be performed as adjuvant therapy in septic shock, despite the lack of conclusive evidence [21–23].

The survey identified clear areas for knowledge translation. Indeed, a considerable fraction of respondents reported to not that this life-saving strategy would be implemented. Traditionally, several factors have been considered risk factors for developing refeeding syndrome, including pre-existing malnutrition and prolonged starvation [24]. However, a recent observational

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Table 8
Practical aspects and protocols regarding micronutrient management.

	n (%)
Responsible for prescribing parenteral micronutrients	
Intensivist	276 (82.6%)
Dedicated internal nutritional team	27 (8.1%)
Dedicated intensivist with nutritional expertise	17 (5.1%)
Dedicated external nutritional team	8 (2.4%)
Pharmacist	4 (1.2%)
Nurse	2 (0.6%)
Protocol in place for parenteral micronutrient administration	119 (35.6%)
Which prevents inactivation from daylight[a]	66 (55.5%)
Which takes incompatibilities into account[a]	58 (48.8%)
Protocol to avoid omission of micronutrients in patients receiving parenteral nutrition	76 (22.8%)
Prescribe enteral or parenteral micronutrients on top of full enteral nutrition in some occasions	170 (50.9%)

[a] Percentage calculated relative to the number of respondents with a protocol in place for parenteral micronutrient administration.

study has shown that refeeding syndrome could not be predicted by upon-admission risk factors [11]. This underscores the potential importance of measuring phosphate on a routine basis in critically ill patients.

Although speculative, potential differences in parenteral micronutrient administration could explain the divergent impact of artificial feeding on clinical outcome across recent nutritional RCTs in critically ill and hospitalized patients, apart from differences in patient population, energy and protein target, feeding route, and relative macronutrient content [25–35]. Indeed, in contrast to several RCTs in which micronutrient and mineral administration was protocolized in both study arms [25,28,30–33], other RCTs did not protocolize micronutrient management [26,34] or only advised physicians to prescribe micronutrients in the intervention arm [27,29,35]. Consequently, in RCTs without protocolized and comparable micronutrient management in both arms, it remains unclear whether the results are explained by differences in macronutrient intake, or by insufficient prevention and detection of micronutrient/mineral deficiencies and refeeding syndrome in one of the study arms [36].

The study was designed through collaboration between multiple experts in the field of nutritional management of critically ill patients. Yet, the study inherently has limitations. The number of respondents was relatively low. However, there was a good distribution across Europe and the unique token sent by ESICM prevented double participation. Moreover, most participants were experienced and worked in an academic center, and one could speculate that a considerable fraction may have a particular interest in the topic. Hence, we expect that this potential bias would more likely underestimate rather than overestimate potential inadequacies in current practice. A second limitation relates to the survey itself, whereby we could only inquire the intentions of the respondent. Indeed, previous research has shown that the administered macronutrient intake of critically ill patients often does not correspond to what is prescribed [37]. Hence, we do not know whether the reported micronutrient practice truly reflects the clinical practice of the respondent. However, also for this limitation, we are convinced this potential bias would underestimate rather than overestimate the need for knowledge translation. Third, not all participants provided data on specific micronutrient supplementation, whereby a blank answer may mean either no supplementation or missing data. However, by calculating the percentage of respondents relative to the number of participants who provided at least one answer (i.e. reported to provide at least one specific micronutrient), this potential bias would only underestimate the real percentage of participants not providing early parenteral micronutrients. Fourth, for the majority of questions, we focused on parenteral supplementation of micronutrients. Since micronutrients could also be administered enterally, this may have underestimated the use of routine supplementation. Also, we did not survey potassium monitoring and supplementation, which is equally important in preventing and treating refeeding syndrome. However, we expect that potassium measurements and subsequent supplementation are more routinely implemented, since most blood gas analyzers report potassium concentrations. Finally, despite carefully checking face validity by the focus group, we cannot exclude that some respondents unintentionally provided a wrong answer for some questions.

5. Conclusion

A substantial variation exists in monitoring and parenteral administration of vitamins, trace elements, phosphate and magnesium in critically ill patients. A considerable fraction of intensive care specialists reported to not regularly monitor and/or parenterally administer these micronutrients and minerals in the early phase of critical illness. The absence of routine monitoring and parenteral supplementation in the early phase may lead to undiagnosed deficiencies and unrecognized refeeding syndrome, two entities with non-specific symptoms that may potentially be lethal. Moreover, the shift towards hypocaloric nutrition in the first days of critical illness may increase the risk of developing deficiencies when also micronutrients and minerals would be restricted, although the optimal timing and dose of supplementation remains to be investigated. Hence, besides opening perspectives for comparative studies assessing the most optimal strategy regarding micronutrient monitoring and administration, the survey identified clear areas for knowledge translation.

Statement of autorship

All authors: conception and design of the questionnaire; WV, JG and MPC digitalized the questionnaire, analyzed and interpreted the data and drafted the first manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

Dr. Amrein reports grants, personal fees and other from Fresenius Kabi (Austria), personal fees from Vifor Pharma (Austria), personal fees from Shire now part of Takeda (Austria), outside the submitted work. Dr. Bear reports personal fees from Nutricia (United Kingdom), personal fees from Baxter Healthcare (Global, based in USA), personal fees from Fresenius Kabi (Global, based in Germany), personal fees from Cardinal Health (USA), personal fees from AVANOS (USA), outside the submitted work. Dr. lasocki reports grants and personal fees from VIFOR PHARMA (France), personal fees from PFIZER (France), personal fees and non-financial support from MASIMO (France), non-financial support from PHARMACOSMOS (Denmark), outside the submitted work. Dr. Reintam Blaser reports grants from Fresenius Kabi (Germany), personal fees from Fresenius Kabi (Germany), personal fees from Nestlé (Switzerland), outside the submitted work. Rousseau reports non-financial support from Fresenius (Belgium), personal fees and non-financial support from Baxter (Belgium), non-financial support from Nutricia (Belgium), non-financial support from Nestlé (Belgium), outside the submitted work. Dr. van Zanten reports grants, personal fees and non-financial support from Nutricia Danone (Netherlands), grants from Mermaid (Denmark), personal fees and non-financial support from Fresenius Kabi (Belgium and Netherlands), grants and non-financial support from Cardinal Health (USA), personal fees from Nestle (USA), grants and personal fees from Amomed (Netherlands and Austria), grants and personal fees from Lyric (USA), personal fees from Baxter (Belgium), outside the submitted work. Dr. Casaer reports personal fees from Fresenius Kabi, (Belgium) outside the submitted work. MPC holds a postdoctoral research fellowship supported by the Research Foundation Flanders (1832817N). Gunst J holds a postdoctoral research fellowship supported by the Clinical Research and Education Council of the University Hospitals Leuven (Belgium). The other authors reported no competing interests.

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Appendix A. Supplementary data

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