**Micronutrient use in critical care: survey of clinical practice**

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## **ABSTRACT**

#### Background & Aims

Micronutrients, principally vitamins and minerals, play an important role both in health and in disease. Parenteral micronutrient products are commonly prescribed for critically ill patients both in-line with the terms of the product’s license, and for other indications where there is an underpinning physiological rationale, or precedent, for their use but little evidence. This survey sought to understand United Kingdom (UK) prescribing practice in this area.

#### Methods

A 12-question survey was circulated to healthcare professionals working in UK critical care units. The survey was designed to explore several aspects of micronutrient prescribing or recommendation practice by the critical care multidisciplinary team, including indications and underpinning clinical rationale for using these products, dosing, and considerations with respect to micronutrients delivered as part of nutrition. Results were analysed, exploring indications, considerations relating to diagnoses, therapies including renal replacement therapies, and method of nutrition.

#### Results

*2*17 responses were included in the analysis, with 58% from physicians and the remaining 42% from nurses, pharmacists, dietitians and other healthcare disciplines. Vitamins were most commonly prescribed or recommended for Wernicke’s encephalopathy (prescribed or recommended by 76% of respondents), treatment of refeeding syndrome (64.5%), and for patients with unknown or uncertain alcohol intake history (63.6%). These clinically suspected or confirmed indications were cited more frequently as a reason to prescribe than laboratory identified deficiency states. 20% of respondents indicated that they would prescribe or recommend parenteral vitamins for patient requiring renal replacement therapy. The practice of vitamin C prescribing was very heterogeneous, including dose and indication. Trace elements were prescribed or recommended less often than vitamins, with the most frequently reported indications being for patients requiring parenteral nutrition (42.9%), biochemically confirmed deficiency states (35.9%), and for treatment of refeeding syndrome (26.3%).

#### Conclusions

Micronutrient prescribing in ICUs in the UK is heterogeneous, with clinical scenarios where there is an evidence base or an established precedent for their use often guiding decisions to use micronutrient products. Further work to examine the potential benefits and harms on patient-oriented outcomes of micronutrient product administration should be undertaken, to facilitate their judicious and cost-effective use, with a focus on areas where they have a theoretical benefit.

## Key Words

Vitamins, micronutrients, ICU, critical care, critical illness, trace elements

**INTRODUCTION**

Micronutrients are essential components of nutrition in health and disease. While deficiencies in hospitalised patients are more frequent than previously acknowledged, the exact requirements during critical illness are unknown (1). Furthermore, clinical studies exploring micronutrient status in critically ill patients vary in their conclusions which may be due to differences in patient characteristics, comorbidities, degree of inflammation, and analytical methods (2). Several clinical guidelines from international societies, experts and specialist groups are available (2-8). However, the recommendations are not always consistent, and importantly, most are based on consensus and expert opinion due to lack of good quality evidence-based data.

In the United Kingdom (UK), parenteral multivitamin preparations, for example Pabrinex®, are prescribed frequently for critically ill patients. The licensed indication for Pabrinex® is for “rapid therapy of severe depletion or malabsorption of the water soluble vitamins B and C”. In the critical care setting, this may arise in a multitude of clinical scenarios, including reduced enteral intake, decreased ability to absorb from the gastrointestinal tract in shocked states, due to medications with anti-motility actions, or ileus, increased losses associated with medications (e.g. loop diuretics) or use of extracorporeal therapies, increased requirements due to intercurrent disease states, difficulties associated with identifying deficiency states, refeeding syndrome, and a potential modifying role for B vitamins in some psychiatric states, including delirium (2, 9-12).

There has been controversy in recent years over the role of vitamin C administration in sepsis, with multiple randomised controlled trials (RCTs) and meta-analyses performed to explore modifying effects on outcomes including mortality, length of ICU stay, and vasopressor requirements (13-18). Since many vitamins have a role as co-factors in fundamental cellular processes, and requirements may theoretically be increased under physiological stress conditions of critical illness and for the reasons mentioned above, the role of vitamin C for sepsis remains a regular focus of discussion among experts.

Given the numerous reasons a critically ill patient may have low levels of micronutrients, and uncertainties from the evidence base about their place in therapy, this survey sought to explore clinical practice of micronutrient prescribing for critically ill patients in the National Health Service (NHS) in the UK.

## **MATERIALS AND METHODS**

### Survey design

Two members of the study team designed the survey (LKC and MO) in September 2018 using the platform onlinesurveys.ac.uk. Survey questions were derived principally from knowledge of local practice at the host institution, then developed through an iterative process, with review and input from other members of the research team, and questions assessed for content and face validity by sending them to three experienced clinicians (an Intensive Care Unit Consultant, junior doctor and a senior clinical pharmacist) to trial before its launch. Critique and feedback were requested regarding the length of the survey, content and structure. The comments were considered and incorporated into the final version (Appendix 1).

The first part of the survey contained general questions related to the professional background of the healthcare professional and their place of work, followed by questions related to their use of micronutrients in clinical practice.

The questions were primarily designed to explore use of parenteral vitamins against licensed indications for proprietary products, local uses (extrapolated from the institutional guideline from the authors’ institution), and from knowledge of UK critical care practice. In addition, we explored the respondents’ willingness to participate in future clinical trials and invited general comments.

Survey questions were predominantly in multiple choice format, however free text options were made available where necessary. The survey was designed such that only the demographics fields mandated answers; other domains could be left blank if the respondent preferred not to complete. Respondents had the option to give multiple answers to certain questions. Where multiple answers were given (e.g. a respondent believed vitamins should be used for more than one indication), responses were not ranked.

### Ethical approval and consent to participate

The survey was fully anonymised, and consent to participate was assumed by virtue of voluntary participation. The nature of the survey meant informed consent to participate, and signing of a consent form, was not necessary. Respondents had the option to provide their contact details if they had indicated willingness to participate in further research in this field, however the contact details field was not mandatory. The project was approved by the National Institute of Health and Care Research (NIHR) Research Ethics Committee and Health Research Authority in the UK and adopted as a NIHR portfolio study (CPMS ID 42954).

The final 12 item-survey was circulated to 2086 members of the Intensive Care Society UK via a monthly electronic newsletter (October - December 2019), to 643 members of the UK Clinical Pharmacy Association (UKCPA) via the UKCPA Forum (October 2019 - February 2020) and to the British Dietetic Association Critical Care Specialist Group (335 members) through a web-based forum (October 2019 - January 2020). Importantly, some individuals are members of more than one professional group and may have received the survey from a number of sources. Additionally, there may have been recipients who received the survey but are not healthcare professionals or are based outside the UK. After the survey’s launch, two further reminders were sent out asking recipients to consider completing.

### **Statistical Analysis**

Data are presented as numbers (percentage) for categorical variables and median (interquartile range) for continuous variables. Data were initially extracted from the onlinesurveys.ac.uk platform to Microsoft Excel. The statistical analysis was performed using IBM SPSS Statistics version 22.0. Graphs are presented using Microsoft Powerpoint 365.

## **RESULTS**

In total, 227 responses were received of which 10 were excluded (4 from respondents who were not UK based, 5 because of incomplete responses [demographics only, no micronutrient questions answered] and 1 respondent did not work in critical care), giving a final total of 217 responses. (Table 1) The majority of responses were from physicians (58%), and most reported working in an ICU with specialty beds including: cardiac (24.4%), severe respiratory failure (23%), trauma (19.4%), neurology/neurosurgery (19.4%), burns (7.8%) and liver (6.5%) as well as other specialty services including oncology, gastrointestinal and hepatobiliary services.

### **Use of parenteral vitamins**

The indications for which respondents stated they would prescribe or recommend parenteral vitamins were heterogeneous (Figure 1). The most frequently reported indications were Wernicke’s encephalopathy (76%), treatment of refeeding syndrome (64.5%), and unknown or uncertain alcohol intake history (63.6%). Additionally, 57% stated they would prescribe vitamins for prophylaxis of refeeding syndrome, and 53% for patients receiving parenteral nutrition. These were all higher than the number who stated they would prescribe for a biochemically confirmed deficiency state (49.3%). 14% of participants indicated they would prescribe for all critically ill patients and a quarter of respondents said they would prescribe for septic shock. Other free-text responses were “for patients with raised body mass index with history suggestive of high proportion of diet carbohydrates” and “when out of hours parenteral nutrition is prescribed”.

In terms of the specific product, Pabrinex® was most commonly used (64.5% of respondents), followed by Solivito N (8.8%) and Cernevit (6.9%); and 2.8% used other (unnamed) products.

#### Micronutrient supplementation during RRT

20% of respondents indicated that they would prescribe or recommend parenteral vitamins for any patient requiring renal replacement therapy (RRT). When asked about their primary rationale for prescribing parenteral vitamins and trace elements in this scenario, 20.3% of respondents stated it was to replace water soluble vitamins lost via the filter circuit; 8.3% felt it was as an intervention to treat concurrent disease states; 24% said it was a combination of both; and 17.5% were unsure. Respondents who stated it was for another reason mentioned taking a lead from dietetic colleagues.

#### Vitamin C prescription

The median daily dose of vitamin C prescribed or recommended was 1g (IQR 500mg-2g). By professional group, nurses reported prescribing / recommending the highest daily dose (1500mg vitamin C [IQR 500-1750mg]), followed by physicians (1g vitamin C [IQR 500mg-2g]), pharmacists (500mg vitamin C [IQR 500mg-2250mg]) and dietitians (500mg vitamin C [IQR 500mg-1g]).

#### Perception of benefits of parenteral vitamins

In terms of the specific vitamins that were felt to be of benefit to critically ill patients receiving RRT, 37.8% responded that vitamin C conferred a benefit, 30.9% felt thiamine (vitamin B1) was beneficial, and vitamin B9, vitamin B6, vitamin B2, and vitamin B12 were felt to be of benefit by 22.6%, 22.1%, 21.2% and 20.7% of respondents, respectively.

#### Roles of parenteral vitamins in agitation and delirium management

With a specific focus on the role for parenteral vitamins in managing delirium and/or agitation, 31.5% of respondents indicated that they felt there was a role, 22.2% stated that there was no role, and 46.3% were unsure. 27.6% of respondents stated that vitamin B1 (thiamine) had a role in the management of agitation and/or delirium; responses for a perceived role for all other B vitamins were <10%.

#### Thiamine status measurement in clinical practice

Clinical history (excessive alcohol intake [25.8%], cachexia/malnutrition [19.4%]) was used more commonly to identify likely thiamine deficiency than direct laboratory measurement of thiamine status: 18.4% respondents stated that they had ever (routinely, occasionally or seldom) requested measurement of a thiamine level whereas 68.6% said they had never measured thiamine status.

### **Use of parenteral trace elements**

The most frequently reported indications for trace element prescribing were: ‘patients requiring parenteral nutrition’ (42.9%), ‘biochemically confirmed deficiency states’ (35.9%) and ‘treatment of refeeding syndrome’ (26.3%). (Figure 2) Free-text responses included “following dietitian’s advice”, “failure to wean”, “patients recovering from prolonged critical illness”, “raised BMI with history indicative of high ratio carbohydrates in diet”. More than 20% of respondents felt selenium (26.7%) and zinc (23.5%) were of benefit to critically ill patients.

### **Method of nutrition delivery**

Parenteral vitamins and trace elements were prescribed / recommended irrespective of the nutrition modality (i.e. parenteral nutrition, enteral nutrition, some combination of the two) by 26.7% of respondents. 31.3% stated that they would use these products in patients who receive parenteral nutrition (PN), and 24% said they would use them in patients who are not meeting their nutritional requirements.

### **Use of guidelines**

Respondents from the majority of institutions reported not having a guideline pertaining to the use of parenteral vitamins and micronutrients. (Table 2) Where a guideline was available, less than a third of respondents stated they followed it ‘always’ or ‘sometimes’. Where products were prescribed, indications for parenteral vitamins were described as being clear 60% of the time.

**Future research**

75.7% of respondents stated that more research was necessary to explore the role of micronutrient supplementation in critical care.

## **DISCUSSION**

The results of this survey show critical care clinicians prescribe parenteral vitamin products, and to a lesser extent trace element products, for heterogeneous indications and with heterogeneous intentions. The established role in the treatment of thiamine in Wernicke’s encephalopathy, refeeding syndrome and the pharmacokinetic and pharmacodynamic basis of poor thiamine absorption and biotransformation to the active form occurring in patients who have a history of excessive alcohol consumption correlates with the most frequently reported indications amongst respondents of this survey. Prescribing for most other indications was reported by less than 20% of respondents, so was incongruous with recommendations international guidelines (3). This may relate to the lack of randomised controlled trials in this area to guide practice, noting guidelines are broadly based on physiology, observational data and international expert opinion.

Around a quarter of respondents stated they would prescribe parenteral vitamins for septic shock. Literature pertaining to the role of Vitamin C in sepsis is less clear. Although some randomised controlled trials have shown a beneficial effect on vasopressor duration and severity of illness, the most recent “Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit” (LOVIT) study investigated the role of high dose Vitamin C (50mg/kg every 6 hours for up to 96 hours) and showed a higher mortality (35.4% vs 31.6%) and higher risk of persistent organ dysfunction (9.1% vs 6.9%) at 28 days in patients randomized to vitamin C compared to the placebo group (15). Until then, most studies had not reported any major adverse effects from parenteral vitamin administration which may have influenced a prescribing decision in favour of giving vitamin C supplementation. However, intravenous vitamin C administration is known to be linked to oxalate crystals deposition in kidney tubules and an increased risk of acute kidney injury (19).

Two-thirds to three-quarters of pharmacist or dietician respondents noted having no local guideline for micronutrient supplementation. Over half of respondents stated they would prescribe parenteral vitamins for patients requiring parenteral nutrition (PN). Where a patient is receiving PN international guidelines recommend: “*Adequate amounts of all essential trace elements and vitamins shall be supplied to all patients receiving medical nutrition from the beginning of the period of nutritional support*.” (3), which for many commercially available standard formulations of PN will mean additional supplementation with micronutrients is indicated. Owing to stability and shelf-life concerns, this may be in the form of an addition to the bag shortly prior to administration to the patient, or may be prescribed and administered by staff on the critical care unit as a separate product. Although the proportion of respondents stating there was no institutional guideline accounting for this appears high, we cannot infer that this means patients cared for in these centres will not receive micronutrient supplementation, as its prescription, formulation or administration may be the responsibility of different team members (i.e. it may be added to the bag in a pharmacy compounding unit as standard). Further, there is potential for unintended therapeutic duplication if micronutrients are added to PN and also administered separately, if the indication for the separate prescription is not clearly stated (as was felt by 40% of respondents to be the case). While the clinical risk to the patient associated with this is likely to be minimal, the financial impact and environmental impact must not be overlooked.

In terms of why many responses stated institutional guidelines did not reflect their own prescribing practice, we did not address this, but hypothesise that it may reflect *(i)* that guidelines may be too generic, where micronutrient requirements are individual and not amenable to a guideline approach; *(ii)* that respondents may not feel the available empirical evidence justifies the guideline; *(iii)* that they think another team member is more appropriately placed to make decisions relating to micronutrient supplementation so defer to individual patient review rather than a guideline approach; *(iv)* a feeling that guidelines apply to a subset of critically ill patients, so can’t be followed all or most of the time; *(v)* don’t believe prescription of these products alters outcome; or *(vi)* prefer to supplement via a different route. For others, it may be directly related to the fact that local protocols to integrate lengthy international guidelines into local recommendations do not exist, and taking steps at institutional level to create local, accessible protocols may alter prescribing practice in this area. Further work may generate interesting insights beyond our hypotheses (*(i) – (vi)* above).

Around half of respondents stated they would prescribe parenteral vitamins for a biochemically confirmed deficiency state. Access to serum micronutrient levels in UK hospitals is not ubiquitous, so it is possible that wider access to assays of micronutrients may give greater opportunity for testing and identification of deficiency states. However, reference ranges in critical illness are not defined, and whether measured plasma concentrations reflect tissue levels in critical illness is an area of uncertainty. Further, the correct clinical interpretation of plasma micronutrient levels can be made only with knowledge of the degree of inflammatory response (20). Finally, the value of supplementation on patient-oriented outcomes has not been tested across the range of vitamins, and for some, including vitamin D, the benefit to the patient beyond “making the laboratory value higher” remains unclear.

Fewer than 20% of respondents stated they would prescribe parenteral vitamins for patients requiring RRT. Although several studies have confirmed losses of micronutrients into the effluent fluid during RRT (2, 9, 10, 21), the role of micronutrient supplementation in this patient population has not been formally studied.

When considering which trace elements were of benefit to critically ill patients, selenium and zinc were most frequently mentioned by respondents. Selenium has an important role in many cellular processes including anti-oxidative processes, while zinc is implicated in virtually all metabolic pathways. Both have been investigated in several trials in different patient populations (22-29). Selenium was not shown to improve clinical outcomes in critically ill patients (30), but guidelines (3) recommend measuring selenium levels in patients who are likely to receive PN for more than 2 weeks, with consideration given to enteral administration of 50-150micrograms/day owing to its favourable bioavailability. Zinc measurement and supplementation is recommended in guidelines in specific clinical circumstances, including patients with excessive gastrointestinal losses, and those with burns. (3)

Only 12% of respondents felt that chromium supplementation was of benefit to critically ill patients, despite a recommendation to consider a trial of chromium administration in cases of hyperglycaemia/insulin resistance in ICU to reduce insulin requirements. (3) Conversely, 23.3% of respondents felt manganese may benefit critically ill patients, when studies show that manganese deficiency is not common in critically ill patients (31).

The financial cost of parenteral micronutrient supplementation must be considered when writing guidelines or making recommendations for prescribing practice in the setting of inconclusive evidence of benefit on patient-orientated outcomes. In the NHS, 1 pair of Pabrinex® ampoules costs around £3, with one Addaven® ampoule currently costing around £2.50 (32). While most intervention studies, with the important exception of the LOVIT trial, looking at patient-outcomes with vitamin administration have reported no evidence of harm, the financial costs associated with these products, and especially with daily or greater administration across a long critical care admission, must not be overlooked. Conversely, the costs associated with complications of micronutrient deficiency in critically ill patients are difficult to quantify. In future this may be an important area for health economic analysis to inform robust policy, protocol and decision making in this sphere.

Apart from heterogenous practice, this survey also demonstrated gaps in nutritional knowledge, similar to previous reports in the literature (33). For instance, more than 20% of respondents felt that administration of vitamins B1, B2, B6, B9 and B12 as well as vitamin C were of benefit to critically ill patients. Notably, Pabrinex (the most frequently prescribed vitamin product) does not contain folic acid (B9) or cobalamin (B12).

## **Strengths and Limitations**

This survey adds to the literature and complements previous surveys (34) by focusing on the indications critical care clinicians prescribe for, in the absence of a robust evidence base and in the presence of conflicting guidance. It was circulated widely amongst health care professionals who are involved in the management of critically ill patients. However, some limitations need to be acknowledged. First, the exact response rate is not known as many professionals are members of more than one group. Further, not all members of the targeted groups are health care professionals. Even accounting for this, the response rate was low. We do not know all the reasons underpinning the response rate, but acknowledge it may reflect a global lack of knowledge around, or low levels of interest in, micronutrient prescribing. Second, as parenteral vitamin prescribing for some indications can be controversial, responses may have been more likely from those who hold strong opinions either for or against their use. Third, the survey was conducted before concern was raised about the validity of the study by Marik et al (35) and before the LOVIT trial (15) was published. It is possible that the responses would be different today. Fourth, participation was entirely voluntary, and with any survey, it is possible that the responses may not fully reflect clinical practice in the NHS. Finally, in order to keep a balance between the number of questions and time needed to complete the survey, we had to leave out some questions, including those related to the method of administration, laboratory measurement of micronutrients, adjustments in the context of extracorporeal therapies and local laboratory facilities. Additionally, a deeper exploration of trace element prescribing practices (including questions around iron prescribing, which was not specifically addressed in this work) may have generated interesting results, and could be considered for future work.

## **CONCLUSIONS**

This work demonstrates that clinicians in critical care in the UK prescribe micronutrient products for a broad range of indications. However, there is possibly a lack of prioritisation of, interest in and expertise amongst critical care clinicians in this important topic. Guidelines, laboratory measurement of micronutrient serum levels and delivery of extracorporeal therapies potentially resulting in losses were less important to survey respondents in guiding therapeutic decisions than identification of clinical states in which vitamins and micronutrients have established precedent or evidence base for their use. Further work to better define the role for micronutrients in critical care should be undertaken, which can be integrated into guidelines and protocols, to facilitate their judicious and cost-effective use.

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**Conflict of interest**

MO has received research funding from Fresenius Medical and Baxter.

LKC, NL, EC and CMcK have nothing to disclose.

## **Author contributions**

LKC devised the survey questions, circulated the survey, collated the results, and drafted the manuscript

NL undertook the statistical analysis and revised the manuscript

EC contributed to data collection and revised the manuscript

CMcK reviewed the survey questions and revised the manuscript

MO generated the original idea for the work, secured funding and revised the manuscript.

All authors approved the final draft.

## Appendices

#### Appendix 1

PDF of survey

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## **Figure Legends**

Figure 1: Bar graph to show percentages of respondents who stated they would prescribe parenteral vitamins for each indication (n=217)

Figure 2: Bar graph to show percentages of respondents who stated they would prescribe parenteral trace elements for each indication