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Editor's Note

Enteral nutrition (EN) is the preferred method of nutrition support when oral intake fails because it is not possible or is inadequate. There are, however, challenges with delivery of EN—difficulties with formula, feeding tubes, or pumps. This issue of *Nutrition in Clinical Practice* (*NCP*) addresses some of those challenges.

A study by Yeh and colleagues retrospectively evaluated effects of implementing an aggressive EN protocol in the intensive care unit (ICU). Patients who received EN via the aggressive protocol received a higher percentage of calorie and protein needs and had a lower protein deficit vs those treated with a historical EN protocol. The intervention group also had fewer late infections vs the historical control group. An article by Wilmskoetter et al reviewed predictors and factors leading to removal of a gastrostomy tube following dysphagic stroke. While most of the factors they identified were related to stroke disease or severity, the strongest predictor of tube removal was documentation of absence of aspiration. Beth Lyman and her colleagues address a safety issue with EN—bacterial growth in enteral formulas. They tested bacterial growth at 12 and 21 hours in formula from feeding sets that were rinsed, refrigerated, or left at room temperature (only for ready-to-hang formulas). The ready-to-hang formula left at room temperature showed the least amount of growth, and the refrigerated method was found to be acceptable when formulas are not available in ready-to-hang form. Yamaoka et al developed a novel imaging test to detect EN residues in feeding tubes as well as proliferation of microorganisms in the tubes. While this test is not clinically available, it provides insight into the effect of different types of formula, viscosities, and flushing practices on tube residue. Albrecht et al summarize the success of placing gastrostomy/jejunostomy tubes via computed tomography when endoscopic placement was not feasible. Their report includes 57 patients requiring tubes for jejunal feeding and 45 for gastric compression. Hajjat and Rahhal conducted a retrospective study that evaluated complications and outcomes in children who received 2 different types of low-profile nonballoon gastrostomy tubes. Their report included 160 tube placements in 45 children. A study by van der Linden et al looked at 240 patients who underwent chemoradiotherapy and compared characteristics of 195 patients who received EN vs those who did not receive EN as well as patients who underwent percutaneous endoscopic gastrostomy (PEG) placement vs those who did not. Presence of nodal disease and planned neck irradiation were factors in predicting EN and PEG placement. Bedside placement of nasoenteric feeding tubes using an electromagnetic device (EMD) has been described in adults; Goggans et al report one of the first series using the EMD to place feeding tubes in 40 critically ill children. Use of the EMD reduced confirmation time for placement as well as cost and radiation exposure.

This issue also reviews challenges with regard to EN formulas and delivery of EN formulas. Use of blenderized EN formulas has gained recent popularity, as evidenced by the survey by Epp et al. Their study involved a survey of 216 individuals regarding use of blenderized formulas. While this group may not accurately reflect the entire home EN population, almost 90% of the pediatric population and 65% of the adult participants in this survey used blenderized formulas for at least a portion of their EN. Samela et al conducted a study using a commercially prepared formula containing real food ingredients in children with intestinal failure; 9 of the 10 children tolerated transition from an elemental formula to the new formula. Blenderized feedings are among formulas with an increased viscosity. Hurt and his team addressed the use of ENFit connectors with gravity feeding. Their study found a variability in flow dynamics with different formulas using the ENFit. They concluded that although the ENFit is needed to improve safety, there could be flow dynamic problems with home EN patients who have large diameter feeding tubes used for blenderized formulas, medication administration, or venting. Lisa Musillo and her group compared EN volumes delivered to patients in the ICU comparing the volumes recorded in the EN pumps vs the electronic medical record. They concluded that there was a large discrepancy between the 2 methods of recording EN delivery, calling for a platform that could electronically transmit pump volumes to the medical records.

In addition to these articles on EN, a number of articles in this issue of *NCP* focus on micronutrients such as phosphorus, aluminum, vitamin D, and B vitamins.

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Review of Copper Provision in the Parenteral Nutrition of Adults

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Abstract

The essential trace element copper (Cu) is required for a range of physiologic processes, including wound healing and functioning of the immune system. The correct amount of Cu must be provided in parenteral nutrition (PN) if deficiency and toxicity are to be avoided. While provision in line with the standard recommendations should suffice for most patients, Cu requirements may be higher in patients with increased gastrointestinal losses and severe burns and lower in those with cholestasis. The tests of Cu status that are currently available for clinical use are unreliable. Serum Cu concentration is the most commonly ordered test but is insensitive to Cu deficiency and toxicity and is misleadingly increased during the acute phase response. These limitations make it difficult for prescribers to assess Cu status and to decide how much Cu to provide. There is a need for better tests of Cu status to be developed to decrease uncertainty and improve individualization of Cu dosing. More information is needed on Cu requirements in disease and Cu contamination of PN components and other intravenous fluids. New multi–trace element products should be developed that provide Cu doses in line with the 2012 American Society for Parenteral and Enteral Nutrition recommendations. This article discusses the evaluation and treatment of Cu deficiency and toxicity in patients treated with PN. (*Nutr Clin Pract*. 2017;32:153-165)

Keywords

copper; copper deficiency; copper toxicity; parenteral nutrition; nutritional support

Copper (Cu) is an essential trace element (TE) required for metabolism in all living cells. It has been known to be an essential component of parenteral nutrition (PN) since 1972.[1] Provision of the correct amount of Cu is necessary, not only to avoid deficiency and toxicity, but also to promote optimal recovery.[2] This article covers the relevant physiology of Cu. It then discusses Cu deficiency and toxicity and examines the evidence behind the recommendations on Cu provision in PN. It provides practical guidance on assessment of Cu status and Cu requirements. The article focuses on adults because provision of Cu in pediatric PN has recently been covered elsewhere,[3] but pediatric studies have been cited where considered appropriate.

Physiology

Cu is among the 3 most abundant transition metals in biological systems, the other 2 being iron (Fe) and zinc (Zn). The human body contains around 100 mg of Cu, more than half of which is in bone and muscle. The highest concentrations are in liver, kidney, and brain, reflecting the high metabolic activity of these organs.[2] Only 5% is in blood, about 95% of this being bound to ceruloplasmin (Cp) and the remainder to albumin and amino acids.[4] The serum Cu concentration therefore largely reflects the Cp concentration and is affected by factors influencing Cp. Intracellular Cu is usually bound to chaperones and other proteins because free Cu is potentially harmful to cells.

Cu, which functions as a component of cuproproteins, has a variety of physiologic roles. For example, it is required for humoral immunity and production of inflammatory cytokines.[5,6] It was recently suggested that the immune system uses Cu intoxication as a means of intracellular bacterial killing.[7,8] Cu is required for the physiologic response to low Fe stores. It is needed for absorption of dietary Fe, release of Fe from hepatocytes and production of hemoglobin.[9] Cp oxidizes Fe from the ferrous to ferric state, enabling its transport by transferrin and subsequent use in erythropoiesis. Superoxide dismutase is an antioxidant cuproenzyme that catalyzes the conversion of superoxide radicals to hydrogen peroxide, which is then reduced to water.[10] Cu is also necessary for wound healing because it is required for the synthesis of collagen.

The average daily oral intake of Cu is 1.0–1.6 mg, which exceeds the RDA of 0.9 mg.[11] Dietary Cu is absorbed mainly in the stomach and upper small intestine.[2,12] About 55%–75% of dietary Cu is absorbed, which is a high proportion as compared

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with other TEs.[2] The amount of Cu absorbed depends on dietary intake, Cu status, and the effects of other nutrients. Absorption is decreased by vitamin C, Fe, and Zn.[2] Zn inhibits Cu transport directly and by inducing metallothioneins that bind Cu in intestinal mucosal cells. Short-chain fructo-oligosaccharides[13] and Fe deficiency[9] increase Cu absorption. Once absorbed, Cu is bound to albumin and transcuprein and transported to the liver, where it is stored, released into the systemic circulation, or excreted into bile. Normally, about 80% of Cu excreted from the body is in bile and gastrointestinal (GI) secretions, and about 20% is in urine.[14,15] About 10%–15% of biliary Cu is reabsorbed, returning to the liver in an enterohepatic circulation. External fluid losses from fistulae, bile leaks, or enterostomies predispose to Cu deficiency by decreasing the amount of Cu reabsorbed.

Cu Deficiency

Deficiency occurs when Cu intake is consistently below requirements. This section focuses on Cu deficiency encountered among patients receiving nutrition support. Factors affecting individual susceptibility to deficiency during PN include the size of hepatic Cu stores, the extent of GI losses, and the amount of Cu provided. Cu provision includes supplementation of PN but also the amount delivered by concurrent oral or enteral nutrition and as a contaminant of PN and other intravenous (IV) fluids.

Causes of Cu Deficiency

Overt Cu deficiency is uncommon during short-term PN but has occurred during long-term PN when Cu has been provided below requirements.[16-19] A recent retrospective review of the Cu status of hospitalized pediatric patients treated with PN observed that, after 14 days of treatment, hypocupremia was present in 71% of patients receiving PN unsupplemented with Cu, as compared with 50% of those receiving supplemented PN.[20] Deficiency has also occurred when supplemental Cu has been withheld either because of concern about accumulation during cholestasis[21,22] or because of shortages of multi-TE (MTE) products.[23-25] There is much concern about the clinical implications of such shortages, especially for infants, for whom micronutrient deficiency can have irreversible consequences.[26] The prevalence of marginal Cu deficiency among patients treated with PN is unknown but could be anticipated to be higher than that in the general population, given the higher prevalence of risk factors for deficiency in hospitalized patients.

Short bowel syndrome. Patients with short bowel syndrome (SBS) are at risk of Cu deficiency even after weaning onto oral diet. A recent study investigated 22 adults with SBS following intestinal resection, of whom half had been weaned onto oral diet and half remained dependent on PN.[27] Patients in the PN group had a small intestine with a median length of 25 cm (range, 10–100), and 6 patients had a colon. Patients in the orally fed group had a small intestine with a median length of 110 cm (range, 40–210), and 9 patients had a colon. Serum Cu concentrations were significantly lower for the patients treated with PN (69 ± 24 μg/L, $P < .05$) and patients taking oral diet (72 ± 26 μg/L, $P < .05$), as compared with a control group (109 ± 16 μg/L; reference range, 70–140 μg/L). Similarly, Cu deficiency can occur during transition from PN to enteral nutrition (EN). A study of transition to EN for pediatric patients reported Cu deficiency as the most common among micronutrients, affecting 56% of patients.[28] After full EN was established, deficiency of Cu was less prevalent (22%) than vitamin D (68%), Zn (67%), or Fe (32%). These findings emphasize the importance of monitoring Cu status among patients with SBS, irrespective of the type of nutrition support.

Teduglutide—an analogue of glucagon-like peptide 2, which is an intestinal growth factor—has been used in patients with SBS to improve absorption of dietary nutrients and decrease dependence on PN. A recent case series reported on adverse events during weaning of patients treated with teduglutide.[29] One patient developed overt Cu deficiency, despite Cu supplementation, which did not respond to oral supplementation and necessitated recommencement of PN. In this patient, it appears that Cu absorption did not improve in response to teduglutide. Glucagon-like peptide 2 has recently been observed to improve bile flow in an animal model of cholestasis,[30] but its effect on Cu balance in humans is unknown.

Enteral tube feeding. Patients receiving long-term EN, especially those fed through a jejunostomy tube, are at risk of developing Cu deficiency. For example, one case series compared 23 patients fed through percutaneous endoscopic jejunostomy and 36 patients fed via percutaneous endoscopic gastrostomy.[31] After 6 months of EN, serum Cu was significantly lower in the percutaneous endoscopic jejunostomy group ($P < .001$). Six patients in this group had severe Cu deficiency with hematologic features. There have also been reports of severe Cu deficiency in patients on home EN via percutaneous endoscopic gastrostomy.[32] Enterally fed patients appear to be at risk of Cu deficiency because of decreased bioavailability rather than inadequate intake. The risk is higher in jejunostomy-fed patients because the main sites of Cu absorption are bypassed. In addition, interindividual variation in Cu absorption is high. Furthermore, absorption may be impaired by high enteral intake of Zn or Fe.

Bariatric surgery. Cu deficiency can occur after bariatric surgery, more commonly after biliopancreatic diversion than after Roux-en-Y gastric bypass. A 5-year follow-up study observed hypocupremia postoperatively in 30.3% of patients with biliopancreatic diversion, compared with 3.8% of patients with Roux-en-Y gastric bypass.[33] None of the patients had hematologic or neurologic features of deficiency, which suggests that, for overt deficiency to occur, deficiency must be sustained

long-term. Cu deficiency after bariatric surgery has recently been reviewed.[34,35] Clinical Cu deficiency has been described but is unusual for patients receiving adequate supplementation. The American Association of Clinical Endocrinologists' guidelines for perioperative support of the patient undergoing bariatric surgery recommend that Cu does not need to be routinely measured postoperatively but should be measured if there are hematologic or neurologic features consistent with deficiency or if there is impaired wound healing.[36] Clinicians should monitor patients carefully for these features.

Zn excess. Zn-induced Cu deficiency (ZICD) has been caused by excessive ingestion of Zn, but there is limited awareness among clinicians of this potential side effect of Zn supplementation.[37] It tends to occur with oral Zn doses >850 mg/d for 1 year, but negative Cu balance has resulted from doses of 18.5 mg/d for 2 weeks.[38] Misdiagnosis of Zn deficiency during an acute phase response (APR) can result in inappropriate Zn supplementation. ZICD should therefore be considered for patients treated with PN, many of whom have an ongoing APR and high Zn requirements. For patients treated with PN, the source of excess Zn may not necessarily be parenteral. For example, excessive intake of Zn from a denture adhesive was recently reported to cause ZICD for a patient on long-term PN containing standard Cu provision.[39] The patient presented with mild pancytopenia and perioral paraesthesia, which did not respond to additional Cu provision but resolved after the adhesive was switched to a Zn-free product. To facilitate diagnosis of ZICD, it has been recommended that, following the finding of hypocupremia, TE laboratories should automatically measure the Zn of the specimen.[40] Similarly, the finding of hyperzincemia should prompt the measurement of Cu to exclude ZICD. To avoid ZICD, it has been suggested that, to treat Zn deficiency, 1 mg of Cu should be given for every 8–15 mg of Zn (elemental doses).[36] Zn and Cu should be taken at least 2 hours apart to maximize the absorption of Cu.[41]

Other causes of Cu deficiency. Cutaneous exudative Cu losses amounting to 37 mg/wk have been reported for patients with severe burns.[42] There is evidence that supplementation of Cu in combination with other micronutrients improves the clinical outcome for patients with burns[43] or pressure ulcers.[44] The results of 2 randomized controlled trials were combined in which patients with burns received placebo or a combination of Cu, selenium, and Zn at doses up to 4 mg, 500 μg, and 40 mg, respectively, by IV infusions not associated with PN use.[45] In total, 41 patients were investigated for up to 21 days. There was a significant reduction in nosocomial pneumonia in patients supplemented with TE. The extent to which this outcome was attributable to Cu is unknown.

As with other micronutrients, Cu is readily dialyzed. Continuous renal replacement therapy can result in significant Cu losses, especially if prolonged. If Cu provision is insufficient to replace losses, this will lead to negative Cu balance. Effluent losses of 0.41 mg/d have been reported,[46] an amount similar to the recommended Cu provision in PN. In the same study, Cu was undetectable in replacement solutions. Hemodialysis and peritoneal dialysis have not been associated with Cu deficiency in human subjects, but a recent study in an animal model concluded that hemofiltration may necessitate Cu replacement at doses exceeding standard provision.[47]

Chemotherapy with cisplatin should be considered a risk factor for Cu deficiency. Patients with esophageal cancer treated with cisplatin and PN had significantly lower serum Cu concentrations postchemotherapy ($P = .015$).[48] This change was prevented by additional TE supplementation. Iatrogenic Cu deficiency has also been observed following overtreatment with chelating agents, such as penicillamine, trientine, and tetrathiomolybdate, but this has not been reported in the context of PN.[49]

Features of Cu Deficiency

When intake is below requirements, Cu is initially replenished from hepatic stores. As a result, features of deficiency may occur long after the causal insult. When deficiency has occurred after omission of Cu from PN, clinical features have taken between 6 weeks and 15 months to appear.[21-23,25,50,51] In a series of 26 cases of neurologic complications occurring after bariatric surgery, overt Cu deficiency presented as late as 9 years postoperatively.[52]

The clinical features of Cu deficiency are mainly hematologic and neurologic, reflecting the requirement for Cu in erythropoiesis and synthesis of myelin.[53] The most common features are a microcytic or normocytic anemia, unresponsive to Fe supplementation, and neutropenia.[54] The mechanism whereby anemia develops is uncertain, but decreased Cp may result in impaired mobilization of Fe stores. Cu deficiency is also implicated in increased oxidative stress and deterioration in cognitive function for patients with Alzheimer's disease.[55]

The most common neurologic feature of Cu deficiency is myelopathy, but peripheral neuropathy and demyelination have also been reported.[56] The deficits of myelopathy resemble those of subacute combined degeneration of the cord resulting from vitamin B_{12} deficiency.[57] Patients typically present with a disordered gait and sensory ataxia. The mechanism of neurologic damage is unknown, but cuproenzymes such as cytochrome C oxidase have vital roles in the nervous system, the impairment of which would be expected to have adverse effects. When neurologic features consistent with Cu deficiency are present, the patient should be investigated by measurement of serum Cu and by spinal magnetic resonance imaging. In a case series of 25 patients with Cu deficiency myelopathy, abnormalities on magnetic resonance imaging were found in 44%, the most common being an increased T2 signal of the dorsal column in the cervical and thoracic cord.[58] In this case series, the duration of patients' symptoms prior to diagnosis of Cu deficiency ranged

from 2 months to 10 years. Treatment with Cu supplementation may arrest the neurologic deficits and result in improvement in sensory symptoms, but most patients have residual deficits resulting from irreversible neurologic injury. This emphasizes the importance of early diagnosis. Several months of Cu supplementation are likely to be required before the features improve. A study of 12 patients with Cu deficiency, all of whom had neurologic features, observed significant improvements in functional activities of daily living ($P = .007$) over 12 months of Cu supplementation.[59]

Nephrotic syndrome was recently reported as a feature of Cu deficiency for a patient treated with PN following bowel resection.[60] The patient also had anemia, neutropenia, and deteriorating kidney function, which responded to Cu supplementation. The urinary protein loss was attributed to loss of the protective effect of Cp on glomeruli. While this is the only published case report of nephrotic syndrome resulting from Cu deficiency, urinary protein loss has been reported to correlate with urine Cu for patients with nephrotic syndrome.[61]

Cu deficiency should be considered when metabolic bone disease occurs for patients treated with PN. The earliest reported case of Cu deficiency for a patient treated with PN was an infant who presented with osteoporosis and growth delay.[1] Osteoporosis resulting from Cu deficiency was also reported in 2 preterm infants with SBS treated with long-term PN.[62] It was diagnosed at 5 months of age following investigation for musculoskeletal discomfort. Both patients had severe hypocupremia and responded to IV supplementation of Cu. Pseudoscurvy has been reported as a feature of Cu deficiency,[63] as demonstrated in a 4-month-old female infant treated with PN from which TEs had been omitted.

There is evidence from numerous sources that Cu deficiency impairs the activity of the immune system, thereby predisposing to bacterial infection.[5,64] In vitro studies have observed decreased neutrophil function, decreased secretion of interleukin 2 from lymphocytes, and decreased cytotoxic activity of natural killer cells. Mortality from infection is higher in Cu-deficient animals.[65] For humans, it has long been known that Cu deficiency impairs phagocytosis[66] and increases mortality from infection.[67] Pulmonary and urinary tract infections are more common for patients with Menkes's disease, an inherited disorder of severe Cu deficiency.[68] The results of supplementation studies for patients with burns, discussed above, also suggest that Cu deficiency predisposes to pneumonia.[45] The conclusions that can be drawn from clinical studies regarding the role of Cu deficiency in infection are limited, given that micronutrient deficiencies do not occur in isolation; but, when taken together, the evidence is compelling to suggest that Cu deficiency impairs the immune system.

The clinical consequences of marginal Cu deficiency are unknown but may include neurologic,[57] cardiac,[69] and immune dysfunction.[5,70] A low-Cu diet has resulted in decreased proliferation of mononuclear cells.[71] Given the extensive role of Cu in Fe metabolism, it could be anticipated that marginal Cu deficiency may compromise utilization of Fe. These observations suggest that marginal Cu deficiency could be detrimental for patients treated with PN, but this awaits investigation.

Treatment of Cu Deficiency

The underlying cause of deficiency should be sought and treated. For patients already supplemented with Cu, the dose should be reviewed and possible factors decreasing bioavailability considered. Ideally, supplementation should be delivered orally or enterally, to enable absorption according to requirements and to avoid bypassing homeostatic mechanisms. However, for patients treated with PN, enteral tolerance or bioavailability of Cu may be limited by intestinal failure. In addition, the need to ensure delivery of Cu for patients with severe deficiency may necessitate IV administration. Supplementation should continue until normal serum Cu concentrations are restored and clinical features resolve. This should be followed by long-term supplementation sufficient to prevent recurrence of deficiency. When Cu deficiency has occurred for patients treated with PN, serum Cu concentrations have normalized, and clinical features have improved within 6 weeks of supplementation.[21,22,72] The hematologic features resolve within about 4 weeks, but neurologic features improve relatively slowly and may be in part irreversible. The rate of resolution of Cu deficiency is likely to depend on the severity of deficiency, route of supplementation, and Cu dosage. If features of deficiency do not respond to increased Cu provision, ZICD should be ruled out.

Cu dosing should be individualized according to the severity of hypocupremia and clinical features. Cu is available as MTE products, which typically provide 0.4–1.0 mg/mL, oral tablets (2 and 5 mg), and injection (0.4–2 mg/mL).[73] Severe Cu deficiency in adults can be treated with IV Cu (2–4 mg/d) for 6 days, followed by oral Cu sulfate or gluconate (3–8 mg/d).[36] In a reported case of severe Cu deficiency, it was possible, following IV Cu supplementation, to maintain the serum Cu concentration in the reference range by high-dose oral supplementation (8 mg/d), despite loss of absorptive surface area.[74] This suggests that sufficient absorption may be achieved by supersaturation of the remaining Cu transport capacity.[75]

When Cu deficiency occurs during EN, there are various treatment options. Enteral Cu provision can be increased by giving either pharmaceutic Cu products or cocoa powder, of which 100 g contains 3.61–3.79 mg of Cu.[76] In practice, daily doses of 10–40 g of cocoa powder have been used[31] that, in this study, were reported to deliver Cu doses of 1.36–2.56 mg/d. Clinicians should be aware that Cu may be poorly absorbed when given through a jejunostomy tube.[77] If necessary, IV Cu can be given. It is advisable to monitor Cu status for patients on long-term EN.

Cu Toxicity

Patients with acute Cu toxicity present with vomiting, diarrhea, and abdominal pain and, if more severe, hepatic necrosis, renal failure, encephalopathy, and death.[78] Acute toxicity has been reported following consumption of Cu-contaminated water but would be unlikely to occur during PN, unless an error resulted in overdose. For patients treated with long-term PN, there is concern about hepatotoxicity resulting from chronic hepatic accumulation of Cu in PN-associated liver disease (PNALD). Accumulation may occur if biliary excretion of Cu is impaired, either because of immaturity of excretory mechanisms or because of cholestasis. Overload may be exacerbated by excessive provision of Cu resulting from inappropriately formulated MTE products, contamination of PN, or additional intake from other sources.

There is extensive evidence that hepatic Cu accumulation occurs in PNALD. This is usually at concentrations below the diagnostic threshold for Wilson disease (WD)—that is, <250 μg/g, dry weight (reference range, <35 μg/g).[79,80] In 2005, Blaszyk et al measured hepatic Cu concentrations for patients treated with long-term PN who had abnormal liver enzymes and for control subjects who had drug-induced cholestasis.[81] In 89% of PN patients, hepatic Cu was >35 μg/g and in 29%, >250 μg/g (range, 10–2248). Hepatic Cu was also increased in the control subjects. It did not correlate with the serum Cu concentration or duration of PN. These findings suggest that cholestasis is the main causal factor in hepatic Cu accumulation for patients treated with PN, but they do not exclude the possibility that excessive provision is harmful. Given that about 30% of adult patients receiving long-term PN develop PNALD, the results from this small study, if typical of the PN population, suggest that about 10% of adults on long-term PN have significant hepatic Cu accumulation. An autopsy study of tissue TE concentrations was carried out in 8 adults with short bowel treated with long-term PN, compared with 45 control subjects on oral diet who had not suffered from GI disease.[82] Cu dosing was in accordance with 1979 recommendations,[83] the mean daily dose being 1.4 mg for 14 years. Cu concentrations were increased in liver and kidney specimens from patients receiving PN, being highest (>250 μg/g) in 2 who died of liver failure.

While the clinical outcome in PNALD appears to be poor for patients with severe hepatic Cu accumulation, it is unclear whether the Cu is directly hepatotoxic. Various observations suggest that Cu accumulation may be harmful. Supraphysiologic concentrations of Cu are known to be pro-oxidant, generating reactive oxygen species that can cause oxidative damage to macromolecules.[78] In addition, Cu accumulation in WD is hepatotoxic, neurotoxic, and nephrotoxic.[79,84] However, PNALD and WD are not directly comparable, because they have different causes and clinical features and the extent to which Cu causes harmful oxidative effects in vivo in PNALD is unknown, as are its macromolecular targets.[85] Moreover, the observation that neonates tolerate high hepatic Cu concentrations without adverse effects suggests that Cu accumulation per se is not necessarily harmful.[86] Whether Cu is hepatotoxic may depend on factors other than its total hepatic concentration, including its subcellular location and extent of protein binding. It has also been suggested that Zn decreases the hepatotoxicity of Cu in WD,[87] but whether it does so in PNALD is unknown. Until the results of further research clarify whether Cu is hepatotoxic in PNALD, Cu should be considered potentially harmful for patients treated with long-term PN. Chronic Cu toxicity is also implicated in atherosclerosis and neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.[88]

Assessment of Cu Status

Serum Cu

All currently available biomarkers of Cu status are unreliable. The serum Cu concentration is the most useful and most frequently ordered test, but its limitations need to be considered.[89] When interpreting individual results, the clinician should first consider how reliably this can be done through the population reference range. Second, when interpreting serial results, the clinician must decide whether a change between consecutive results is significant, possibly requiring clinical intervention, or can be accounted for by a combination of biological variation and analytic imprecision. Regarding use of the reference range, serum Cu has an index of individuality of 0.41, which is low (ie, a ratio of intraindividual variation to interindividual variation).[90] Consequently, results within the reference range do not exclude the possibility that there has been a disease-related change in concentration that is highly significant for the individual. Unless a previous result is available for comparison, the clinician will be unaware of the significance of the result. Clearly, this low index of individuality decreases the value of the population reference range for interpreting individual serum Cu results. Regarding serial results, critical difference values can help clinicians interpret the significance of changes. Serum Cu has been reported to have a critical difference of 2.3 μmol/L (14.6 μg/L), suggesting that a relatively small change between consecutive results is likely to be significant.[90] Critical differences should ideally be determined by all clinical laboratories because the values are influenced by analytic imprecision, which varies among laboratories.[91]

The serum Cu concentration is insensitive to deficiency, tending to remain within the reference range except in severe deficiency. A normal or increased serum Cu result does not therefore rule out deficiency.[15] It is also insensitive to hepatic Cu accumulation, tending to plateau once requirements are met and correlating poorly with tissue accumulation.[14,81,82] The lack of correlation with Cu status makes serum Cu an unreliable test for guiding supplementation of PN, except at extremes.[92] Hypocupremia can occasionally occur in the absence of deficiency (eg, for patients with WD).[93] When the

cause of hypocupremia is uncertain, WD can be ruled out by the finding of a 24-hour urinary Cu ≤0.6 μmol.[94]

Confounding factors cause serum Cu to increase in the absence of Cu excess, the most common being the APR, during which proinflammatory cytokines stimulate the synthesis of Cp irrespective of Cu status. Indeed, hypercupremia is to be expected in hospitalized patients with trauma or infection or in those who are postsurgical.[95] A recent retrospective review of Cu status in hospitalized patients treated with PN observed that serum Cu correlated with C-reactive protein concentrations >4 mg/dL (P = .03).[20] This APR-associated increase in serum Cu concentrations can mask deficiency[2] or cause unnecessary concern about toxicity, either of which could result in inappropriate clinical action. In addition, serum Cu concentrations measured for monitoring the treatment of deficiency should be interpreted with caution if there is a concurrent APR. Cp synthesis is also stimulated by estrogens, resulting in increased serum Cu concentrations among women who are pregnant or taking estrogens. In the presence of these confounding factors, serum Cu concentrations within the reference range do not exclude deficiency, but hypocupremia is consistent with a diagnosis of Cu deficiency.[14,15,96,97]

It is advantageous to measure the Cp concentration when measuring serum Cu. Both increase in parallel because their concentrations are approximately linearly related. Any increase in Cu caused by a confounding factor will then be readily apparent. To allow for changes in Cp caused by age, sex, or inflammation, authors have suggested routinely adjusting serum Cu for the Cp concentration[98] or calculating the Cu:Cp ratio.[99] Laboratories should determine their own adjustment equation or ratio because these depend on the methods used and population studied.[100]

Cuproproteins

Many cuproproteins other than Cp have been investigated as possible markers of Cu status, but none reliably detect early deficiency or toxicity.[5,101] Assays are unstandardized, necessitating that individual laboratories determine local reference ranges. These tests are also subject to high intraindividual variation. Lability of cuproenzymes may necessitate rapid specimen processing, confining analysis to hospitalized patients. There is also limited information available on the diagnostic sensitivity and specificity of these tests.

Superoxide dismutase in red blood cells is considered a relatively sensitive marker of Cu deficiency, decreasing in Cu deficiency and in subjects with low Cu intake, but the change occurs slowly because of slow turnover of red blood cells.[102] Plasma diamine oxidase decreases in Cu-deficient subjects but has limited use in diagnosis because it increases during tissue injury. Studies have also investigated platelet cytochrome C oxidase as a biomarker of Cu status, but it is limited by lability and high interindividual variation. Neither marker is routinely measured in clinical practice. These are discussed in detail elsewhere.[4,89]

Cu chaperone for superoxide dismutase (CCS) is the most promising potential biomarker of Cu status. In humans, mononuclear cell mRNA for CCS increases in malnourished Cu-deficient patients and decreases in response to Cu supplementation.[102,103] A recent study observed that neither CCS protein nor mRNA transcripts were influenced by inflammatory status, supporting their use as biomarkers of Cu status.[104]

Liver Cu

The most reliable indicator of Cu status is liver Cu concentration, but this has limitations.[97] First, underestimation may result from inhomogeneous distribution of Cu.[105] Second, liver biopsy may be unsafe or contraindicated for some patients and is not feasible to repeat frequently, because of its invasive nature. A recently established technique called *laser ablation–inductively coupled plasma–mass spectrometry* has been used to measure liver Cu concentrations.[106] It is more accurate, quicker, and cheaper than standard metal deposit measurement and can simultaneously measure Zn and selenium. When applied to liver specimens from patients with WD, it has confirmed that hepatic Cu is inhomogeneously distributed, but the technique has not yet been applied to PNALD. The prognostic value of this method is worthy of assessment, but ideally, hepatic Cu would be measured noninvasively. This may eventually be possible through imaging techniques.[101]

Metabolomics and Transcriptomics

Clinically useful biomarkers of micronutrient status may be identified by using *-omics* techniques to detect changes in response to supplementation.[107] As yet, few such approaches have been described in relation to Cu status. A recent study of proteins correlating with micronutrient status in undernutrition unexpectedly identified a Ras protein that explained variation in plasma Cu concentration additional to that explained by Cp. This protein merits further investigation as a biomarker of Cu status.[108] A network of proteins representing the Cu interactome identified ATPases 7A and 7B as proteins worthy of further assessment as markers of Cu status.[102]

There is a clinical need for biomarkers, ideally measurable in peripheral blood, that can detect Cu accumulation before the onset of clinical features. Studies in animals have shown that *-omics* approaches can sensitively detect Cu toxicity by observing genetic and metabolic changes. A transcriptomics approach observed downregulation of genes associated with cholesterol synthesis, as in a mouse model of WD, and upregulation of metallothionein and catalase.[109] A metabolomics approach identified a metabolic signature of Cu exposure.[110] These techniques have not yet been applied to the study of Cu exposure in humans. At present it is difficult to predict which patients are

Table 1. Parenteral Copper Requirements in Adults.

Condition: Requirement, mg/d	Year	Reference
Stable		
0.5–1.5	1979	83
0.3–0.5	2002	112
317–518[a]	2014	113
Diarrhea: 0.4–0.5	1981	92
Cholestasis: 0.15	1981	92

[a]Values in μg/d.

susceptible to Cu accumulation, but the ability to do this could guide Cu provision. Gene testing may have predictive value because it is likely that genetic factors contribute to interindividual variation in the effects of Cu exposure. For example, individuals who are heterozygous for ATP7B mutations for WD may be predisposed to liver disease when exposed to excess Cu during long-term PN. The carrier frequency for these genes is relatively common at 1 in 90.[111] These are all key areas for future research.

Practical Considerations

Standard Requirements

In 1979 the American Medical Association published recommendations on Cu supplementation of PN based on knowledge of oral intake and estimated absorption of Cu from a normal diet.[83] The amount recommended for adults was 0.5–1.5 mg/d. Subsequently, the results of Cu balance studies suggested that the dose should be lower.[92] In response to this, the American Society for Parenteral and Enteral Nutrition (ASPEN) changed the standard recommendation to 0.3–0.5 mg/d, which has remained unchanged since 2002[112] (Table 1). The European Society for Clinical Nutrition and Metabolism (ESPEN) made the same recommendation in its guidance on perioperative PN.[114] These recommendations were supported by a recently published systematic review of TE supplementation in PN.[115]

Individualization of Cu Provision

Standard recommendations should be considered a starting point for estimating individual requirements and adjusting Cu provision accordingly. However, studies suggest that in practice this is poorly done. A 2013 Canadian review of 135 patients treated with long-term PN observed that Cu supplementation was 0.64 ± 0.35 mg/d, exceeding the standard recommendation.[116] Supplementation did not appear to be influenced by factors such as the GI anatomy of individual patients or indication for PN. This failure to adjust Cu provision risks causing deficiency or toxicity. Similarly, a retrospective observational study of TE status and dosing among 26 adult patients treated with long-term PN reported that 95.5% of Cu doses delivered exceeded the standard recommendation.[117] Cu doses of 1 mg/d resulted in hypercupremia in 22.5% of the tests performed. The excessive Cu dosing observed in these studies is in part a consequence of inappropriately formulated MTE products.

In practice, prescribers have insufficient information to enable them to fully individualize Cu doses. This would require knowledge of the patient's Cu status, the disease-specific requirements, and the amount of bioavailable Cu already present in the PN and other sources. Nevertheless, individual clinical circumstances should be carefully assessed and Cu provision adjusted if necessary. In what follows, situations are considered in which individual requirements may differ from the standard recommendation. The discussion is confined to Cu, but in practice all micronutrients should be considered together.

Increased requirements. Cu requirements increase for patients with prolonged, increased GI losses or persistent malabsorption.[16,118] In this situation, it may be appropriate to give higher doses of Cu. Balance studies have suggested that patients with persistent diarrhea (GI secretions >300 g/d) require 0.4–0.5 mg/d to maintain balance (ie, doses at the upper end of the standard recommendation).[92] This study investigated patients receiving total PN. In practice, however, many patients with short bowel take some oral diet, the effect of which on parenteral Cu requirement is difficult to predict. Oral diet resulting in net Cu absorption will decrease the requirement. However, oral diet also stimulates the production of Cu-containing secretions, potentially resulting in net Cu loss and an increased requirement. In practice the net effect of oral diet on parenteral Cu requirement is unknown because it is not feasible to carry out balance studies with individual patients.

The observations of high exudative Cu losses for patients with severe burns suggest that Cu requirements are likely to increase in these patients. ASPEN has recommended higher Cu provision in this situation.[73] ESPEN has recommended increasing provision 5-fold (3.0–3.5 mg/d) especially while wounds remain open.[119] Higher Cu doses may also be required to replace dialysate losses for patients treated with continuous renal replacement therapy.[46] Increased Cu provision should also be considered for patients treated with cisplatin.[48] Clearly, higher doses are required for patients with Cu deficiency. If deficiency is suspected, it may be appropriate to increase Cu supplementation to provide at least 1.0 mg/d in PN.[16]

Decreased requirements. Various publications suggest that for critically ill patients the amount of Cu that would be required in PN is decreased. ESPEN recommends that, except for patients with severe burns, parenteral Cu requirements are below the amount provided by currently available MTE products.[119] Elsewhere, authors have recommended against delivery of Cu to

Table 2. Practical Assessment of Cu Status During Parenteral Nutrition.

Assessment	Rationale
Clinical workup	
History	Elicit possible causes and consequences of Cu deficiency and toxicity.
Examination	Elicit anemia, poor wound healing, and neurologic abnormalities, which may occur in deficiency. Features of liver disease may occur in PNALD.
Biochemistry (serum)	
Cu	Hypocupremia is consistent with Cu deficiency.
Cp	Assists with interpretation of serum Cu results.
CRP	Assists with interpretation of serum Cu by quantifying APR.
Zn	Overprovision of enteral or oral Zn can cause Cu deficiency.
Fe status	Fe deficiency may coexist with Cu deficiency.
Vitamin B_{12}, D, E	Vitamin deficiency may coexist with Cu deficiency.
Full blood picture	Microcytic or normocytic anemia and neutropenia can occur in Cu deficiency.
Liver Cu	Confirmation of Cu accumulation.
Bone imaging	Osteoporosis can occur in Cu deficiency.

APR, acute phase response; Cp, ceruloplasmin; CRP, C-reactive protein; Cu, copper; Fe, iron; PNALD, parenteral nutrition–associated liver disease; Zn, zinc.

critically ill patients at doses >1.2 mg/d.[120] In a study of Cu provision for critically ill patients treated with PN, doses of 0.3 mg/d were sufficient to maintain constant serum Cu concentrations.[121] In consideration of these recommendations, it should be remembered that critical illness encompasses a diverse range of conditions and disease severities.

It may be necessary to decrease Cu provision for patients with cholestasis. A difficulty in practice is that cholestasis is difficult to quantitate and its severity varies widely. Ideally, it would be quantitated by direct measurement of bile flow, but this cannot be done in clinical practice. Clinicians therefore have to rely on surrogate measures and the presence of clinical features. Cholestasis can be considered to be present if there is direct (conjugated) hyperbilirubinemia with (1) direct bilirubin >1 mg/dL when total bilirubin is <5 mg/dL or (2) direct bilirubin >20% of total bilirubin when it is >5 mg/dL.[3]

Limited data are available on which to base guidance on parenteral Cu provision for patients with cholestasis. However, the observations of liver Cu accumulation for patients with cholestasis suggest that caution is necessary.[81,82] Howard et al recommended that Cu be withheld once liver aminotransferase and alkaline phosphatase levels increase to twice that of reference values and before serum bilirubin levels increase.[82] ASPEN has recommended decreasing or withholding Cu provision for patients with significant cholestasis or liver disease.[73] On the basis of balance studies, a dose of 0.15 mg/d has been suggested.[92] Doses below this, if continued indefinitely, risk the development of deficiency. This contention is supported by the reports of severe Cu deficiency occurring for patients with cholestasis after Cu has been withheld from PN.[21,22] The risk of deficiency would be expected to be higher if GI losses increase or if there is high Zn provision. To avoid the development of Cu deficiency for patients with cholestasis, it may be preferable to decrease Cu provision rather than to withhold it altogether. Whether decreased or withheld, Cu provision should be kept under close review because individual requirements may change.

Monitoring of Cu Status

Serum Cu should be measured regularly for patients treated with long-term PN and in any patient in whom Cu deficiency is suspected. There are limited data available to guide the frequency of measurements, the recommendations being based on expert opinion. ESPEN guidelines on home PN recommend measuring serum Cu every 6 months.[122] The frequency of measurements should be increased for patients who are clinically unstable.[123] A recent study of TE monitoring among critically ill patients observed that significant cost savings could be made by targeting the sickest patients for monitoring, as opposed to automatic testing of all patients.[124] For patients with cholestasis supplemented with Cu provided by a standard MTE product, 6-monthly monitoring of Cu should suffice,[16] but 3-monthly monitoring has been recommended for patients with increased total bilirubin attributed to liver disease.[125] For patients treated with PN from which supplemental Cu has been withheld, monthly monitoring has been recommended to facilitate early detection of Cu deficiency.[16,125]

Serum Cu results should be considered in the clinical context and along with the results of other investigations. Factors to consider in the practical assessment of Cu status are summarized in Table 2. Causes and features of Cu deficiency should be sought and C-reactive protein measured to assess the APR.[113] If Cu deficiency is suspected, a full blood picture should be ordered, to exclude hematologic features of deficiency, and a trial of supplementation considered.[22,72] Resolution of features in response to supplementation may help to confirm the diagnosis. Serum Zn should be measured during long-term PN to exclude Zn excess. Zn excess can also

be excluded by 24-hour urine Zn <19 μmol.[40] Vitamin B_{12} status should be assessed, especially after gastric surgery. Its deficiency may coexist with that of Cu, as can deficiencies of Fe and vitamins D and E. If Cu accumulation is suspected, features of cholestatic liver disease should be sought and liver function tests measured. Liver biopsy may be considered to measure the liver Cu concentration.

Cu Contamination

Contamination of PN with Cu may result in excessive delivery of Cu. One study that examined 8 component solutions observed that Cu was 1 of 12 TEs present in amounts >1 μg/L in every solution.[126] Cu was a minor contaminant present in PN at a final concentration of 82 μg/2L. Cu was present as a contaminant in the amino acid solutions and sterile water but not in potassium chloride, sodium chloride, and calcium gluconate solutions. More recently, Cu was reported as a contaminant from 5 of 14 PN components undeclared on the product label.[127] The actual amount of Cu was estimated to exceed the prescribed amount by 7%–426%. The total Cu contamination of a PN regimen depends on the volume of individual components added and has been reported to range from 0.1–0.4 mg/d.[15] Patients treated with PN may receive Cu in other IV fluids, causing the total amount delivered to greatly exceed the amount prescribed. Contamination is highest in blood products such as packed red blood cells and frozen plasma and in albumin solutions (0.5 mg/L) and crystalloids (0.14 mg/L).[128] Berger and Cavadini estimated that critically ill patients, with burns or trauma who were treated with large volumes of these fluids, received Cu doses 2.3 times the RDA.[128]

The inadvertent delivery of Cu raises safety concerns. Whether safety is compromised depends on the individual clinical circumstances and on the amount of Cu delivered. The concerns are greatest for patients with cholestasis who are treated with long-term PN. ASPEN has recommended that Cu contamination of composite PN regimens delivered to adults should not exceed 0.1 mg/d.[73] To achieve this target, all components of PN should be considered.

Stability Considerations

Unwanted interactions among components of PN can result in precipitation or degradation of micronutrients. Cu has been reported to interact with cysteine to form precipitates that are trapped by the filter, thereby decreasing the bioavailability of both nutrients. The mechanism of precipitation is uncertain, but spectroscopic examination of precipitates recently identified Cu and sulfur as the main elements.[129] Cu may react directly with cysteine to form Cu cysteinate. Alternatively, it may react with hydrogen sulfide, formed from cysteine by heat sterilization, to form Cu sulfide.[130] The probability of precipitation is highest at high concentrations of both nutrients, the Cu concentration in one reported case being 170 μg/L.[131] It may also be influenced by the timing of additions. When cysteine was added to PN immediately before infusion, no significant differences were observed between prefilter and postfilter concentrations of Cu and cysteine, nor was there visible precipitation.[132] The authors concluded that L-cysteine added to PN immediately before infusion is stable over 24 hours of infusion. This interaction can be prevented by omission of Cu from PN, but this is impractical. Instead, limiting the Cu concentration to 157 μg/L with the use of low-pH cysteine-containing amino acid solutions has been suggested.[133] When Cu requirements are high, it may be necessary to deliver some or all of the Cu by a separate IV infusion. The feasibility of providing Cu enterally should also be considered.

Ascorbic acid is the biologically active form of vitamin C. It is an unstable component of PN, being reversibly oxidized anaerobically to dehydroascorbic acid that, in the presence of oxygen and Cu, is irreversibly oxidized to inactive diketogulonic acid.[134] This is then further oxidized to oxalate. The oxygen for this reaction reaches PN either in component solutions or by permeation through the wall of the bag. Ascorbate can be protected during storage of PN by using multilayered bags that are less permeable to oxygen.[135,136] As new PN regimens are developed, the potential for interaction of components with Cu should be considered.

MTE Products

It is difficult for prescribers to comply with the current ASPEN recommendations on Cu provision in PN because of the formulation of most MTE products currently available in the United States and Europe. These products provide up to twice the recommended amount of Cu, which exceeds most patients' requirements, and a recent review concluded that they were potentially toxic.[73] Moreover, the formulation of these products is not conducive to individualization of Cu dosing. When prescribers wish to decrease or withhold Cu, the MTE product must be withheld and the PN regimen supplemented individually with the necessary doses of Cu, selenium, and Zn. When Cu provision is being increased, it is not safe to increase the MTE dosage, because this could result in excessive provision of manganese and other TEs. In this situation, the PN regimen can be supplemented with an individual Cu product, unless stability considerations demand that the Cu be delivered by a separate IV infusion. These approaches are costly and labor intensive and increase the risk of errors.

ASPEN has made a call to action to bring safer products to the market, recommending that Cu doses provided by adult parenteral MTE products are decreased to 0.3–0.5 mg/d.[137] Similarly, the Australasian Society for Parenteral and Enteral Nutrition has recommended that Cu dosing in MTE products, for the Australian and New Zealand market, be decreased to 315 μg/d.[113] In addition, there may be a place for low-Cu MTE products for use among patients whose requirements are below the standard recommendations. Ideally, a range of products should

be developed with doses of Cu and other TEs appropriate for situations commonly encountered in practice. The availability of such products would greatly facilitate individualization of Cu provision. There is also a need for pharmaceutic companies to routinely provide information on Cu contamination—in PN products and other IV fluids as well. The availability of this information would inform decisions on supplementation.

ASPEN has provided guidance on managing product shortages,[26,138] summarized briefly here. Most important, supplies should be reserved for the most vulnerable patients—namely, those with existing deficiency or at high risk of developing deficiency if micronutrients are withheld. TEs should be supplemented orally for patients with sufficient GI absorptive capacity. Rationing may be necessary—for example, by delivering standard doses 3 times weekly rather than daily or by providing daily delivery of half the standard dose. If rationing is necessary, clinicians should be alert to possible deficiencies and should monitor patients accordingly. Supplies should be sought for micronutrients, including Cu, for which deficiency is likely to occur if the micronutrient is withheld. Advice on strategic planning for future shortages is available elsewhere.[139]

Future Directions

Prescribers of micronutrients should aspire to individualize provision. However, much research and development will be necessary before true individualization of Cu provision is possible. More information is required on the Cu provision required to maintain optimal status in different diseases, especially critical illness. Sensitive and specific biomarkers of Cu status will need to be developed, enabling mild derangements in Cu status to be detected and provision to be adjusted before the onset of clinical features. It is likely that new tests will emerge from studies using *-omics* technologies or from studies of the effects of Cu deficiency on physiologic systems such as the immune system. The availability of better tests of Cu status will decrease the uncertainty that affects decisions on Cu provision in PN. It will also facilitate the study of marginal Cu deficiency in hospitalized patients and in the general population. There is an urgent need for a range of appropriately formulated MTE products to be developed, both to enable compliance with the 2012 ASPEN recommendations and to facilitate adjustment of parenteral Cu doses.

Statement of Authorship

C. Livingstone conceived and drafted this article, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Factors Associated With Gastrostomy Tube Removal in Patients With Dysphagia After Stroke: A Review of the Literature

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Abstract

Gastrostomy feeding tubes are commonly placed in patients with dysphagia after stroke. The subsequent removal of the tube is a primary goal during rehabilitation. The purpose of our review was to identify predictors and factors associated with gastrostomy tube removal in patients with dysphagia after stroke. We conducted a literature review following the PRISMA statement and included the search databases PubMed, Scopus, Web of Science, and CINAHL. Articles were included in the final analysis per predefined inclusion and exclusion criteria. Our search retrieved a total of 853 results consisting of 416 articles (after eliminating duplicates). Six articles met our final eligibility criteria. The following factors were identified in at least 1 article as being significantly associated with gastrostomy tube removal: reduced age, decreased number of comorbidities, prolonged inpatient rehabilitation stay, absence of bilateral stroke, nonhemorrhagic stroke, reduced dysphagia severity, absence of aspiration, absence of premature bolus loss, and timely initiation of pharyngeal swallow. Aspiration was the only factor that was investigated by 2 studies—both using multiple regression and both showing stable results, with absence of aspiration increasing the chances for tube removal. In conclusion, little is known about factors associated with gastrostomy tube removal in patients with dysphagia after stroke. Most of the identified factors are associated with stroke or disease severity; however, the role of the individual factors remains unclear. The strongest predictor appears to be absence of aspiration on modified barium swallow studies emphasizing the importance of instrumental swallow studies in this patient population. (*Nutr Clin Pract*. 2017;32:166-174)

Keywords

stroke; deglutition; deglutition disorders; enteral nutrition; gastrostomy; jejunostomy; dysphagia

About 55% (37%–78%) of patients with acute stroke suffer from swallowing disorders, called *dysphagia*.[1] Common sequelae of dysphagia are aspiration pneumonia,[1] malnutrition, and dehydration,[2] which can necessitate the placement of a gastrostomy feeding tube, such as a percutaneous endoscopic gastrostomy (PEG) tube. Our research has shown that approximately 5% of all patients hospitalized for stroke receive a PEG tube placement.[3]

Besides the benefits that patients can gain from PEG tubes, risks and complications can also occur, such as tube displacement, infection (skin, wound, abdominal wall), tube obstruction and migration, leakage (stomal), gastric hemorrhage and fistula, peritonitis, ulceration, diarrhea.[4-6] PEG tubes have also resulted in a decrease of quality of life for patients and families.[7] Additionally, we have shown that PEG tube placement is an independent risk factor for 30-day readmissions for patients after discharge from an acute care hospital for stroke.[8] Therefore, the removal of a PEG tube, if indicated, can have a significant positive impact on the patient's course of the disease.

The removal of a feeding tube may be possible in some patients after stroke because dysphagia following stroke may be reversible due to spontaneous and/or treatment-induced recovery, even in chronic stages.[9-15] If nutrition and hydration needs are accomplished orally and no other contraindications exist, gastrostomy tubes should be removed. However, the process of identifying patients who are candidates for tube removal is complex and usually requires a thorough assessment by multiple health care professionals to ensure the best possible outcome for a patient. An understanding of patient characteristics and other factors that influence the decision to remove a tube could assist clinicians in their patient assessment. Also, the ability to predict which patients are likely to have their tubes removed is crucial to planning and advocating for health care resources. Clinicians could individualize the health care trajectory for specific patients by fostering rehabilitative strategies that target tube removal and by scheduling reevaluations to

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identify patients who have feeding tubes that are no longer medically justified. Clinicians could also better counsel patients and families during and after the decision-making process to place a feeding tube. Optimally, a better understanding of factors contributing to gastrostomy tube removal could lead to improved poststroke care by reducing PEG tube–related complications, burdens, and costs. Thus, we sought to review the current body of literature regarding possible predictors and factors that clinicians could use to identify patients with dysphagia after stroke who have good chances for tube removal.

Methods

Search Strategy

We conducted a systematic literature review to find publications investigating predicators or factors associated with the removal of a gastrostomy tube in patients with dysphagia after stroke. We included studies investigating the removal of PEG, gastrostomy-jejunostomy, or jejunostomy tubes—we further refer to all these tube types as *PEG/J*. Not in the scope of our systematic review were tube removals due to end-of-life decisions and nutrition discontinuation, as we focused on swallow recovery as the underlying cause for tube removal. Furthermore, we did not include therapy or intervention studies, as we targeted the best possible generalizability of our findings to the common management of stroke.

We based our methodological approach on the principles of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[16] The following databases were searched: PubMed, Scopus (which includes Excerpta Medica–EMBASE records), Web of Science, and the CINAHL. No limitation for search years was applied. Therefore, all available years in each database were searched through February 2014. Our target was to ensure an extensive but comparable search process across all 4 databases. To identify indexed publications, we searched with Medical Subject Headings by using the terms "stroke," "enteral nutrition," and "deglutition disorders." In addition, we used a standard search of manually entered search terms to identify nonindexed publications with the following search entry: ("Enteral Nutrit*" OR "Enteral Feed*" OR "Force Feed*" OR "Tube Feed*" OR "Feeding Tube*") AND (Stroke* OR Apople* OR CVA OR "Cerebrovascular Accident*" OR "Brain Vascular Accident*") AND ("Deglut* Disorder*" OR "Swallow* Disorder*" OR dysphagia).

Process of Study Identification

After eliminating all duplicates across the 4 databases, we screened titles and abstracts for inclusion or exclusion. One rater (J.W.) screened all titles and abstracts, and a second rater (H.S.B.) independently screened 20% of those for reliability. The following screening criteria for inclusion were applied: article language in English or German, article including patients with stroke, article discussing the removal of feeding tubes, and any article appearing to fit the topic of this systematic review. Afterward, the full texts of all remaining records were thoroughly assessed for eligibility by applying the following extended inclusion criteria: the full text is published; the article is an original research article and peer reviewed; the article analyzes patients with stroke separately; the article analyzes the removal of PEG/J tubes separately; PEG/J feeding tube removal is analyzed due to recovery and not end-of-life decisions; the article compares patients with and without PEG/J feeding tube removal; and the data from the article are not based on a therapy or intervention study. Finally, all references of the full-text articles were reviewed to determine any other eligible articles not previously identified with the search.

Extracted Key Elements

The remaining studies after review underwent a qualitative analysis. Two raters (J.W., H.S.B.) independently extracted key elements related to predictors or factors associated with the removal of PEG/J tubes in patients with dysphagia after stroke. For clarity, we use the term *predictor* to refer to factors assessed in multivariable modeling analyses and the term *factor* to refer to factors assessed in univariate analyses. The results were compared between the raters, and in case of any inconsistencies, agreement was determined in a consensus meeting. These key elements were as follows: study design, study setting, patient characteristics (number, age, sex, stroke characteristics, and dysphagia characteristics), PEG/J tube placement (tube type, placement type, and timing), PEG/J tube removal (number of patients with tube removal, timing of removal), care/intervention between PEG/J tube placement and removal, follow-up time of the study, and the analyzed predictors/factors for PEG/J tube removal (type, measurement, results).

Assessment of Level of Evidence

The resulting studies were assessed regarding their levels of evidence according to the Scottish Intercollegiate Guidelines Network (SIGN) grading system.[17]

Results

As shown in Figure 1, our search retrieved a total of 853 results (PubMed: 283 results, Scopus: 316 results, CINAHL: 120 results, Web of Science: 138 results). After removing duplicates, we reviewed all titles and abstracts and identified 112 articles for a full-text assessment. Interrater reliability for full-text identification was 92.8% and rater agreement was 100% after consensus. A total of 106 studies did not meet our inclusion criteria and were excluded with reason. No further eligible studies were identified after review of all reference lists from the full-text articles. In the end, 6 articles fit our criteria and were included in our qualitative analysis and synthesis.

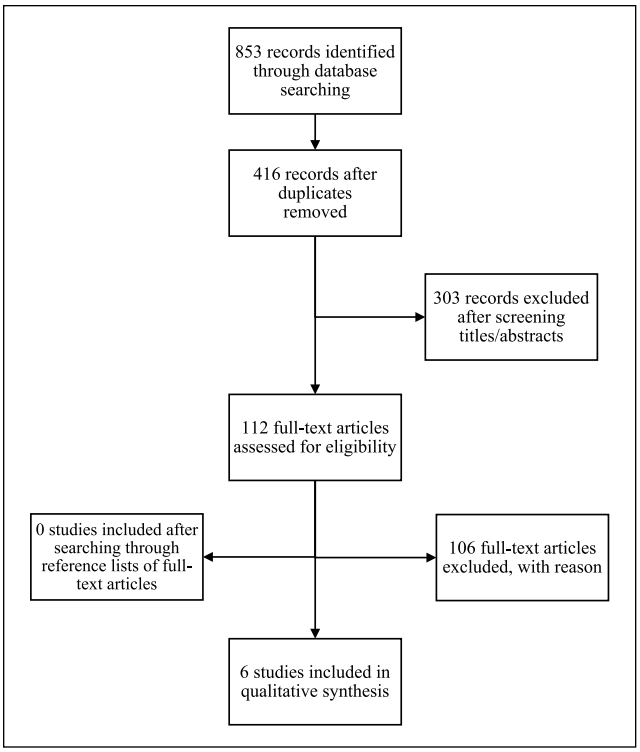

Figure 1. Article selection according to the PRISMA statement.[16]

Level of Evidence

We reviewed the studies with the grading system provided by the SIGN.[17] All 6 articles were based on cohort study designs (see Table 1). All studies were retrospective. Two of the 6 studies[18,19] controlled for multiple variables through regression analyses and therefore had lower risk of confounding or bias.

Study Setting and Patient Characteristics

Table 2 provides information about the study setting and patient characteristics. Four of 6 studies took place in hospitals, with the remaining 2 in rehabilitation units. The number of studied patients with dysphagia after stroke who were receiving or had received a PEG/J varied across the studies (N = 32–83). The mean/median age was >69 years in all included studies. Except for 1 study,[20] all studies provided information regarding stroke characteristics. The majority of studies (5 of 6) stated that they had used a bedside swallow examination (BSE) to identify and describe dysphagia in the patient population. In addition to or instead of the BSE in all or some patients, 4 of the 6 studies used a modified barium swallow study (MBSS). One study[20] did not provide information about its dysphagia assessment.

Gastrostomy Tube Placement and Removal

Most studies investigated patients with percutaneous gastrostomy tubes (see Table 3). Two of the 6 studies included patients with gastrostomy-jejunostomy tubes.[18,21] The procedure of placement (endoscopic, radiologic, or surgical) was stated in 4 studies: 3 studies reported the use of endoscopic placement procedures, and 1 study (the only study using only percutaneous gastrostomy-jejunostomy tubes) utilized a fluoroscopic/radiographic procedure. The percentage of patients who had their PEG/J tubes removed varied across the studies, from 16.3%–75%. The studies also varied broadly regarding duration of follow-up—ranging from 30 days[20] to presumably almost 8 years. None of the included studies described procedures, treatments, or care offered to the patients in the time between PEG/J placement and removal. Two of the 6 studies[18,21] identified their patient cohorts in a rehabilitation setting; therefore, these patients likely received some rehabilitation. However, it is unclear if the rehabilitation targeted swallowing function with a goal of feeding tube removal.

Predictors and Factors for Gastrostomy Tube Removal

The 6 included studies used medical records as the data source with different statistical methods to analyze factors associated with gastrostomy tube removal. All study authors stated that they compared the 2 groups of patients with and without tube removal regarding their analyzed factors. However, 3 studies[21-23] did not report the statistical difference tests used, and 2 studies did not report any statistical values.[22,23] Two of the 6 studies conducted multivariable regression analyses to identify predictors for tube removal.[18,19]

The following predictors and factors were analyzed in at least 1 of the 6 included studies regarding their association with PEG/J tube removal (Table 4): demographic data (eg, age, sex), stroke characteristics (eg, type, extent, location), comorbidities, functional scales (eg, communication, cognition, activities of daily living), MBSS components and performance at time of PEG/J insertion or during inpatient rehabilitation stay, BSE components and performance at hospital admission or during rehabilitation stay, time interval between stroke and PEG/J placement, and laboratory findings (eg, albumin, creatinine, C-reactive protein) at time of PEG/J insertion. The most often analyzed variable was age, which was investigated in 5 of 6 studies. Three of those studies found no association between age and tube removal.[19-21] In contrast, 2 studies did find a significant association, with younger patients being more likely to have the PEG/J tube removed.[18,22]

Stroke characteristics (absence of bilateral stroke in comparison with unilateral stroke, nonhemorrhagic stroke) were significantly associated with tube removal in 2 of 4 studies that investigated those variables.[18,22] Two of 3 studies found a positive association between tube removal and fewer comorbidities (defined in 1 study as the presence of a prior stroke, dementia, depression, or Parkinson's disease[22] and measured in another study with the Charlson Comorbidity Index[18]). Yi et al found no difference in blood laboratory findings.[19] Two

Table 1. Study Design and Level of Evidence.

Study	Study Design	Level of Evidence[a]
Ha and Hauge (2003)[20]	Retrospective cohort study	2+
Ickenstein et al (2003)[18]	Retrospective cohort study	2++
Scolapio et al (2000)[22]	Retrospective cohort study	2+
Teasell et al (2001)[21]	Retrospective cohort study	2+
Wijdicks and McMahon (1999)[23]	Retrospective and follow-up cohort study	2+
Yi et al (2012)[19]	Retrospective cohort study	2++

2++, High-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+, Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
[a]Level of evidence based on the Scottish Intercollegiate Guidelines Network grading system.[17]

studies that analyzed functional scales did not confirm an association with PEG/J tube removal.[18,19]

Specific MBSS components (aspiration, premature bolus loss, and pharyngeal trigger delay) were analyzed in 2 studies, and both found significant associations with tube removal.[18,19] Across all investigated factors in all studies, aspiration was the only factor analyzed by >1 study, which showed a stable impact on feeding tube removal. One study investigated the relation of bedside swallow assessments and PEG tube removal.[22] The authors found that mild dysphagia was associated with removal, but they did not describe their operationalization of "mild" dysphagia.

Ickenstein et al and Yi et al were the only studies that conducted logistic regression analyses to model the event of PEG/J tube removal.[18,19] Ickenstein and colleagues found that absence of bilateral stroke (odds ratio [OR], 16.9), absence of aspiration on MBSS (OR, 17.8), and younger age (≤52 years; OR, 1.15) were independent predictors for PEG/J tube removal.[18] Likewise, Yi and colleagues found that absence of aspiration (OR, 11.4) and absence of pharyngeal trigger delay (OR, 15.1) were independent predictors for the removal of a PEG tube.[19]

Discussion

Main Results

The aim of this systematic review was to identify, compare, and summarize all published peer-reviewed studies investigating predictors and/or factors associated with the removal of gastrostomy/jejunostomy feeding tubes in patients with dysphagia after stroke. According to our criteria, we identified 6 eligible articles. All data are based on retrospective cohort studies. Only 2 studies conducted regression analyses and therefore assessed the influence of multiple variables or confounders on the outcome of tube removal.

We found that the proportion of patients who had their PEG/J tubes removed varied broadly across the studies (16.3%–75%). This broad range of "success" emphasizes the need to investigate factors that are associated with tube removal to improve patient care. For example, if we identify modifiable factors influencing tube removal, we can develop strategies to target these factors to provide better care for patients with stroke with feeding tubes.

The following factors were related to PEG/J removal in the studies: reduced age, decreased number of comorbidities (measured by the Charlson Comorbidity Index score or separate comorbidities), prolonged rehabilitation hospital stay, absence of bilateral stroke, nonhemorrhagic stroke, reduced dysphagia severity assessed by BSE (assessed during the hospital stay of PEG/J insertion), absence of aspiration on MBSS (assessed either at the time of PEG/J insertion or during inpatient rehabilitation stay), absence of premature bolus loss, and absence of pharyngeal trigger delay on MBSS (assessed at time of PEG/J insertion). Importantly, all of those factors were reported as being noteworthy in only 1 of the 6 studies, except for the absence of aspiration and age, which were significantly associated with tube removal in 2 studies. The importance of aspiration as a predictor of tube removal was supported by regression analyses in 2 studies, which revealed significance even after adjusting for other factors. First, Ickenstein et al[18] identified absence of bilateral stroke, age <53 years, and absence of aspiration on MBSS as independent risk predictors for PEG/J removal. Second, Yi et al[19] identified the absence of pharyngeal trigger delay and the absence of aspiration as independent predictors for PEG tube removal. Therefore, absence of aspiration, as seen on MBSSs, was the strongest predictor and factor for tube removal across all studies, because it was the only factor investigated by >1 study, by multiple regression, and showed consistent results in terms of its impact on tube removal. This highlights the importance of instrumental swallowing assessments in the treatment of patients with dysphagia after stroke and may help clinicians advocate for their patients to receive clinically indicated swallowing assessments.

There was disagreement regarding the majority of predictors/factors across the studies included in our review. The most often studied predictor/factor, age, was statistically significant in 2 of 5 studies. The disagreement regarding this parameter could be due to broad variations across the studies. One example of variation is the follow-up duration. Studies with a shorter follow-up duration (4 weeks[22]) or with the

Table 2. Study Setting and Patient Characteristics.

	Patients		
Study: Study Setting[a]	Sample, n; Age, y; Sex	Stroke Characteristics	Dysphagia[b]
Ha and Hauge (2003)[20]: county hospital, Norway	*Sample:* 83 patients with dysphagia after stroke receiving PEG tube placement and 115 nonstroke patients who received PEG tubes as controls *Age:* 77 (median), 34–89 (range) *Sex:* 46% male	No information provided	Authors stated that all patients were dysphagic, but no information was provided on assessment and definition of dysphagia. Indications for PEG tube placement were defined as inability to swallow, weight loss, problems with nasogastric tube feeding, or need for enteral nutrition during rehabilitation.
Ickenstein et al (2003)[18]: urban rehabilitation hospital, USA (according to authors' affiliation; country of studied hospital not explicitly stated)	*Sample:* 77 severe patients with dysphagia after stroke receiving gastrostomy/ jejunostomy feeding tube placement *Age:* 69.8 ± 13.1 (mean ± SD) *Sex:* 40% male	81.8% (n = 63) ischemic and 18.2% (n = 14) hemorrhage; 83.1% (n = 64) unilateral and 16.9% (n = 13) bilateral; 83.1% (n = 64) supratentorial and 16.9% (n = 13) infratentorial	All patients received a clinical assessment of feeding and swallowing, performed by a trained speech-language pathologist; 71.4% of the patients also received a videofluoroscopy swallowing study.[c] Only patients with severe dysphagia were included, defined as a functional communication measure score for swallowing <3 (severe dysphagia, feeding tube dependent) at admission to the rehabilitation hospital.
Scolapio et al (2000)[22]: St Luke's Hospital–Mayo Clinic, Jacksonville, Florida, USA	*Sample:* 32 patients with acute stroke receiving PEG tube placement *Age:* 71.3 (mean), 18–94 (range) *Sex:* 50% male	78% (n = 25) ischemic; 19% (n = 6) primary intracranial hemorrhage (intracerebral hemorrhage: 4; subarachnoid hemorrhage: 2); 3% (n = 1) hemorrhagic stroke	Swallow evaluation was performed by a speech-language pathologist; results were abnormal in 21 of 23 patients (4 mild, 7 moderate-severe, 10 severe dysphagic). A swallow evaluation prior to PEG tube placement was not performed in 9 patients due to poor cognition.
Teasell et al (2001)[21]: rehabilitation unit in a tertiary care hospital, Canada	*Sample:* 563 consecutive patients with stroke, of whom 32 (5.7%) received a PGJ tube *Age:* No information provided for subgroup of patients with PGJ removal *Sex:* No information provided	53.1% (n = 17) brainstem stroke, 46.9% (n = 15) hemispheric stroke	Bedside swallow evaluation was performed in all 32 patients, VMBS[c] in 17 patients before PGJ placement and in 14 patients after placement; 31 of 32 patients receiving a PGJ were considered dysphagic (28 of 31, aspiration on VMBS), 1 nondysphagic patient received a PGJ tube because of persistent poor oral intake.
Wijdicks and McMahon (1999)[23]: Saint Mary's Hospital (Mayo Medical Center), Rochester, Minnesota, USA; follow-up in nursing homes (all surviving patients were discharged to nursing homes)	*Sample:* 63 acute stroke, receiving PEG tube placement *Age:* 74 (median), 41–98 (range) *Sex:* 61% male	42.9% (n = 27) ischemic hemispheric stroke, 31.7% (n = 20) intracerebral hematoma, 22.2% (n = 14) brainstem stroke, 3.2% (n = 2) hemorrhage in the pons or cerebellum	All patients underwent clinical swallowing evaluation by an occupational therapist; when a high clinical index of aspiration was documented, a video fluoroscopy[c] was performed. No information about dysphagia severity provided.
Yi et al (2012)[19]: Seoul National University Bundang Hospital, Seongnam, South Korea	*Sample:* 49 patients with dysphagia after stroke, PEG tube placement between January 2003 and December 2010; patients were divided into 2 groups: removal group (n = 8) and a sustaining group (n = 41) depending on the presence of a PEG tube at the end of the study follow-up (December 31, 2010) *Age:* removal group, 70.6 ± 11.9 (mean ± SD); sustaining group, 69.3 ± 10.9 *Sex:* Removal group: 62.5% male; sustaining group: 58.5% male	*Lesion type:* removal group: 25% (n = 2) hemorrhagic strokes, 75% (n = 6) infarction strokes; sustaining group: 46% (n = 19) hemorrhagic strokes, 54% (n = 22) infarction strokes *Stroke profiles:* removal group: 50% (n = 4) bilateral, 25% (n = 2) left, 25% (n = 2) right, 25% (n = 2) stem involvement, 25% (n = 2) recurrent stroke; sustaining group: 27% (n = 11) bilateral, 37% (n = 15) left, 37% (n = 15) right, 20% (n = 8) stem involvement, 39% (n = 16) recurrent stroke	All patients received a swallowing examination via a bedside swallowing test or videofluoroscopy swallowing study[c] within 72 h after admission. All patients were then followed up every 1 wk to 3 mo according to the initial findings of the swallowing screening examination. No information about dysphagia severity provided.

PEG, percutaneous endoscopic gastrostomy; PGJ, percutaneous gastrojejunostomy; VMBS, videofluoroscopic modified barium swallow.
[a]Institution/hospital, country.
[b]Diagnostic tools, severity.
[c]Various terms were used for the modified barium swallow study. We assumed that each of these referred to the same evaluation procedure.

Table 3. Gastrostomy Tube Placement and Removal.

Study	Gastrostomy Tube Placement		Gastrostomy Tube Removal[b]	Care/Intervention[c] and Follow-Up[d]
	Tube Type and Placement[a]	Time From Stroke Onset		
Ha and Hauge (2003)[20]	*Type:* Freka PEG, Fresenius, Floracare PEG, Nutricia *Placement:* Endoscopic, standard procedure for pull technique	In acute stage for 61 patients, on later readmission for 22 patients	*Patients:* 20 of 75 survivors (27%) during 1 y *Time poststroke:* 4% during first month (19% died), 13% after 3 mo (33% died), 27% during first year (~45% died)	*Care/intervention:* No information provided *Follow-up:* Between 30 d and 1 y after PEG placement
Ickenstein et al (2003)[18]	*Type:* Feeding gastrostomy / jejunostomy tubes, no further information provided *Placement:* No information provided	63 of 77 (81.8%) of the patients had the gastrostomy / jejunostomy tube placed before admission to the rehabilitation hospital; 14 (18.2%) of the patients had the tube placed during inpatient rehabilitation	*Patients:* 24 of 77 (31.2%) before discharge from rehabilitation hospital; of 53 patients discharged with tube in place, follow-up data were available for 46: 23 died, and in 4 of the surviving 23 patients, the tube had been removed (17.4%) *Time poststroke:* No information provided, but tube remained in place on average 62.5 d for patients with tube removal during rehabilitation and 164.3 d for patients with tube removal after discharge.	*Care/intervention:* No specific information provided; however, patients were all in a rehabilitation hospital, at least at the beginning of the study *Follow-up:* Mean duration between discharge from the rehabilitation hospital and follow-up was 2 y (722 ± 317 d).
Scolapio et al (2000)[22]	*Type:* PEG, no further information provided *Placement:* No information provided	8.4 d poststroke (mean), 1–26 d (range)	*Patients:* At 4 wk, 9 of 32 patients had died (28%); 5 of the 23 surviving patients (22%) had PEG removed; at 4-mo follow-up, 18 of 32 patients had died (56%); 10 of 14 surviving patients (71.4%) had PEG removed *Time poststroke:* No exact information about PEG removal provided; however, for the 5 patients who regained swallow function in <4 wk, swallow recovery was identified between 6–27 d.	*Care/intervention:* No information provided *Follow-up:* 4 mo poststroke (mean)
Teasell et al (2001)[21]	*Type:* PGJ feeding tubes, no further information provided *Placement:* Tubes placed under fluoroscopic control by a radiologist	37 ± 30 d (mean ± SD), 2–111 d (range); 18 of 32 tubes (56%) had been placed before the patients' admission to the rehabilitation service; 14 tubes (44%) were placed during inpatient rehabilitation	*Patients:* 11 of 32 patients (34.3%) had PGJ removed before discharge; 24 of 32 (75%) had PGJ removed within 1 y *Time poststroke:* Patients with tube removal before discharge had their tubes in place on an average of 47.2 d. Patients with tube removal after discharge had their tubes in place an average of 153 d.	*Care/intervention:* No specific information provided; however, patients were all in a rehabilitation hospital, at least at the beginning of the study. *Follow-up:* 1 y after discharge from rehabilitation unit
Wijdicks and McMahon (1999)[23]	*Type:* PEG, no further information provided *Placement:* Percutaneous gastrostomy placement was performed using standard techniques (endoscopic)	11 d (median), 5–27 d (range)	*Patients:* 18 of 63 (28%) patients had PEG tube removed *Time poststroke:* No information provided; however, PEG was removed 4 mo (median), 2–36 mo (range) after placement.	*Care/intervention:* No specific information provided; however, all surviving patients were discharged to nursing homes after the acute hospital care. *Follow-up:* Long-term follow-up information was available (2–36 mo; median, 6 mo) for 48 patients.
Yi et al (2012)[19]	*Type:* PEG, no further information provided *Placement:* No information provided	367 d (range, 38–1215 d) in the removal group and 289 d (range, 14–4529 d) in the sustaining group. The time after stroke onset was comparable between the 2 groups (P = .223).	*Patients:* 8 of 49 patients (16.3%) had PEG tube removed *Time poststroke:* No information provided; however, mean duration from PEG insertion to removal was 4.8 mo (range 68–276 d).	*Care/intervention:* No information provided *Follow-up:* Time not stated clearly. All patients who underwent PEG tube insertion at the study site between January 2003 and December 2010 were evaluated for presence of a PEG tube on Dec 31, 2010; therefore, a range from 0–8 y can be assumed.

PEG, percutaneous endoscopic gastrostomy; PGJ, percutaneous gastrojejunostomy.
[a]Endoscopic, radiographic, or surgical.
[b]Number of patients with tube removal and time poststroke of tube removal.
[c]Care/intervention between tube placement and removal.
[d]Follow-up duration of all patients to determine tube removal.

Table 4. Predictors and Factors for Gastrostomy Tube Removal.

Study	Predictors/Factors	Results
Ha and Hauge (2003)[20]	Age	Not significant (Mann-Whitney *U* test)
Ickenstein et al (2003)[18]	Age, stroke type (infarct or hemorrhage), extent of stroke (unilateral or bilateral), stroke location (supratentorial or infratentorial), preexisting comorbidities (Charlson Comorbidity Index score), Functional Independence Measure eating subscore on admission, Functional Communication Measure score on admission, presence/absence of aspiration on videofluoroscopy swallowing study on admission/during rehabilitation stay	Tube removal before discharge was associated with younger age ($P < .001$), lower Charlson comorbidity score ($P < .017$), longer rehabilitation hospital length of stay ($P < .006$), absence of bilateral stroke (bilateral vs unilateral, $P < .05$), absence of aspiration on VSS ($P < .005$). No association found with characteristics of stroke (ischemic vs hemorrhagic, supratentorial vs infratentorial) and functional scores for eating or swallowing on admission. On logistic regression analysis, bilateral stroke ($P = .022$, OR: 16.9, 95% CI: 1.5%–190.7%), aspiration on VSS ($P = .012$, OR: 17.8, 95% CI: 1.9%–169.8%), and older age ($P < .001$) were independent predictors of tube retention. Age >52 y was associated with tube retention (OR for retention, 1.15 for every year increase; 95% CI: 1.06–1.25). The model for predicting failure of tube removal before discharge from inpatient rehabilitation included stroke bilaterality, aspiration during VSS, and age >52 y (sensitivity: 91%, specificity: 63%, positive predictive value: 84%, negative predictive value: 75%).
Scolapio et al (2000)[22]	Age, sex, comorbidities (prior stroke, dementia, depression, Parkinson's disease), stroke type (ischemic, intracerebral hemorrhage, subarachnoid hemorrhage, hemorrhagic infarct), stroke subtype (cardioembolic, large-vessel disease, small-vessel disease, other determined etiology, unknown etiology), Glasgow outcome score, swallow evaluation (normal, mildly abnormal, moderate-severe abnormal, severely abnormal). All information was extracted from medical charts of the hospital stay of PEG placement.	PEG removal within 4 wk was associated with younger age, mild dysphagia, fewer comorbidities, and nonhemorrhagic stroke (no statistical tests or values provided).
Teasell et al (2001)[21]	Age	Age was not significantly different between patients whose feeding tube was removed in <1 year and patients whose PGJ was not removed in 1 y ($P = .198$; statistical test not mentioned).
Wijdicks and McMahon (1999)[23]	Time interval from stroke onset to PEG placement, stroke type, stroke location	No differences found for analyzed factors (no statistical tests or values provided).
Yi et al (2012)[19]	Demographic data (age, sex, body mass index), medical history (hypertension, diabetes mellitus, history of pneumonia, presence of T-cannula, Charlson's Comorbidty Index), stroke location (bilateral, left, right, stem involvement, recurrent), stroke type (hemorrhagic, infarction), functional scales (modified Barthel Index, mini-mental state examination, clinical dementia rating), laboratory findings (blood urea nitrogen, abnormal creatinine, abnormal creatinine, hemoglobin, C-reactive protein, glycated hemoglobin, serum glucose), VFSS findings (oral phase delay, premature bolus loss, decreased laryngeal elevation or epiglottic folding, aspiration, vallecular residue, pyriform sinus residue, pharyngeal trigger delay, abnormal upper esophageal sphincter relaxation). All information reflected the patient's status before or at the time of PEG insertion.	No statistical difference between the removal and sustaining groups for demographic data, medical history, stroke lesion location, stroke lesion type, functional scales, laboratory findings, and in 3 of 5 VFSS findings. But, the VFSS findings of premature bolus loss ($P = .032$), aspiration ($P = .012$), and pharyngeal trigger delay ($P = .010$) were more prevalent in the sustaining group than in the removal group. After adjusting for age and Charlson Comorbidity Index, absence of aspiration ($P = .045$, OR: 11.4) and absence of pharyngeal trigger delay ($P = .036$, OR: 15.1) were identified as independent predictive factors for PEG removal. Statistical tests: Mann-Whitney *U* test, Pearson's χ^2, Fisher's exact tests, and multiple logistic regression analysis.

OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; VFSS, videofluoroscopic swallowing study; VSS, video swallow study.

duration of inpatient rehabilitation[18] found that age is a significant predictor/factor, whereas the study by Teasell et al,[21] with a longer follow-up duration (1 year) after discharge from a rehabilitation unit, did not find age as a significant factor. The 2 remaining studies that investigated the impact of age[19,20] included a range of follow-up durations across patient populations and did not provide exact follow-up information. The cumulative findings could suggest that age is a predictor/factor influencing tube removal in the early stages of stroke recovery but a less important factor in the later stages. The lack of clarity regarding age as a significant predictor/factor for tube removal is in line with research on the impact of age on stroke outcome in general. Whether numeric age is directly related to stroke outcome is still controversial; instead, the discussion is that other factors associated with age (eg, comorbidities, fitness levels) are the true drivers for outcome differences.[24] In addition, it has been discussed that age indirectly imposes different prognostic expectations that influence the care that a patient receives.[25]

Another disagreement across studies is the importance of medical history, presence of comorbidities, and stroke characteristics on PEG/J tube removal. Yi et al[19] did not find statistical differences between patients with and without PEG removal, but Ickenstein et al[18] and Scolapio et al[22] identified medical history, comorbidities, and stroke characteristics as significant factors. Again Ickenstein et al and Scolapio et al used a shorter follow-up duration than did Yi and colleagues. Yi et al also reported a drastically longer time between stroke onset and PEG placement (367 days [range, 38–1215 days] and 289 days [range, 14–4529 days] for patients with and without PEG removal, respectively) than Teasell et al[21] (8.4 days) and Ickenstein et al[18] (PEG/J placed during the inpatient rehabilitation stay). This difference in the latencies between stroke and PEG/J tube placement suggests variations in not only practice patterns but also the studied patient cohorts—both of which may be the cause of divergent findings.

Beyond the identification of potential predictors and factors, the 6 studies showed that PEG/J tube removal can occur after months or even years following stroke or tube placement (this is in line with findings from James et al[15] and Raha et al[26]). This raises the question of how and when patients can best be identified for tube removal. Ickenstein et al[18] were the only researchers who investigated length of rehabilitation hospital stay as an associated factor for tube removal. They found that patients with a tube removal prior to discharge had a significantly longer rehabilitation stay versus patients without tube removal (69.7 vs 50.3 days). In a previous study not included in this review, Krieger and colleagues[27] also found that a longer length of stay for in-patient rehabilitation was a predictor for tube removal in a mixed group of patients with stroke with PEG and nasogastric tubes. Ickenstein and colleagues hypothesized that patients who stayed longer in inpatient rehabilitation had longer access to the rehabilitation team and, therefore, greater opportunities to resume oral feeding.[18] Access to health care, especially to reevaluations for chronic patients, should be a target in future studies. Since we can expect that at least some patients will recover their swallow function even after years (to the extent that a tube can be removed), future studies should focus on the implementation and standardization of protocols to reevaluate patients with dysphagia after stroke for potential tube removal.

Limitations

Several limitations warrant attention. All included studies suffered from a relatively small sample size and were likely underpowered (in total varying from 32–83 included patients), especially for patients with PEG/J removal (varying from 5–24 patients). Furthermore, all studies were retrospective and therefore faced typical limitations for those study designs. The focus of our review was patients with dysphagia after stroke. All included studies defined their patient cohorts according to our criteria; however, Scolapio et al[22] conducted the only study that did not exclusively include patients with dysphagia after stroke (21 of 32 patients were assessed as dysphagic). A quantitative comparison of findings across studies is not feasible, as all 6 studies varied broadly regarding setting, design, statistical methods, and included patients.

None of the included studies in this review gave sufficient information about patient care and treatment between PEG/J placement and removal/nonremoval. However, these are well-known factors that influence the success of tube removal. For example, weaning of a PEG/J tube requires a multidisciplinary involvement of speech-language pathologists, dietitians, nurses, and physicians[28]; moreover, reevaluation by the clinical team of tube-fed patients is necessary to avoid a delay or to miss a tube removal.[28-31]

Interestingly, none of the studies described how patients were identified for PEG/J removal. The criteria for PEG/J removal could have varied widely across the studies and affected the selection of patients with or without PEG/J removal. Based on that lack of information, it remains unclear whether most of the studies and the identified predictors and factors are generalizable.

Due to the main objectives of our systemic review, we did not include intervention studies. However, several studies investigating specific dysphagia treatments showed that such treatment can result in PEG/J tube removal.[11,12,32-35] Therefore, providing specific dysphagia therapy could be a main factor to promote PEG/J removal, but it was not addressed in our review.

Conclusion

Our systematic review revealed that very little is known and less is agreed on regarding predictors/factors associated with PEG/J tube removal in patients with dysphagia after stroke. This topic appears to be underrepresented in the current literature, with (1) available studies based on a rather lower level of evidence (we found no published prospective and/or

randomized studies) and (2) studies that had divergent findings with regard to important predictors/factors. We found that most of the identified predictors/factors are associated with disease severity. However, the generalizability of these predictors/factors is reduced due to the methodological limitations and lack of comparability among the studies. The strongest predictor/factor appears to be absence of aspiration on MBSS. This emphasizes the need for instrumental swallow assessments in the care of patients with dysphagia after stroke.

We strongly believe that additional knowledge about predictive parameters is much needed, because it could help patients, families, and health care providers estimate and plan patients' needs and resources in the long term (options of care and discharge options). Future studies are needed to investigate predictors/factors arising from differences in health care and rehabilitation that influence PEG/J tube removal in patients with dysphagia after stroke.

Statement of Authorship

J. Wilmskoetter and H. S. Bonilha equally contributed to the conception of the research and to the acquisition, analysis, and interpretation of the data; and J. Wilmskoetter drafted the manuscript. All authors contributed to the design of the research, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Implementation of an Aggressive Enteral Nutrition Protocol and the Effect on Clinical Outcomes

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Abstract

Background: Macronutrient deficiency in critical illness is associated with worse outcomes. We hypothesized that an aggressive enteral nutrition (EN) protocol would result in higher macronutrient delivery and fewer late infections. *Methods:* We enrolled adult surgical intensive care unit (ICU) patients receiving >72 hours of EN from July 2012 to June 2014. Our intervention consisted of increasing protein prescription (2.0–2.5 vs 1.5–2.0 g/kg/d) and compensatory feeds for EN interruption. We compared the intervention group with historical controls. To test the association of the aggressive EN protocol with the risk of late infections (defined as occurring >96 hours after ICU admission), we performed a Poisson regression analysis, while controlling for age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and exposure to gastrointestinal surgery. *Results:* The study cohort comprised 213 patients, who were divided into the intervention group (n = 119) and the historical control group (n = 94). There was no difference in age, sex, BMI, admission category, or Injury Severity Score between the groups. Mean APACHE II score was higher in the intervention group (17 ± 8 vs 14 ± 6, $P = .002$). The intervention group received more calories (19 ± 5 vs 17 ± 6 kcal/kg/d, $P = .005$) and protein (1.2 ± 0.4 vs 0.8 ± 0.3 g/kg/d, $P < .001$), had a higher percentage of prescribed calories (77% vs 68%, $P < .001$) and protein (93% vs 64%, $P < .001$), and accumulated a lower overall protein deficit (123 ± 282 vs 297 ± 233 g, $P < .001$). On logistic regression, the intervention group had fewer late infections (adjusted odds ratio, 0.34; 95% confidence interval, 0.14–0.83). *Conclusions:* In surgical ICU patients, implementation of an aggressive EN protocol resulted in greater macronutrient delivery and fewer late infections. (*Nutr Clin Pract*. 2017;32:175-181)

Keywords

enteral nutrition; nutritional support; intensive care unit; critical illness; clinical protocols; protein

Background

The prevalence of baseline malnutrition in hospitalized patients is estimated around 40% and is thought to be even higher in the critically ill.[1–3] Well-nourished patients can develop malnutrition during hospitalization due to a combination of disease effects and iatrogenic underfeeding. This has potentially important implications, as malnutrition has been associated with increased healthcare costs, prolonged hospital length of stay (LOS), greater readmission rates, more complications, and higher in-hospital mortality.[1,3–7]

While the delivery of "sufficient" nutrition has been associated with improved outcomes,[8,9] it is well recognized that actual delivery of essential macronutrients (ie, calories and protein) falls short of ideal.[8,9] Worldwide, only about 50%–60% of prescribed calories and proteins are actually delivered, with the surgical patients receiving comparatively less macronutrients than their medical counterparts.[10–13] However, high-performing intensive care units (ICUs) have demonstrated an ability to consistently deliver >80% of prescribed calories and protein via enteral nutrition (EN).[14]

Recently, trials comparing permissive (or intentional) underfeeding or trophic rate feeding to "full" EN have reported no difference between the 2 strategies in terms of ventilator-free days, infectious complications, and 60-day mortality.[15,16] This has led some to conclude that early iatrogenic starvation is noninferior and potentially beneficial for critically ill patients.[17,18] Close examination of the patient population

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studied reveals that these trials enrolled predominantly young, mostly medical patients who were fairly well nourished. These results may not be appropriately extrapolated to older, surgical, and malnourished patients. Conversely, a robust body of evidence supports the stance that early and aggressive EN confers both nutrition and nonnutrition benefits.[13,19] Nonnutrition benefits include improving gastrointestinal (GI) absorptive capacity and motility, maintaining gut integrity, promoting insulin sensitivity, and attenuating oxidative stress.[19] These benefits are likely to be greatest in those patients requiring prolonged ICU stay. Importantly, a distinction must be made between infections present upon ICU admission or developing early in the course of critical illness and those that occur in a delayed fashion. Nutrition therapy is unlikely to have a significant effect on the former type of infection but may have a more discernible influence on the latter. We hypothesized that an aggressive EN protocol would result in higher calorie and protein delivery and that this improved macronutrient delivery would be associated with lower rates of late infections in the surgical ICU.

Materials and Methods

This study was approved by our local institutional review board, and the requirement for informed consent was waived, given that this was a quality improvement initiative. We enrolled adult (age ≥18 years) surgical ICU patients who received >72 hours of EN from July 2012 to June 2014. The data were collected prospectively in a dedicated research registry. Exclusion criteria were as follows: EN prior to ICU admission and previous ICU stay during the same hospital admission. Data collected included demographic information such as age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Charlson Comorbidity Index, and the admission category (elective surgery, emergent surgery, trauma, or nonoperative). The 2 surgical ICUs admit trauma and postsurgical patients after elective and emergent surgery in the following specialties: general surgery, surgical oncology, hepatobiliary surgery, neurosurgery, thoracic surgery, vascular surgery, transplantation, urology, orthopedic surgery, gynecology, otolaryngology, plastic surgery, and trauma (operative and nonoperative). Medical patients are admitted as well when there is overflow from the medical ICU. Burn and cardiac surgical patients are not admitted to the surgical ICUs. Nutrition information included assessment of initial nutrition status by registered dietitians (RDs), hours from ICU admission to EN initiation, prescribed calories, actual calories received, prescribed protein supplementation, actual proteins received, cumulative ICU caloric deficit, and cumulative ICU protein deficit. Daily caloric and protein deficits were calculated by subtracting the actual calories/protein received from the 24-hour prescription goal (based on American Society for Parenteral and Enteral Nutrition [ASPEN] guidelines). Nutrition data were collected until oral intake was initiated and sustained, the patient was discharged from the ICU, 14 consecutive days of EN, or patient death. After transition to oral intake, the RD continued to follow the patient, although formal calorie counts were not routinely performed. Sustained oral intake was defined as >50% intake of meals. Clinical outcomes assessed included hospital length of stay (LOS), ICU LOS, 28-day ventilator-free days (VFDs), complications, 30-day mortality, in-hospital mortality, and discharge destination (home/jail, rehabilitation, skilled nursing facility) in survivors. Complications were further subdivided into total complications, infectious complications, GI complications, and cardiac complications. Infectious complications recorded were pneumonia, urinary tract infection, bloodstream infection, and surgical site infection; cardiovascular complications included new-onset atrial fibrillation, congestive heart failure, and myocardial infarction; and GI complications included emesis, diarrhea, abdominal distention, and gastric residual volume (GRV) >500 mL. Infections were further classified as early (present on admission or occurring <96 hours after ICU admission) or late (occurring after 96 hours after ICU admission). BMI was determined by one of the following methods in order of decreasing priority: review of electronic medical records from prior encounters, preoperative weight and height as documented by the anesthesiologist, or measurements taken shortly after ICU admission.

The initial calorie and protein targets were 25 kcal/kg/d and approximately 1.5 g/kg/d based on actual body weight. Ideal body weight was used for BMI >30. All patients received consultation by a licensed RD within 48 hours of EN initiation. Standard polymeric formula (1 kcal/cc) was initiated and subsequently adjusted as necessary during routine follow-up assessment. Calories derived from propofol were taken into consideration by the RDs when assessing and prescribing formula, and care was taken to avoid overfeeding patients. In previously well-nourished patients, parenteral nutrition (PN) is not initiated until enteral intake (PO or EN) has been inadequate for 10 days. Early supplemental PN is not routinely used but is considered selectively in baseline malnourished patients.

The surgical intensivists in our practice believe that delivering >80% of calorie and protein requirements to critically ill patients is a desirable goal.[20] Therefore, we have undertaken intensive quality improvement efforts to analyze our practice and identify opportunities for improvement. In October 2013, we changed our standard surgical ICU policy by increasing our protein prescription targets and also allowing for compensatory feedings after EN interruptions with the intent to improve overall calorie and protein delivery. This quasi-experimental study compares patients before and after the policy change.

Intervention

Our intervention consisted of increasing protein prescription targets (approximately 2.0 g/kg/d) and implementing compensatory feeds around the time of EN interruption. Based on accumulating evidence of the importance of protein delivery, we chose to selectively increase our protein prescription.[21–23]

This was relatively easier to achieve because of the availability of protein supplements: Beneprotein (Nestlé, Vevey, Switzerland; whey powder 25 kcal/6g protein per packet) or Prosource liquid protein (Medline Industries, Mansfield, MA; 60 kcal/15 g protein per packet). Of note, Beneprotein requires 120 mL of carrier fluid per 6-g packet, and Prosource requires 90 mL of fluid per 15-g packet. Ultimately, clinical judgment was exercised when deciding how much protein could be reasonably prescribed, taking into consideration the amount of required carrier fluid and the number of packets required. When EN was interrupted and then subsequently resumed (eg, for an operation or for airway management), the amount of volume "lost" during the interruption was calculated and then subsequently administered to the patient by temporarily increasing the hourly rate of EN up to a maximum of 150 mL/h to target delivery of >80% of prescribed volume by the end of the 24-hour midnight-to-midnight time period. The protocol was publicized and promoted, but the study staff did not actively intervene to enforce compliance, and all decisions were ultimately left to the clinical team.

Statistical Analysis

Continuous variables were summarized using mean ± standard deviation (SD) or median with interquartile range (IQR) and compared using 2-sample *t* test or Wilcoxon rank-sum tests, whichever is more appropriate, between intervention and control groups. Categorical variables were summarized using frequency with percentage and compared using χ^2 tests. The numbers of complications were compared using Poisson models. To test the association of the aggressive EN protocol with the risk of late infections (defined as occurring >96 hours after ICU admission), we performed a Poisson regression analysis while controlling for age, sex, BMI, APACHE II score, and exposure to GI surgery.

Results

The study cohort comprised 213 patients, who were divided into the intervention group (n = 119) and the control group (n = 94). There was no difference in age, sex, BMI, admission category, or Injury Severity Score between groups (Table 1). Mean APACHE II score was higher in the intervention group (17 ± 8 vs 14 ± 6, $P = .002$) and median Charlson Comorbidity Index was higher in the intervention vs control group (3: IQR 1–5 vs 2: IQR 0–3; $P < .001$, respectively). A higher percentage of patients in the intervention group received additional protein supplementation (58% vs 28%, $P < .0001$), and the intervention group received significantly more calories (18.6 [5.0] kcal/kg/d vs 16.5 [5.9] kcal/kg/d, $P = .005$) and protein (1.2 [0.4] g/kg/d vs 0.8 [0.3] g/kg/d, $P < .0001$), received a higher percentage of prescribed calories (77% vs 68%, $P = .0004$) and protein (93% vs 64%, $P < .0001$), and accumulated a lower overall protein deficit (123 [282] g vs 298 [233] g, $P < .0001$) compared with control patients (Table 2). The ICU LOS and hospital LOS were both significantly shorter in the intervention group (10 [7–17] vs 15 [10–27] days, $P = .0003$ and 20 vs 29 days $P < .0001$, respectively). In the intervention group, there was a trend of fewer late infections (mean 0.7 vs 0.9, $P = .07$). In the Poisson regression analysis adjusting for age, sex, BMI, APACHE II score, and GI surgery, implementation of the aggressive EN protocol was associated with a significantly lower risk of late infection (adjusted risk ratio, 0.69; 95% confidence interval [CI], 0.50–0.95; $P = .024$).

Discussion

In this before-and-after study, introduction and implementation of a more aggressive EN protocol was associated with a greater percentage of calorie and protein delivery, as well as lower cumulative protein deficits. These improvements in nutrition delivery after the new EN protocol was introduced were associated with a lower risk of late (>96 hours after ICU admission) infections.

Our results are consistent with others. In a prospective multicenter observational study, Heyland et al[24] also demonstrated that greater amounts of delivered calories and protein were associated with fewer late infectious complications, although the association just missed statistical significance. The new protocol was well tolerated, as evidenced by the fact that there was no observed increase in GI complications or total complications.

Although there is little debate that EN protocols reduce practice variability and improve delivery,[25,26] we recognize that all protocol components may not be appropriate for all patients. Furthermore, despite best intentions and considerable effort, all components of a protocol bundle may not be optimally implemented. Others have described the process of developing and implementing tailored interventions to overcome barriers to increasing EN delivery to critically ill patients.[27–29] In our study, we attempted to do the same using a multidisciplinary focus group to identify barriers, facilitate implementation, and evaluate outcomes. Peev et al[30] have previously reported that the majority of EN interruptions in the surgical ICU were unavoidable. Therefore, rather than attempt to decrease the frequency of interruptions, we decided to appropriately compensate for the interruptions instead. In addition, we recognized that protein delivery was intimately tied to caloric delivery when the sole source of protein was tube feeds. Therefore, our revised protocol placed more emphasis on increasing protein modular delivery via syringe, which could be given independently of tube feedings. These medical foods are listed in the electronic medical record and are scanned and recorded like medications, improving the accuracy of data recorded in the medical record.

Our study was not intended to identify the optimal amount of calories/protein to *prescribe* to surgical ICU patients but rather to optimize our *delivery* of nutrition once a calorie/protein goal was determined. We sought to better align our practice with current recommendations.[31] Not all studies have demonstrated benefit of early and aggressive nutrition therapy

Table 1. Demographic Data and Clinical Outcomes.[a]

Characteristic	All (N = 213)	Control (n = 94)	Intervention (n = 119)	*P* Value
Age, y	61.3 ± 18.0	62.6 ± 17.1	60.2 ± 18.6	.33
Male	152 (71%)	67 (71%)	85 (71%)	.98
BMI	27.4 ± 6.5	27.2 ± 6.3	27.5 ± 6.6	.71
APACHE II score	15.7 ± 7.5	14.0 ± 6.3	17.1 ± 8.1	.002
CCI	2 [0–4]	2 [0–3]	3 [1–5]	.001
Injury Severity Score[b]	29.7 ± 13.0	31.6 ± 12.2	28.4 ± 13.5	.32
Admission category, %				.41
Elective	28	33	24	
Emergency surgery	17	17	17	
Trauma	30	29	31	
Nonoperative (medical)	25	21	29	
Hospital LOS[c]	24 [15–38]	30 [20–42]	21 [14–32]	.0004
ICU LOS[c]	11 [7–20]	15 [9–26]	10 [7–17]	.0004
28-day VFD	20 [14–24]	19 [11–25]	21 [16–24]	.092
Total complications	2 [1–3]	2 [1–3]	2 [1–4]	.77
Infectious complications	1 [0–2]	1 [0–2]	1 [0–2]	.63
Cardiovascular complications	0 [0–1]	0 [0–1]	0 [0–1]	.66
Gastrointestinal complications	0 [0–1]	0 [0–1]	0 [0–1]	.92
30-day mortality	29 (13.6)	7 (7.4)	22 (18.5)	.038
In-hospital mortality	38 (17.8)	15 (16.0)	23 (19.3)	.67
Discharge disposition				.026
Home	33 (15.5)	12 (12.8)	21 (17.6)	
Rehabilitation	116 (54.5)	61 (64.9)	55 (46.2)	
SNF	23 (10.8)	5 (5.3)	18 (15.1)	
Death	41 (19.2)	16 (17.0)	25 (21.0)	

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCI, age-adjusted Charlson Comorbidity Index; ICU, intensive care unit; LOS, length of stay; SNF, skilled nursing facility; VFD, ventilator-free day.
[a]Intervention patients had higher APACHE II scores. Values are presented as mean ± standard deviation, number (%), or median [interquartile range] unless otherwise indicated.
[b]Only available in 64 patients.
[c]Excluding patients who died in the hospital.

in critically ill patients; some have even concluded harm associated with early, aggressive EN.[32,33] These studies must be interpreted with caution, though, as some did not adjust for the confounding bias of duration of exposure to EN or that of timing of advancement to oral diet. For example, patients who are less critically ill and do not require prolonged ICU support are likely to do well despite minimal EN in the first few ICU days. Similarly, a patient who is taking oral nutrition per os may be incorrectly coded as receiving 0% nutrition because of the lack of tube feedings. When these factors are taken into consideration and the effect is recalculated, increasing nutrition adequacy is once again associated with improved outcomes.[34]

The EDEN trial randomized 1000 patients with acute lung injury requiring mechanical ventilation to either trophic rate enteral feeding or "full" enteral feeding.[16] This large, multicenter trial was unable to demonstrate a difference between groups in their primary outcome, 28-day VFDs, despite adequate separation of groups. This may lead some to conclude that intentional underfeeding is equivalent to early and adequate feeding in *all ICU* patients. However, it is important to recognize that this trial recruited predominantly medical patients who were relatively younger (mean age 52 years) than our patient cohort. Trauma patients comprised <5% of all patients. Thus, their conclusions may not be applicable to older, surgical patients. In addition, the "full" feeding group received approximately 1300 kcal/d; when divided by the average weight of 87 kg in that group, this amounts to approximately 15 kcal/kg/d. This falls far short of the recommended 25–30 kcal/kg/d currently recommended by ASPEN, so it is debatable whether the "full" feeding group actually received adequate nutrition. Another recently published study, the PermiT trial, randomized 894 critically ill adults to either permissive underfeeding (46%–60% of calculated requirements) or standard enteral feeding (70%–100%) and concluded no difference in the primary end point of 90-day mortality.[15] In this study, the separation of groups was less, with the underfeeding group receiving an average of 835 kcal/d compared with 1299 kcal/d in the standard feeding group. As in the EDEN trial, the actual caloric delivery of the control group ("standard") was about 16 kcal/kg/d, which is much less than recommended.

Table 2. Nutrition Prescription and Delivery Comparing Control to Intervention.[a]

Characteristic	All (N = 213)	Control (n = 94)	Intervention (n = 119)	*P* Value
Nutrition				
PN	20 (9)	9 (10)	11 (9)	.93
Protein supplements	95 (45)	26 (28)	69 (58)	<.0001
Propofol	185 (87)	87 (93)	98 (82)	.029
Initiation of enteral nutrition				.46
Within 48 hours after admission	143 (67)	63 (67)	80 (67)	
48–72 hours after admission	30 (14)	10 (11)	20 (17)	
72–96 hours after admission	14 (7)	7 (7)	7 (6)	
>96 hours after admission	26 (12)	14 (15)	12 (10)	
Baseline nutrition prescription				
Mean calorie, kcal/d	1703 ± 349	1708 ± 389	1699 ± 316	.86
Mean calorie, kcal/kg/d	24.2 ± 5.2	23.7 ± 6.2	24.7 ± 4.2	.22
Mean protein, g/d	90 ± 21	87 ± 21	93 ± 21	.025
Mean protein, g/kg/d	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	<.0001
Daily nutrition				
Mean calories, kcal/d	1239 ± 382	1184 ± 406	1282 ± 357	.064
Mean calories, kcal/kg/d	17.7 ± 5.5	16.5 ± 5.9	18.6 ± 5.0	.005
Mean protein, g/d	71 ± 28	55 ± 22	83 ± 26	<.0001
Mean protein, g/kg/d	1.0 ± 0.4	0.8 ± 0.3	1.2 ± 0.4	<.0001
ICU nutrition deficit				
Mean daily caloric deficit, kcal/d	471 ± 375	524 ± 436	429 ± 313	.075
Mean protein deficit, g/d	21 ± 26	32 ± 22	12 ± 26	<.0001
Mean total caloric deficit, kcal	4595 ± 4274	4950 ± 4418	4315 ± 4155	.29
Mean total protein deficit, g	200 ± 275	298 ± 233	123 ± 282	<.0001
Percent calories delivered, %	73 ± 20	68 ± 19	77 ± 19	.0004
Percent protein delivered, %	80 ± 30	64 ± 20	93 ± 30	<.0001

ICU, intensive care unit; PN, parenteral nutrition.
[a]Values are presented as mean ± standard deviation or number (%). Intervention patients were prescribed more protein and received significantly more calories and protein. Protein deficits were lower in the intervention group.

Protein intake was approximately 57 g/d in both groups; with an average weight of approximately 80 kg in both groups, this meant that both groups received only about 0.7 g/kg/d, which is far short of the 1.2–2.0 g/kg/d currently recommended by ASPEN.[35] In both these studies, it is possible that the primary end points, VFDs and mortality, were not sensitive to differences in nutrition adequacy. For example, a post hoc analysis of a different trophic vs full EN study by Rice et al[36] revealed that patients receiving full EN were more likely to be discharged home without assistance rather than to a rehabilitation facility compared with those receiving only trophic nutrition. Similarly, 1-year follow-up of the EDEN survivors demonstrated a higher 12-month cumulative incidence of admission to a rehabilitation facility in the trophic group compared with the "full" EN group (23% vs 15%, $P = .01$).[37] Yeh et al[38] have also demonstrated that nutrition adequacy in surgical patients is associated with higher rates of discharge home. It should also be pointed out that most patients in both the EDEN and the PermiT studies had a BMI of approximately 29. A large international study had previously demonstrated that patients with a BMI from 25–35 are unlikely to benefit from increased calories.[13] Recently, a nutrition risk assessment tool, the modified Nutrition Risk in the Critically Ill (NUTRIC) score, has been described and externally validated for ICU patients.[39] Rahman et al[39] have demonstrated that the effect of nutrition adequacy on 28-day mortality is strongly influenced by nutrition risk, with a strong positive association for patients with a high NUTRIC score and diminishing association for lower NUTRIC scores. Thus, the concept of nutrition risk is important when considering nutrition interventions, as enrollment of patients with low nutrition risk is likely to result in "negative" trial findings, no matter what end point is chosen.

The practice of compensatory nutrition has been described by others.[40,41] We felt that it could be safely performed by gradually refeeding the missed nutrition by temporarily increasing the hourly rate (to a maximum of 150 mL/h). During this time, patients were carefully monitored for signs of intolerance. An alternative strategy is to provide the missing nutrition as a single bolus injection. A recent pilot study demonstrated the feasibility and safety of providing compensatory and perioperative EN.[42]

Although we consider our results to be important, we must acknowledge the limitations. First, this study was performed at a single urban academic hospital, and the surgical population

consisted mainly of trauma, general surgical, and orthopedic patients. Therefore, we cannot generalize our findings to other populations in other practice settings. Second, our study design precludes us from drawing any conclusions about causality, as we can only demonstrate association. While we have attempted to control for likely confounders, it is possible that uncontrolled differences in the 2 patient cohorts were responsible for the observed findings. For example, despite increased average APACHE II scores following implementation, we noticed a dramatic decrease in ICU LOS and hospital LOS without a significant difference in 28-day VFD. It is likely that other changes in hospital processes of care were simultaneously occurring to account for these changes in outcomes. In addition, it is concerning that the 30-day mortality was noted to significantly increase after implementation (although total in-hospital mortality was about the same). As Table 1 illustrates, whereas only about half (7 of 15) of the deaths occurred in the first 30 days in the control group, nearly all (22 of 23) hospital deaths in the intervention group occurred in the first 30 days. Careful review of those deaths revealed that the majority of the deaths occurred in older patients with either overwhelming injury or overwhelming multiple-organ failure at ICU admission who were transitioned to comfort care in the first 2 weeks (data not shown). It is unlikely that aggressive EN contributed to their 30-day mortality. Third, because this was an observational study, we did not attempt to enforce compliance with the new protocol. Despite significant improvement, our efforts still fell short of delivering the recommended 25 kcal/kg/d and 1.5 g/kg/d. For example, we could not always prescribe 2.0 g/kg/d in every patient during the intervention period because of the considerable amount of carrier volume required. Clinical judgment was preferred to blind adherence to the protocol as written. Therefore, opportunities for improvement remain, and we continue to search for ways to improve macronutrient delivery. The calculated requirements were made according to ASPEN recommendations,[35] although we acknowledge that they are less accurate than the gold standard, measured resting energy expenditure. However, indirect calorimetry is not routinely used for all ICU patients at our hospital, and this is another acknowledged limitation of this study. In addition, while all intensivists felt comfortable with the increased protein prescription (and supplementation) in our population, there was variable acceptance of the compensatory feedings, as this is a relatively new concept, which has not been extensively studied. Some felt uncomfortable providing EN at a rate of up to 150 mL/h. We felt it was prudent to allow for clinician judgment. However, there is accumulating evidence that the compensatory feeding strategy, a volume-based (rather than rate-based) approach to EN, is safe and well tolerated.[42,43] With the recognition that implementation and compliance were <100%, the impact may be even greater after full protocol maturation. Because of the before-after study design, one potential flaw is that our findings may be due to secular trends rather than the protocol itself. We feel this is unlikely for 2 reasons. Because the control and intervention years were back-to-back consecutive years, it is improbable that the 2 protocol interventions (increased protein prescription and increased delivery of calories and protein) had significantly changed in a similar direction by some trend unrelated to the more aggressive feeding protocol. In addition, it is worth noting that APACHE II and Charlson Comorbidity Index were higher in the intervention group, implying a higher severity of illness and more baseline comorbid conditions compared with the control group. Unfortunately, we did not calculate Sequential Organ Failure Assessment scores, another measure of critical illness disease severity, and we acknowledge this as a limitation of this study. Finally, we did not track nutrition delivery *after* 14 days, ICU discharge, or progression to oral intake mainly because of the feasibility and inaccuracy of caloric counting. While this is a limitation, it may also be interpreted as a reemphasis of the message that nutrition practices early in the hospital/ICU course may be influential on later outcomes, *regardless* of how much nutrition is delivered afterward. This is analogous to early goal-directed therapy, early initiation of appropriate antimicrobial therapy, and "hemostatic" resuscitation in massive transfusion.

In conclusion, we report that a more aggressive EN protocol increasing protein prescription targets and enabling compensatory feedings was associated with improved nutrient delivery and decreased incidence of late (>96 hours after ICU admission) infections. The implications of these findings are that early aggressive EN may be of more benefit for patients requiring longer ICU stay and the effects of macronutrient adequacy may not be evident in the first few ICU days. These results should be confirmed in randomized controlled trials.

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Statement of Authorship

D. D. Yeh contributed to the conception/design of the research; D. D. Yeh, C. Cropano, E. Fuentes, S. A. Quraishi, and Y. Chang contributed to the acquisition, analysis, or interpretation of the data; D. D. Yeh drafted the manuscript; D. D. Yeh, C. Cropano, S. A. Quraishi, E. Fuentes, H. M. A. Kaafarani, J. Lee, Y. Chang, and G. Velmahos critically revised the manuscript; and D. D. Yeh agrees to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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Is There a Discrepancy? Comparing Enteral Nutrition Documentation With Enteral Pump Volumes

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Abstract

Introduction: Nutrition therapy is essential to the care of critically ill patients. Information that is used to calculate the differences between patients' nutrition prescription and actual provision may be flawed due to errors in manually recording the amount of enteral nutrition (EN) provided. This study's purpose was to evaluate the accuracy of the EN volume delivered as recorded in the electronic medical record (EMR) relative to the EN volume retrieved from the EN pump. *Methods:* This prospective, blinded, observational study occurred from June 2014 to April 2015 with a total of 218 patients. Patients were identified for the study based on their intensive care unit (ICU) admission and need for EN support. Patients were ICU patients receiving EN support. *Results:* The major result of this study was that 14% of patients' EN volumes were underdocumented and 26% were overdocumented. *Conclusion:* These results support the need for a technological platform that directly transmits EN pump volumes in real time to the EMR. (*Nutr Clin Pract*. 2017;32:182-188)

Keywords

enteral nutrition; nutritional support; critical illness; infusion pumps; energy intake; intensive care unit; electronic health record; medical records

Nutrition therapy is essential to the care of critically ill patients. Differences frequently exist between prescribed nutrition requirements and the actual provision of nutrition support.[1,2] It is possible that the information used to calculate the differences between patients' nutrition prescription and actual provision may be flawed due to errors in manual recording of the amount of enteral nutrition (EN) provided. The incompatibility between commercial EN pumps and the electronic medical record (EMR) requires staff to manually enter the volume of EN infused into the EMR. If these data are flawed, there will be unjustified changes in the nutrition prescription. The importance of adequate nutrition support in patient care entails that the data used must be accurate. In addition, accurate documentation of EN provision is crucial in researching patient quality of care and developing procedures to address care inadequacies. The purpose of this study was to compare the accuracy of the EN volume recorded by the registered nurse (RN) in the EMR relative to the EN volume retrieved from the EN pump in an intensive care unit (ICU) environment.

Methods

This prospective, blinded, observational study took place from June 2014 to April 2015 at a 500-bed, regional level 1 trauma center and tertiary care teaching facility in Nassau County, New York. The institutional review board (IRB) at North Shore-Long Island Jewish Health System approved this study.

The study's primary aim was to evaluate the accuracy of the EN volume delivered as recorded in the EMR relative to the EN volume retrieved from the EN pump. The study's population was ICU patients aged 18 years or older who received EN therapy. Pregnant women and prisoners were excluded from the sample. A total of 218 patients were enrolled in the study. The Compat Clinical Enteral Feeding Pump (Nestlé Health Care, Minnetonka, MN) was used; its long-term memory function allowed serial collection of EN volume delivered for comparison to documentation in the EMR. The accuracy of this pump is listed as ±10%.[3] The standard clinical process was not altered for this study. Physicians ordered EN using a volume-based enteral feeding protocol, and a registered dietitian nutritionist (RDN) completed a nutrition assessment. Hourly EN volumes were manually entered by the

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RN into the EMR, which then calculated total daily EN volumes. The RDN separately collected serial measures of each patient's EN volume using the pump's long-term memory function. Critical care RNs were secondary participants due to their role in recording EN volume into the EMR. Collection of pump data is a routine part of nutrition reassessments and quality improvement measures of the nutrition service. RNs are accustomed to seeing RDNs obtain EN pump data. Therefore, there was no observational bias or influence of the Hawthorne effect on the RNs. The Hawthorne effect is a type of reaction in which individuals alter their behavior due to their consciousness of being observed. The data used from the long-term pump memory were then used to compare the accuracy of the EMR documentation.

Data collection was obtained every 1–3 days, from the time of EN initiation to cessation of the therapy for each patient. As patients' duration of EN therapy varied, each patient could potentially have multiple pump data collections. A set for this study was defined as ≥1 days of EN pump data collection. These multiple sets of pump data collection were collapsed to form individual patient-level means to address potential dependency issues. Each EN pump–EMR comparison volume set was treated as an independent observation. The collapsed means were used in each of the statistical analyses and to estimate the outcome measures. Demographic information, including age, sex, ethnicity, reason for ICU stay, and admission/discharge information, was collected at recruitment from patients' medical records.

Primary Outcome Variables and Statistical Methods

A series of statistical analyses was conducted to investigate whether differences existed between the actual volume displayed in the long-term pump memory and documented volume within the EMR. The first outcome measure consisted of the EN volume retrieved from the EN pump as a percentage of the EN volume documented in the EMR (%PUMP/EMR) to identify the accuracy of the EN volume documentation in percentage terms. The second outcome measure was the volume difference between the EN volumes recorded on the EMR based on the actual volume delivered (%EMR-PUMP DIFF). The final outcome measure took %EMR-PUMP DIFF and expressed it in terms of caloric difference. A percentage was then calculated (%KCALDIFF) by dividing %EMR-PUMP DIFF values by individualized caloric requirement to help standardize measures for comparison. All measures were computed after the patients' observations were collapsed.

The first statistical analysis consisted of calculating descriptive statistics to evaluate the demographic and clinical characteristics of the sample population. A *t* test was used to examine whether a statistical difference existed between patients' EN volume delivered and the EN volume recorded in the EMR.

The second statistical analysis examined differences between the EN pump and EMR volumes at 3 levels of EMR accuracy (%PUMP/EMR): %PUMP/EMR <90%, %PUMP/EMR between 90% and 110%, and %PUMP/EMR >110%. We selected these 3 categories based on a generally accepted level of 10% of either side of 100% as being adequate provision of nutrition. Patients were placed in these groups based on their individual levels. In addition, the unweighted average %KCALDIFF levels were evaluated at each of these EMR accuracy levels.

The final statistical analysis examined the average difference in EN volume between the EN pump and EMR when patients received EN volume outside the clinically acceptable range. Clinically significant deviations were defined as %KCALDIFF amounts that were <–10% or >10% based on what is deemed clinically acceptable delivery for this institution: underfed (<90% of prescribed volume), adequately fed (±10% of prescribed volume), or overfed (>110% of prescribed volume). For this analysis, patients were stratified into 3 groups based on %KCALDIFF levels: %KCALDIFF <10%, %KCALDIFF between −10% and 10% (the clinically acceptable level), and %KCALDIFF >10%.

Statistical analysis was performed including 1-way analysis of variance (ANOVA) to evaluate differences between each of the groups. Tukey's post hoc test was used to investigate any statistical differences that existed between the groups. Robust standard errors were generated using the Huber-White sandwich estimator. All statistical analyses were performed in STATA 14 (StataCorp LP, College Station, TX).[4] Level of significance was set at $P < .05$.

Results

The initial sample population consisted of 218 patients with 812 separate patient observations or sets of EN pump–EMR recorded EN volumes. After adjusting for differences in patient pump volume captures (n = 26), the analytic sample consisted of 192 patients. Based on the available data in the overall sample, there were no statistical differences between the analytic sample and the overall sample. On average, each patient in the analytic sample had 3.42 sets of EN pump–EMR comparison volumes with a minimum number of 1 set and a maximum of 18 sets.

As illustrated in Table 1, the EN volume delivered (1804.2 mL) was statistically different from the EN volume recorded in the EMR (1868.2 mL; $P = .000$). The numerical difference between the EN pump volumes and the EMR (PUMP-EMR) was −64.0 mL, with a mean caloric difference of −43.7 calories. Although the overall difference between the EN pump volume and the EMR documented volume was small on average, when stratified by %PUMP/EMR, the differences become more apparent, as demonstrated in Table 2.

Fifty patients fell below 90% of %PUMP/EMR (range, 62.5%–89.6%), reflecting overdocumentation. Patients were documented to have received more calories than actually provided, an unweighed average difference of 11.6% (%KCALDIFF).

Table 1. Patient Characteristic Summary (n = 192).[a]

Characteristic	Analytical Sample		
	Value	Minimum	Maximum
Demographic variables			
Age, mean (SD), y	65.02 (19.23)	19	97
Sex			
Female	39.06 (n = 75)		
Male	60.94 (n = 117)		
Race			
African American	8.33 (n = 16)		
Asian/Indian	22.40 (n = 43)		
White	69.27 (n = 133)		
Admitted to			
MICU	75.00 (n = 144)		
Trauma	18.23 (n = 35)		
Other admission services[b]	6.77 (n = 13)		
Discharged to			
Patient died	30.73 (n = 59)		
Home	21.88 (n = 42)		
Hospice	3.65 (n = 7)		
Nursing home	14.06 (n = 27)		
Rehabilitation/other health facility[c]	21.88 (n = 42)		
Other/unknown service	7.81 (n = 15)		
Indicator variables, mean (SD)			
EN pump volume, mL/d	1804.2[d] (978.25)	139.0	5085.0
EMR recorded volume, mL/d	1868.2 (1011.5)	105.0	5630.0
Difference of EN pump volume and EMR recorded volume, mL	−64.0 (235.6)	−599.0	1088.2
EN pump volume as a percent of EMR recorded volume (%PUMP/EMR)[e]	98.3 (16.6)	62.5	195.2
Estimated caloric needs, kcal/d	1926.9 (314.6)	1100.0	2950.0
Daily volume difference, mL[f]	−43.7 (198.6)	−457.2	772.6
Difference in daily caloric estimated goals and received amount as a percentage of daily estimated caloric goals (%KCALDIFF)[g]	−2.3 (10.8)	−34.6	37.5

EMR, electronic medical record; EN, enteral nutrition; MICU, medical intensive care unit.
[a]Summary statistics for the indicator variables are based on a sample size of 192 patients. Values are presented as percentages unless otherwise indicated.
[b]Other admission services consist of patients who were admitted to one of the following units: general surgery, neurosurgery, obstetrics and gynecology, orthopedic, or coronary care.
[c]Patient was discharged to a rehabilitation unit or another health facility within or outside of the hospital.
[d]Statistically different ($P \leq .05$) from EN pump volume compared with EMR recorded volume.
[e]Unweighted mean of percentage; calculated as (EN pump volume/EMR recorded volume) × 100.
[f]Calculation based on the calculated difference in EN volumes between the EN feeding pump and EMR, adjusted for continuous days on pump.
[g]Unweighted mean of percentage; calculated as {[(EN pump volume – EMR recorded volume) × (kcal/mL formula)]/Estimated caloric needs}× 100.

Twenty-seven patients fell above 110% (%PUMP/EMR) (range, 110.9%–195.2%), reflecting underdocumentation. Patients were documented to have received fewer calories than actually provided, an unweighed average difference of 16.8%. One hundred fifteen patients had a %PUMP/EMR range within a clinically acceptable limit (range, 90.0%–108.8%) (Table 2). The %PUMP/EMR and %KCALDIFF for each patient are graphically depicted in Figures 1 and 2, respectively.

Despite the estimated differences between the EN volume obtained from the EN pump vs the EMR, most patients (70.3%: n = 135) had clinically acceptable provision of their daily caloric goal. Of the patients studied, 16.7% (n = 32) had %KCALDIFF below clinically acceptable levels, and in 13.0% (n = 25) of patients, %KCALDIFF was above clinically acceptable levels (Table 3). The %KCALDIFF calculations for each patient are graphically depicted in Figure 2.

Discussion

There are several barriers to adequate nutrition support within an ICU setting.[5,6] Both underfeeding and overfeeding could result in change of the nutrition prescription or intervention as they have both been shown to produce deleterious effects.[6] In this study, EN volume documented in the EMR statistically differed from the EN volume obtained from the EN pumps: 26% of patients studied were overdocumented and 14% were

Table 2. EN Volume Recording Error Percentage in the EMR (n = 192).[a]

	Pump Volume <90% of EMR Volume[b] (n = 50)			Pump Volume Within ±10% of EMR Volume[b] (n = 115)			Pump Volume >110% of EMR Volume[b] (n = 27)		
Indicator Variable	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum
EN pump volume, mL/d	187.0	1610.2 (788.6)	3273.3	198.0	1936.4 (1007.1)	5085.0	139.0	1600.3 (1103.8)	3830.7
EMR EN recorded volume, mL/d	230.0	1875.5 (884.8)[c,d]	3843.3	220.0	2007.6 (1044.3)[c,d]	5630.0	105.0	1261.0 (888.8)[d,e,f]	3225.0
Difference of EN pump volume and EMR recorded volume, mL	−599.0	−265.3 (120.8)[c,f]	−43.0	−545.0	−71.2 (117.9)[c,e]	329.3	25.0	339.2 (269.1)[e,f]	1088.2
EN feeding pump volume delivered as a percent of EMR recorded volume (%PUMP/EMR)[b]	62.5	84.6 (5.7)[c,f]	89.6	90.0	96.7 (4.9)[c,e]	108.8	110.9	130.5 (20.5)[e,f]	195.2
Difference in daily estimated caloric goals and received amount as a percentage of daily estimated caloric goals (%KCALDIFF)[g]	−34.6	−11.6 (6.7)[c,f]	1.9	−14.8	−2.8 (5.0)[c,e]	15.5	1.2	16.8 (10.4)[e,f]	37.5

EMR, electronic medical record; EN, enteral nutrition.
[a]Recording error calculated as the difference between EN volume retrieved from EN pump and recorded EMR EN volume.
[b]Unweighted mean of percentage; calculated as (EN pump volume delivered/EMR recorded volume) × 100.
[c]Statistically different ($P \leq .05$) from value reported for pump volume >110% of EMR volume.
[d]The mean pump volume delivered statistically differs ($P \leq .05$) from the mean EMR recorded volume.
[e]Statistically different ($P \leq .05$) from value reported for pump volume <90% of EMR volume.
[f]Statistically different ($P \leq .05$) from value reported for pump volume within ±10% of EMR volume.
[g]Unweighted mean of percentage; calculated as {[(Pump volume – EMR recorded volume) × (kcal/mL formula)]/Estimated caloric needs} × 100.

underdocumented. A 10% span on either side of this spectrum is deemed a clinically acceptable measure of adequate or inadequate nutrition support by this institution. Accordingly, the results of this article illustrate that relying on incorrect EMR documentation can result in inappropriate changes in nutrition interventions.

We have found no studies that address the accuracy of EN documentation in the medical record. Previous studies primarily focused on why patients received inadequate nutrition support while using EMR or flow sheet documentation.[5,6] The discrepancies between the volumes recorded in the EMR compared with the volume obtained from EN pump imply that caution is warranted when using EN documentation to determine EN adequacy. Furthermore, in the research setting, if the EMR volume data are inaccurate, any research based on these data would be invalid.

Many of the factors used to explain why patients receive inadequate nutrition support also explain the discrepancies between the EN pump and the EMR EN volumes. The timing, starting, and restarting of EN as well as overall "interruptions" have been identified as factors associated with patients receiving inadequate nutrition support. O'Meara et al[7] noted that EN was interrupted, on average, 1.13 times per patient day with a mean interruption time of 6 hours. De Jonghe et al[1] identified that digestive intolerance, airway management, and diagnostic procedures caused 85.3% of the interruptions found in their study. Additional factors may include mechanical challenges in relation to the infusion system as well as accuracy of the EN pump itself.[2,8] Staff-related variables may also contribute to the discrepancies between the EMR and the EN pump volume, including staffing levels, staff unfamiliarity with the functionality of the EN pump and/or EMR, patient demands on staff time, using memory or relying on easily misplaced handwritten notes (as opposed to actual pump data), and EN pump withholding for numerous reasons by various personnel. Historically, RN practice has focused on documenting a static run rate, but facilities are more commonly using volume-based protocols that can change run rates throughout the day.

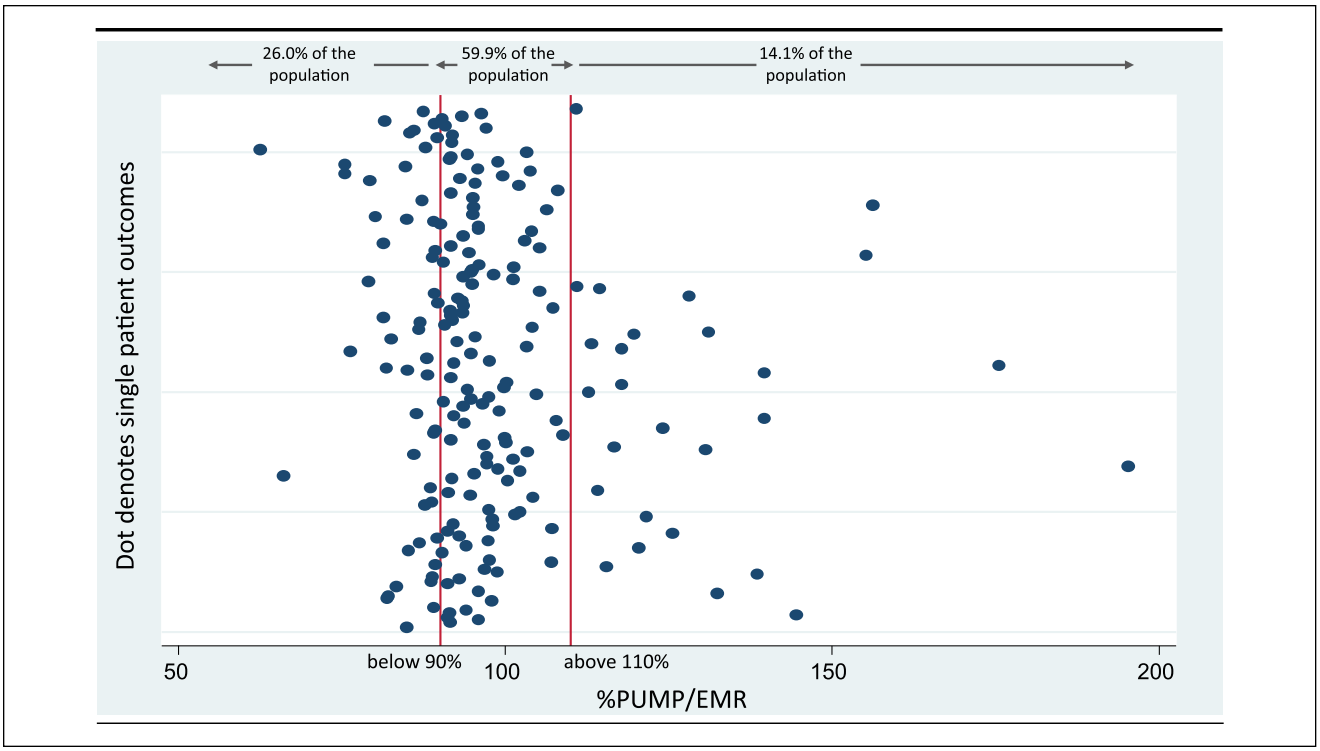

Figure 1. Patients' enteral nutrition (EN) pump volume as a percentage of electronic medical record (EMR) recorded volume. Calculated as (EN pump volume/EMR recorded volume) × 100. Left of the below 90% line represents the 26.0% of patients with a value for EN pump volume as a percent of EMR recorded amount below 90%. The range between 90% and 110% represents 59.9% of patients with values between the acceptable level of 90%–110%. Right of the above 110% line represents 14.1% of patients with values above 110%. %PUMP/EMR, EN pump volume as a percent of EMR recorded volume.

Differences may exist between staff's ability to estimate time that EN is withheld. More severe or complex cases can lead to RNs spending more time at bedside, causing EMR documentation to occur when time is available and not in real time, relying more on memory. Although staff-based factors such as these were not examined in this study, they should be included in future research to better understand the role of such factors in documentation errors. From a clinical perspective, relying on inaccurate documented EN volume could result in inappropriate change in treatment regimens and may influence clinical outcomes in the critically ill. It was estimated in this study that inaccuracies in the EMR recorded volumes resulted in 16.7% (n = 32) of patients who appeared to have received a greater percentage of calories than actually provided; 13.0% (n = 25) of patients appeared to have received a lesser percentage of calories than actually provided. Clinicians would likely use this information to make adjustments as avoidance of underfeeding and overfeeding in the ICU setting is of great importance in preventing or minimizing adverse patient outcomes. The more negative the energy balance, the higher the rate of infection and the longer the ICU stay.[5] Overnutrition has also been associated with complications such as an increase in ventilator-dependent days, infection rates, and hyperglycemia.[6]

Improving protocols, evaluating staffing levels, and providing in-services to staff may optimize the accuracy of EMR-based data. A potential solution is a technological platform that electronically transfers EN pump-based data automatically and in real time to the EMR. Such a system should also transmit information regarding when the pump is started, stopped, and restarted and prompt the user to document reasons for the interruptions. The development of such a system would improve the data used in clinical nutrition research and, more important, help ensure patients receive their nutrition prescription.

The results from this study illustrate the need to better understand the role of recording errors in determining whether patients receive their appropriate EN prescription. However, due to the novelty of this research, a limitation is that it was a single-center study. Additional research is warranted to investigate whether the results found in this study apply to other institutions and could also be expanded to include documentation of other pump-delivered items, including intravenous fluids and medications.

Conclusion

This study identified significant differences between EN documentation provided in the EMR by nursing staff and EN

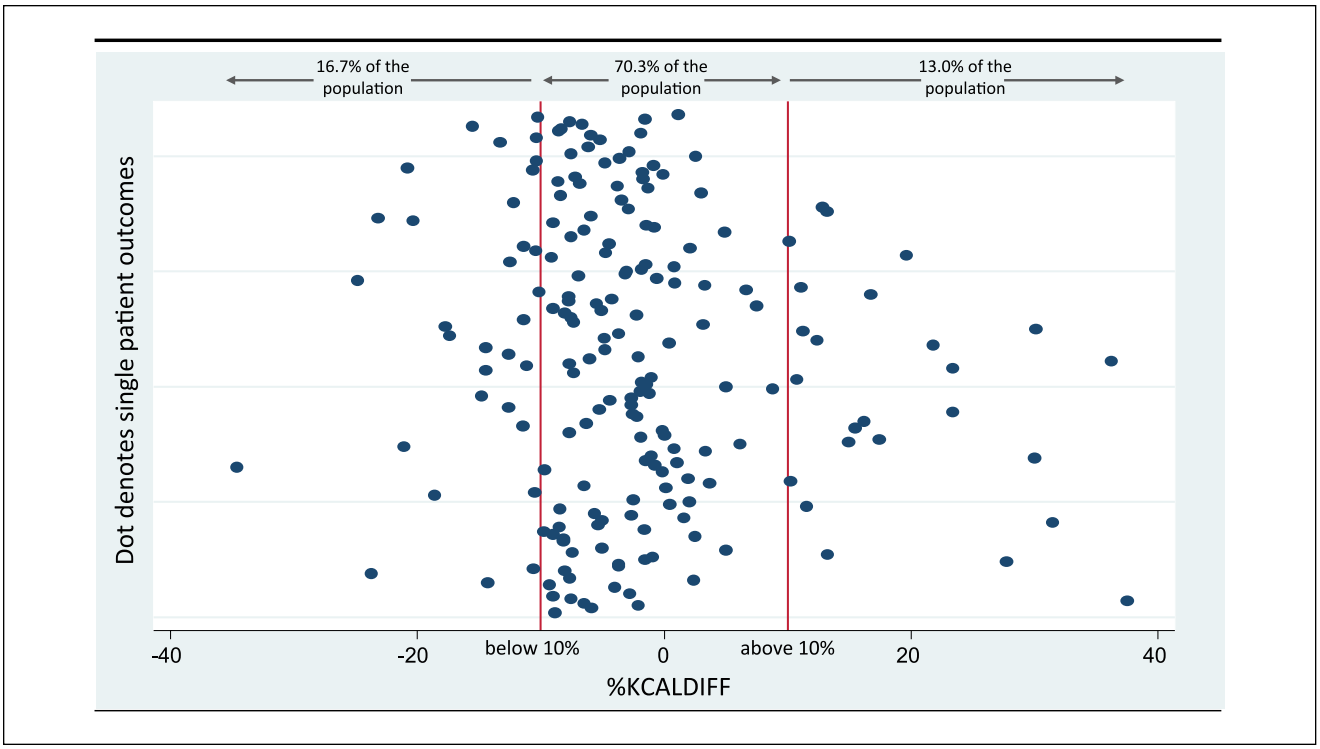

Figure 2. Difference in patients' received amounts and daily caloric estimated goals as a percentage of daily estimated caloric goals. Calculated as {[(EN pump delivered volume – EMR recorded volume) × (kcal/mL formula)]/Estimate caloric needs} × 100. The below −10% represents 16.7% of patients with a value for the dependent variable at or below −10%. The range between −10% and 10% represents 70.3% of patients with values between the acceptable level of −10% to 10%. The above 10% represent 13.0% of patients with values for the dependent variable at or above 10%. EMR, electronic medical record; EN, enteral nutrition; %KCALDIFF, difference in daily caloric estimated goals and received amount as a percentage of daily estimated caloric goals.

Table 3. Enteral Nutrition (EN) Volume Recording Error Percentage by Level of %KCAL (n = 192).[a]

	Difference in EN Feeding Pump and EMR Volumes as a % of Estimated Caloric Needs[b]								
	Volume Difference <10% of Estimated Caloric Needs[c] (n = 32)			Volume Difference ±10% of Estimated Caloric Needs[c] (n = 135)			Volume Difference >10% of Estimated Caloric Needs[c] (n = 25)		
Indicator Variable	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum
EN pump volume, mL/d	617.5	1730.1 (556.3)	3163.7	139.0	1787.2 (1033.0)	5085.0	386.5	1990.7 (1101.6)	4090.0
EMR EN recorded volume, mL/d	935.0	2011.8 (598.8)[d]	3525.0	105.0	1881.1 (1091.2)[d]	5630.0	247.5	1614.9 (967.5)[d]	3760.7
Difference of EN pump volume and EMR recorded volume, mL	−599.0	−281.8 (92.8)[e,f]	−129.5	−570.0	−93.9 (131.0)[f,g]	183.3	78.0	375.8 (255.6)[e,f]	1088.2
EN pump volume as a percent of EMR recorded volume (%PUMP/EMR)[h]	66.0	85.3 (5.4)[e,g]	91.7	62.5	95.5 (8.0)[f,g]	132.4	103.0	130.1 (21.9)[e,f]	195.2

(continued)

Table 3. (continued)

	Difference in EN Feeding Pump and EMR Volumes as a % of Estimated Caloric Needs[b]								
	Volume Difference <10% of Estimated Caloric Needs[c] (n = 32)			Volume Difference ±10% of Estimated Caloric Needs[c] (n = 135)			Volume Difference >10% of Estimated Caloric Needs[c] (n = 25)		
Indicator Variable	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum	Minimum	Mean (SD)	Maximum
Difference in daily estimated caloric goals and received amount as a percentage of estimated caloric goals (%KCALDIFF)[b]	−34.6	−15.2 (5.7)[e,g]	−10.1	−9.7	−3.2 (4.2)[f,g]	8.8	10.1	19.2 (8.6)[e,f]	37.5

EMR, electronic medical record; EN, enteral nutrition.
[a]Recording error is the difference in EN volumes delivered between the amount recorded in patients' EMRs and the amounts obtained from EN feeding pumps.
[b]Unweighted mean of percentage; calculated as {[(EN pump volume – EMR recorded volume) × (kcal/mL formula)]/Estimated caloric needs} × 100.
[c]Patients' caloric needs as calculated by predictive equation.
[d]The mean pump volume statistically differs ($P \leq .05$) from the mean EMR recorded volume.
[e]Statistically different ($P \leq .05$) from value reported for volume difference ±10% of estimated caloric needs.
[f]Statistically different ($P \leq .05$) from value reported for volume difference <10% of estimated caloric needs.
[g]Statistically different ($P \leq .05$) from value reported for volume difference >10% of estimated caloric needs.
[h]Unweighted mean of percentage; calculated as (EN pump volume/EMR recorded volume) × 100.

volume delivered as per the EN pump. These errors can be large and affect patient outcomes. Inaccurate documentation in the EMR can also skew research and quality outcomes regarding EN. The results of this study support the need for a technological platform that directly transmits EN pump volumes in real time to the EMR. Such a system would increase EMR documentation accuracy and allow a greater amount of nursing time spent on direct patient care.

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Statement of Authorship

L. Musillo contributed to the conception/design of the research; L. Musillo, L. M. Grguric-Smith, E. Coffield, J. C. DiGiacomo, and K. Totino contributed to the acquisition, analysis, or interpretation of the data; L. Musillo and L. M. Grguric-Smith drafted the manuscript; and L. Musillo, L. M. Grguric-Smith, E. Coffield, and J. C. DiGiacomo critically revised the manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved the final manuscript.

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Gravity Flow in Proposed Enteral Tube Small-Bore Connectors

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Abstract

Background: Enteral nutrition (EN) misconnections have been identified as a serious and potential deadly problem. An international effort led by EN industry leaders has developed a small-bore enteral connector (ENFit) that in theory will reduce the frequency of misconnections. Despite the potential benefit of preventing misconnections, the full impact of adoption of the ENFit connector is unknown. To assess the impact of transitioning to ENFit on our home EN (HEN) patients, the current study evaluated gravity feeding comparing 2 proposed small-bore connectors to the legacy (current connector) using various commercial formulas. *Methods:* Six commonly used enteral formulas in our facility with varying density and viscosity were tested in triplicate. Forty milliliters of formula was poured into a syringe connected to an ENFit or legacy (current) feeding connector attached to varying French size tubes. The time it took formula to flow through the connectors was recorded, and the test was repeated in triplicate. *Results:* All formulas took significantly longer to flow through the first ENFit connector compared with the legacy connector ($P < .05$). The second ENFit connector demonstrated similar flow dynamics to the legacy connector. *Conclusions:* There is wide variability in the flow dynamics in ENFit connectors with significant potential impact on many facets of HEN, including medicine delivery, blenderized feeds, venting, and compliance with EN due to increased time to administer feeds. We highly recommend additional testing of flow dynamics, including gravity flow, as ENFit tubes are being developed and adopted. (*Nutr Clin Pract*. 2017;32:189-192)

Keywords

home nutrition support; enteral nutrition; tube feedings; nutritional support; home care

Malnutrition due to chronic disease and cancer is one of the most challenging clinical problems facing nutrition support providers. In response to this clinical challenge, the use of nutrition support in the home setting has increased significantly in the past 30 years. Despite this increased use of nutrition support (enteral and parenteral), complications such as infection, thrombosis, tube clogging, buried bumper, and granulation tissue still are common.[1–4] These typically long-term complications of nutrition support are associated with patients in the home setting or in short-term rehabilitation facilities or nursing homes.

In contrast to the long-term complications of home nutrition support, there has been increased awareness of misconnections that occur predominately in acute care settings. These misconnections include connecting enteral feeding to central venous catheters and tracheostomy tubes, which can have deadly consequences.[5,6] A number of reasons have been cited for the misconnections, including lack of healthcare provider education, human error, design flaws (luer-tip connectors), and mislabeling tubes.[7–11] As a result of these enteral misconnections, the Association for the Advancement of Medical Instrumentation (AAMI) and the International Organization for Standardization (ISO) have recommended a small-bore enteral connector for all enteral devices that are physically incompatible with nonenteral devices.[11] This recommendation led to the formation of the Global Enteral Device Supplier Association (GEDSA), which comprises companies that make enteral devices as well as nutrition supplements and supplies.[12,13] In addition, GEDSA has supporting organizations, including the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Oley Foundation. GEDSA spearheaded the development of a small-bore enteral connector that would satisfy the standards recommended by AAMI/ISO and eventually be endorsed by the Food and Drug Administration (FDA).

The GEDSA-proposed global transition for all enteral devices to use the small-bore enteral nutrition (EN) connector is under way. Surprisingly, despite the potential to reduce enteral

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Table 1. Nutrient, Osmolarity, and Viscosity Measurements for the Formulas Used in the Current Study.

Formula Characteristic	Osmolite 1.0	Nutren 1.0	Jevity 1.5	Isosource 1.5	Twocal HN	Nutren 2.0
Calories, cal/mL	1.06	1.0	1.5	1.5	2.0	2.0
Protein, g/mL	0.443	0.40	0.0638	0.676	0.835	0.80
Carbohydrates, g/mL	0.144	0.128	0.2157	0.168	0.2185	0.196
Fat, g/mL	0.347	0.38	0.498	0.648	0.905	0.104
Osmolarity, mOsm/mg H_2O	300	370	525	650	725	745
Fiber, g/mL	0	0	0.022	0.008	0	0
Viscosity (at room temperature)	Thin	Thin	Nectar	Thin	Nectar	Thin

misconnections, to our knowledge, there are no published data that small-bore connectors can achieve this goal. Furthermore, the impact of the small-bore connector on blenderized tube feeding (BTF), venting, and medication delivery is not fully known, with 1 recent study raising concerns.[12,14] In addition, the effect of transitioning to a small-bore connector on patients who receive EN through gravity tube feeding has not been published and subjected to the academic peer-review process prior to global implementation. This is concerning since gravity feeding is how most of our home EN (HEN) patients receive standard formula. The purpose of the current study is to evaluate the effect of 2 proposed ENFit small-bore enteral connectors on gravity flow using standard-size percutaneous endoscopic gastrostomy (PEG) tubes (20 French [Fr], 24 Fr, and low profile). Our hypothesis was that gravity flow rate would be significantly lower in the small-bore connector, with a difference that would be exacerbated with larger feeding tubes or denser formulas compared with the currently used (legacy) connector.

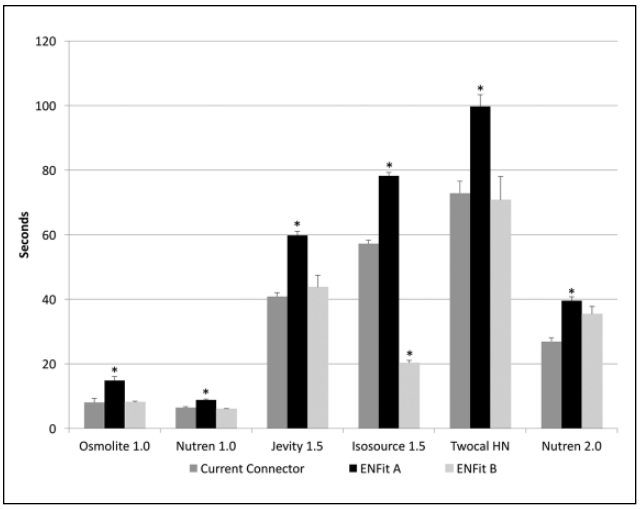

Figure 1. Number of seconds required to flow 40 mL of various formula comparing 20-Fr legacy with ENFit A and ENFit B connectors. Asterisks represent significant statistical difference when compared to the current connector.

Methods

Six sample enteral feeds (Osmolite 1.0 [Abbott Nutrition, Abbott Park, IL], Nutren 1.0 [Nestlé Health Science, Florham Park, NJ], Jevity 1.5 [Abbott Nutrition, Abbott Park, IL], Isosource 1.5 [Nestlé Health Science, Florham Park, NJ], TwoCal HN [Abbott Nutrition, Abbott Park, IL], and Nutren 2.0 [Nestlé Health Science, Florham Park, NJ]) were chosen based on common formulas used by our HEN patients and to ensure varying density and caloric content (Table 1). A total of 40 mL of formula at a time was carefully measured and poured into a 60-mL syringe connected to proposed small-bore connector ENFit A (Covidien/Medtronic, Dublin, Ireland), proposed small-bore connector ENFit B (Haylard, Alpharetta, GA), or legacy (current Haylard) feeding connector. The connectors were subsequently attached to a 24-Fr tube (Haylard), 20-Fr tube (Haylard), or low-profile PEG tube (Mic-key balloon with right angle feeding adaptor) connector set. The length of each tube was the same to ensure uniformity. Each formula was tested with both the small-bore connector ENFit A and the legacy connector and with all 3 tube types. A low-profile version of the ENFit B was not available at the time of testing, and thus only the 24-Fr tube (Haylard) and 20-Fr tube (Haylard) were evaluated. The tubes were clamped prior to loading of the syringe. After the syringe was filled with formula, another investigator used a stopwatch to record the time it took for the formula to pass through the small-bore connector once the tube was unclamped. These studies were repeated in triplicate, and average values were obtained.

The statistical analysis was performed using SPSS statistical software and JMP, version 10 (SAS Institute, Cary, NC). Data are shown as mean ± standard deviation unless otherwise specified. Comparisons between the small-bore connector and current connector groups were performed using a 2-sided Student *t* test, with an α value of 0.05 when comparing 2 groups. Analysis of variance (ANOVA) with paired *t* tests was used when comparing 3 groups.

Results

In the 24-Fr tube, flow through the small-bore connector ENFit A was significantly longer in all formulas tested compared with the legacy connector ($P < .05$) (Figure 1). The effect was magnified in the more dense formulas, with the flow of 40 mL TwoCal HN taking 92.6 ± 6.3 seconds in the small-bore tube

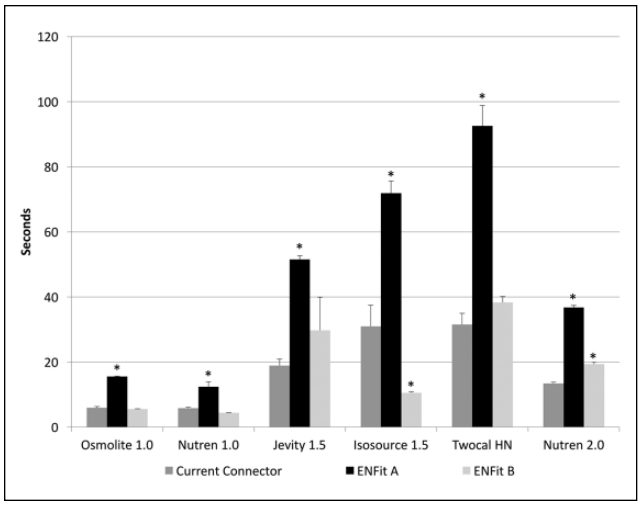

Figure 2. Number of seconds required to flow 40 mL of various formula comparing 24-Fr legacy with ENFit A and ENFit B connectors. Asterisks represent significant statistical difference when compared to the current connector.

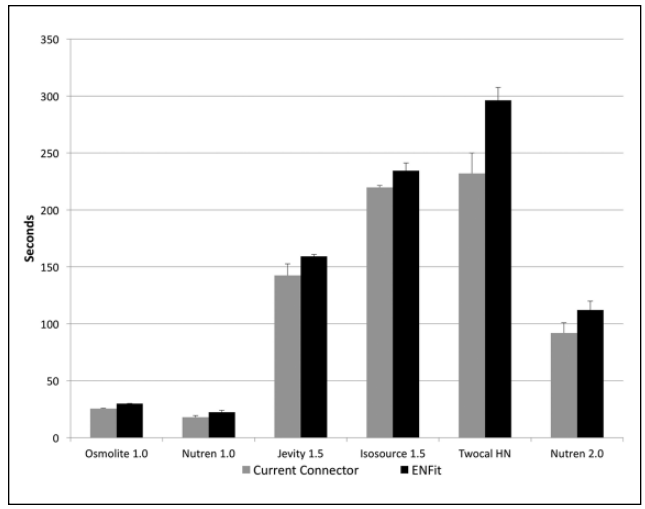

Figure 3. Number of seconds required to flow 40 mL of various formula comparing low-profile legacy with ENFit A.

compared with 31.5 ± 3.4 seconds in the legacy connector (Figure 1). Small-bore connector ENFit B had significantly shorter flow with Isosource 1.5 and longer flow with Nutren 2.0; otherwise, there were no significant differences between the legacy connector and ENFit B (Figure 1). In the 20-Fr tube, flow through the small-bore connector ENFit A was significantly longer in all formulas tested compared with the legacy connector ($P < .05$) (Figure 2). Small-bore connector ENFit B had significantly shorter flow with Isosource 1.5; otherwise, there were no significant differences between the legacy connector and ENFit B (Figure 2). Flow through the low-profile tube was also significantly longer in all formulas tested with the ENFit A compared with the legacy connector ($P < .05$), although the effect compared with the 20- and 24-Fr tubes was decreased (Figure 3). We did not have a low-profile ENFit B connector to test.

Discussion

This article is the first peer-reviewed study we are aware of to test the impact of the proposed small-bore ENFit connector on HEN patients who predominately receive enteral feeds through gravity flow as opposed to infusion pumps typically used in the hospital setting or with jejunal feeds. Based on the current data, there was significant variability between the 2 ENFit connectors, with one demonstrating a decrease in flow rate in 20- and 24-Fr PEG tubes with most formulas and the other not showing a marked difference from the legacy connector. If designs such as ENFit prototype A are implemented, HEN patients could experience an increase in the amount of time it takes to receive feeding using the gravity feeding technique. For example, a patient infusing 500 mL of Isosource 1.5 or Jevity 1.5 will take 2.3 and 2.7 times longer, respectively, when gravity feeding through the proposed small-bore connector. This increase in feeding time could lead to increased noncompliance as our patients have reported early termination of their feeds if it is taking too long to provide them. Although the overall standard has been established, it will still be up to each respective manufacturer to design its own ENFit tube. With some designs such as the ENFit prototype B, there may be minimal impact with gravity feeds. However, with other designs, patients could be affected significantly.

Results from the current study demonstrate that other factors outside of the proposed ENFit standard affect flow of formula since all 3 tubes (legacy, ENFit A, and ENFit B) had internal diameters that were very similar at their shortest constriction (2.6 mm, 2.5 mm, and 2.65 mm, respectively; Figure 4). Perhaps the impact of this constriction can be overcome by increasing the diameter of the main body, relieving the constriction instead of carrying it through the tube, as was seen in ENFit B compared with ENFit A. GEDSA's response to the question regarding smaller diameter acknowledges that enteral-specific syringes with the new ENFit standard could have a smaller internal diameter than the legacy catheter-tip syringe.[15] In addition, they state that the diameter will not likely be smaller than the patient access end of the (bolus) extension set opening on most low-profile devices. They conclude by stating that as long as the end of the extension set remains the smallest hole in the system, the flow rate is not expected to change from the legacy tubes. While we agree with GEDSA, as evident by the current data, that the low-profile tube extension flow will not likely be affected, we have demonstrated that larger diameter tubes will have significantly decreased flow depending on the design. Similar results were noted in measurement of the force needed to compress a syringe of blenderized tube feeding with the ENFit connector compared with legacy connector.[12] Unless significant design changes are implemented, most of our adult HEN patients who use larger diameter tubes could be affected by this connector change.

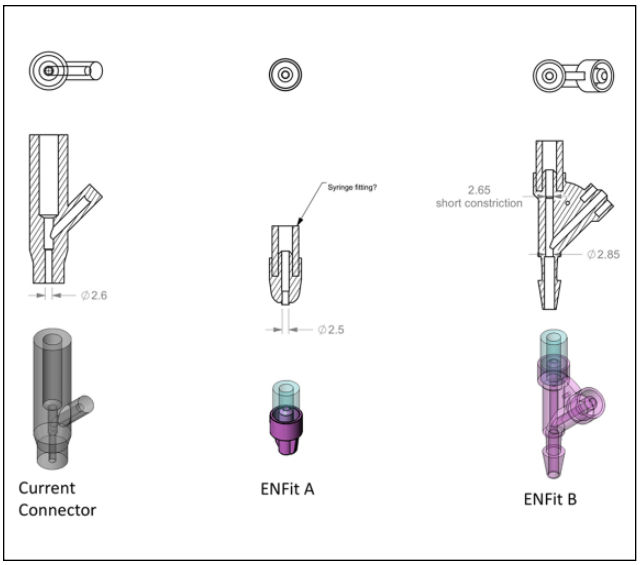

Figure 4. Schematics of legacy (current connector), ENFit A, and ENFit B connectors. Top: a top-down view correlating to the visualized diameter. Middle: mid-line cutout revealing thinnest diameter in millimeters. Bottom: 3-dimensional rendering of tubes. For ENFit A and ENFit B, the syringe fittings have been drawn in with middle and bottom figures.

The primary stated purpose of developing the small-bore enteral connector is to prevent enteral devices from being connected to nonenteral devices, thus reducing complications. We believe that developing a connector that reduces enteral misconnections is an important clinical goal. However, the implementation of the small-bore connector could potentially lead to unintended consequences as it pertains to flow dynamics. GEDSA has stated that venting will work in the same manner as previously, but venting a feeding tube with the small-bore connector will require a syringe with the new connector.[15] In our current experience, we have found that venting through low-profile tubes can be problematic with increased rates of tube clogging and eventual failure. Similar to impact on gravity feeding, we anticipate increased complications when ENFit tubes are used for venting, unless designed appropriately. In addition, patients who use their current tube for venting using leg or bed bags to gravity will also have more difficulty since these products will not connect to ENFit.

There are a number of limitations of the current study evaluating the new proposed small-bore enteral connector and gravity flow. Our study was conducted in a laboratory and not clinically. The true impact of the small-bore connector will be determined only once it is fully available and being used by a significant number of HEN patients. The study was performed at a single center, and our conclusions about the effect of the small-bore tube on our patient population may be different from other centers.

In conclusion, the goal of reducing enteral misconnections is important and may be accomplished by enhanced education and tube redesign. The proposed small-bore enteral connector will likely not change gravity flow through smaller diameter low-profile tubes but will significantly affect larger ones depending on design. This altered flow dynamic will have significant impact on the majority of the HEN patients who currently have larger diameter tubes used for venting, delivery of blenderized tube feeds, and medication delivery. These potential increased complications need to be considered by manufacturers when designing tubes to meet the new ENFit standard.

Statement of Authorship

R. T. Hurt and M. S. Mundi contributed to the conception/design of the trial and drafted the manuscript; and L. M. Epp, A. K. Pattinson, W. M. Duellman, and S. M. Corner assisted with acquisition of the data and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Enteral Feeding Set Handling Techniques: A Comparison of Bacterial Growth, Nursing Time, Labor, and Material Costs

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Abstract

Background: Enteral nutrition therapy is common practice in pediatric clinical settings. Often patients will receive a pump-assisted bolus feeding over 30 minutes several times per day using the same enteral feeding set (EFS). This study aims to determine the safest and most efficacious way to handle the EFS between feedings. *Methods:* Three EFS handling techniques were compared through simulation for bacterial growth, nursing time, and supply costs: (1) rinsing the EFS with sterile water after each feeding, (2) refrigerating the EFS between feedings, and (3) using a ready-to-hang (RTH) product maintained at room temperature. Cultures were obtained at baseline, hour 12, and hour 21 of the 24-hour cycle. A time-in-motion analysis was conducted and reported in average number of seconds to complete each procedure. Supply costs were inventoried for 1 month comparing the actual usage to our estimated usage. *Results:* Of 1080 cultures obtained, the overall bacterial growth rate was 8.7%. The rinse and refrigeration techniques displayed similar bacterial growth (11.4% vs 10.3%, $P = .63$). The RTH technique displayed the least bacterial growth of any method (4.4%, $P = .002$). The time analysis in minutes showed the rinse method was the most time-consuming (44.8 ± 2.7) vs refrigeration (35.8 ± 2.6) and RTH (31.08 ± 0.6) ($P < .0001$). *Conclusions:* All 3 EFS handling techniques displayed low bacterial growth. RTH was superior in bacterial growth, nursing time, and supply costs. Since not all pediatric formulas are available in RTH, we conclude that refrigerating the EFS between uses is the next most efficacious method for handling the EFS between bolus feeds. (*Nutr Clin Pract*. 2017;32:193-200)

Keywords

pediatrics; enteral nutrition; safety; food safety; tube feeding; infection control; bacteria

Introduction

Providing nutrition via an enteral feeding tube is an important and common treatment in pediatric patient care settings. In our pediatric hospital, approximately 35% of patients are on enteral feedings on any given day. Often these infants and children get several feedings per day of formula over 30 minutes using an enteral pump. This allows for consistent administration of enteral formula in children who have demonstrated inability to tolerate gravity bolus feedings where the rate of administration is hard to control. Currently, there is a recommendation for 1 enteral feeding set (EFS), which includes a bag and tubing, to be used for 24 hours.[1] This recommendation is for inpatient and home use, but there is no guidance for how to ensure cleanliness of the EFS in between those periodic feedings.[2]

Bacterial Growth in Enteral Feedings

Overall contamination rates of enteral formulas or the EFS are reported to be between 19% and 59%.[3,4,5–8] Sources of contamination have been identified to originate from any point in preparation to administration of formula. Touch contamination by nursing staff remains a predominant factor in bacterial contamination of enteral formula and is attributed to direct manipulation of the EFS.[5,6,8] Studies have documented the benefits of good hand hygiene, wearing gloves when accessing the EFS, and the use of ready-to-hang (RTH) formula where possible.[6,8,9] Current American Society for Parenteral and Enteral Nutrition (ASPEN) recommendations are for good hand hygiene and avoidance of manipulation of the system as much as possible.[1] No recommendations are given for how to handle the EFS between bolus feedings as there is no evidence to guide that practice.[1,2]

Nursing Practice

Evidence is needed to determine the best practice for 24-hour intermittent EFS handling.[10] A study by Moffitt et al[11]

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documented the safety of RTH enteral formula when it is used for bolus or intermittent feeds in a residential care facility. A RTH formula is used as a "gold standard," as there already is documentation of the microbiologic safety and cost efficiency of this modality in the literature.[11] Refrigeration of the set between bolus feedings is an option for EFS handling because refrigeration is known to retard bacterial growth of dairy products. The method of removing the set from the pump, placing it in a ziplock bag, and refrigerating involves less handling of the set, which has been repeatedly recommended by investigators.[3,4,7,8] Rinsing the EFS with sterile water is commonly used but is time-consuming as there is no quick way to prime the tubing. It is not clear from the existing literature if rinsing an EFS with sterile water or any water is a safe practice.[12] EFS handling will vary from nurse to nurse and nursing unit to nursing unit. Nursing staff may elect to obtain a new set for each bolus feeding as a convenience issue. This adds up to higher than expected usage costs. The challenge for pediatric clinicians is to minimize the risk of bacterial contamination while balancing task efficiency and patient safety.

Labor and Supply Costs

Nursing practice changes can result in a cost savings if the change reduces nursing labor. The United States spends more money on healthcare than any other country in the world, with an average per capita expense of $8233 compared with an average of $3268 in other industrialized countries.[13] The cost of nursing labor grew 58% in 2002–2009, and this trend is expected to continue.[14] Reducing the cost of nursing labor time and supplies could have a significant economic impact on hospital costs, as 35% of our pediatric population receive enteral feedings during their admission.

The use of open-system enteral feeding (which is primarily used in pediatric settings) compared with closed-system RTH formula demonstrated an increase in cost of supplies and wastage. However, this study also factored in nursing time and demonstrated a cost of $7.74 per day for continuous feeding using the open-system approach to enteral feeding practice and $3.30 per day using RTH formula in a pediatric care setting.[15] This study demonstrates savings when the cost of nursing time is factored with procedures and supplies. To be prepared for the challenges of the future, nursing practice must be based on evidence that considers the cost of nursing time as well as patient safety. If 3 procedures are deemed safe for patient care but one is clearly less time-consuming and costly, we can adopt the most efficacious approach.

Purpose

The overall purpose of this study was to identify the safest and most efficacious practice for bolus EFS handling techniques by comparing data among bacterial growth, nursing time, and supply costs using simulation. The specific aims of this study included the following:

1. Determine the bacterial growth over 21 hours of 3 different handling techniques of the EFS between bolus feedings: (a) rinsing the EFS with sterile water after each bolus, (b) refrigerating the EFS between bolus feedings, and (c) using an RTH product that is left at room temperature.
2. Compare the cost of EFS supplies for each handling technique.
3. Perform a cost analysis comparing the average nursing time and labor costs for each handling technique.

Research Design and Methods

The researchers conducted a simulated clinical study on 2 nursing units in a 340-bed Midwestern, urban pediatric hospital to compare the bacterial growth and nursing time of different EFS handling techniques to include (1) sterile water rinse, (2) refrigeration without rinsing of EFS, and (3) use of a RTH product that is capped off and left at room temperature between feeds. The same sterile ready-to-feed (RTF) formula was used for all 3 techniques. To determine if 24-hour EFS use for these practices is safe, we chose 3 time points for cultures: baseline, the midpoint of 12 hours, and the end point of 21 hours. Institutional review board approval from the Children's Mercy Hospital was obtained prior to initiating the study.

Enteral Formula Handling

For each technique, a bolus of 120 mL was delivered over 30 minutes via enteral feeding pump at 3-hour intervals. Baseline cultures of the RTF products were obtained after opening the product and again at 12 and 21 hours. The EFS was rinsed with 75 mL of sterile water and was left on the pump at room temperature between feedings. The refrigerated bag was labeled with the pump number and date, much like any patient, and the EFS would be labeled and stored in a patient's refrigerator in the hospital or home. The RTH formula was left on the pump, with the cap in place, at room temperature between feedings.

Specimen Collection and Handling

Baseline (time 0) cultures were obtained as described above to verify that the formula was sterile at the beginning of the study. Just prior to the fifth bolus feeding (at 12 hours: time 1), a 1-mL aliquot of formula was collected in a sterile, capped tube for subsequent plating. Just prior to the eighth and last bolus feeding (at 21 hours: time 2), the second 1-mL aliquot of formula was collected. This time point was chosen because the bag is to be discarded after that feeding, as this is the last feeding of the 24-hour study period. All specimens were collected as the first few drops of formula leaving the distal port and were plated within 30 minutes in the research laboratory.

Samples of 0.01 mL and 0.001 mL were obtained via sterile loop and placed on blood agar plates. Two samples were plated

at each time point for each formula for quality control purposes. Samples were incubated at 37°C for 48–72 hours.

Specimen Analysis

Analysis of bacteria was done using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF). This technology allows rapid identification of microorganisms using mass spectrometry. MALDI-TOF technology analyzes biopolymers such as DNA, proteins, bacteria, and fungi. The MALDI technology uses a matrix of crystals that are low molecular weight, are acidic, and have strong optical absorption, usually in the UV range.[16] A colony of bacteria is placed on a sample target and overlaid with matrix. Using the laser, ion mirror, and dedicated software, the mass spectra are compared with stored profiles.[17] When this technology is not able to identify a bacterial species, 16S ribosomal RNA (rRNA) gene sequencing is used.[18] For difficult to identify organisms, 16S rRNA gene sequencing was performed. This process allows for genus identification of >90% for most bacteria.[19] The 16S rRNA gene is part of the DNA most commonly used to identify bacteria because it has been determined for a large number of strains, over 90,000 nucleotide sequences.[20,21]

Criteria for determining unacceptable levels of contamination of enteral formulas are based on 1995 Food and Drug Administration (FDA) guidelines: any agar plate growing $>10^4$ colony-forming units (CFU)/mL, 3 or more samples $>10^3$ CFU/mL, or any pure culture of *Bacillus cereus*, *Listeria monocytogenes*, *Staphylococcus aureus*, or coliforms.[22] These guidelines are the most appropriate to assess enteral formula safety as they contain dairy products.

Time Study

A time-in-motion analysis of the nursing time required to perform these procedures was documented on the days of data collection. Unit nurses volunteered to perform the simulated and timed feedings. Time commenced when the nurse left the nurses' station to gather supplies for the bolus feeding and ended when the nurse returned to the nurses' station once the task was completed. Total number of seconds was averaged for each handling procedure. Just prior to starting this study, all investigators who conducted the time-in-motion study were tested 3 times using their stopwatch on a smartphone and were found to be within 5% of each other.

Cost Comparison: Supplies

EFS usage for 1 nursing unit was tracked for 1 month by inventorying sets just prior to a supply delivery. The study bags were factored out of the general inventory so that an accurate count of actual EFS use was determined. For this same time period, investigators on the study units documented the number of patients who received enteral feedings either by continuous drip or bolus to determine the number of EFS that should have been used per day. This number was compared with the number actually used. Nursing staff were not informed about this arm of the study to avoid influencing practice.

Cost Comparison: Nursing

Nursing salaries were based on the study hospital range and were used to compute the labor costs based on the average nursing time per technique. This salary amount was used to calculate the cost to the nursing unit for labor while factoring in the data obtained from the daily count of patients receiving bolus feedings.

Statistical Analysis Methods

The proposed study was well powered for 3 specific aims. The sample size calculation was performed by nQuery Advisor (Statsols, Boston, MA). For the first specific aim, 60 specimens for each handling technique and each sample were cultured for bacterial contamination at baseline, 12 hours, and 21 hours. This sample size ensured 83% power to detect 10% difference in the contamination rates (eg, 3% vs 13%; odds ratio, 4.8) between 2 groups when the type I error rate was set at 0.05. The χ^2 test was used to compare contamination rates among groups. We calculated the contamination rate of positive and unacceptable bacteria growth and the 95% confidence interval of contamination rate for 3 handling techniques at each time point and for overall time.

For the second and third specific aims, we hypothesized that the rinsing method would take longer than refrigeration (eg, 360 vs 240 seconds with a standard deviation of 60 seconds). This sample size ensured >99% power to detect the difference among nursing time. Statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC), and statistical significance was claimed with $P < .05$.

Results

Bacterial Growth

A total of 1080 cultures were performed for this study (360 per handling technique) with an overall bacterial growth rate of 8.7% (95% confidence interval [CI], 7.2%–10.5%). Of note, both the sterile water rinse and refrigeration techniques showed similar bacterial growth with 41 and 37 positive cultures (11.4% vs 10.3%, $P = .63$), as seen in Table 1. Both the sterile water rinse (11.4% vs 4.4%, $P = .0006$) and refrigeration techniques (10.3% vs 4.4%, $P = .003$) had significantly higher bacterial growth compared with 16 positive cultures obtained from the RTH group (Figure 1). There is no significant change in bacterial growth between baseline and time 1 (6.1% vs 6.1%, P = NS), but there is a significant increase in bacterial growth in time 2 compared with baseline (13.9% vs 6.1%, $P = .0005$) (Figure 2).

Table 1. Positive Cultures Showing Bacterial Growth by Intervention and Collection Time.[a]

Collections	Rinsed Bags	Refrigerated	Ready to Hang	Total
Time 0	12/10 (5.7–16.8)	8/6.7 (3.2–12.8)	2/1.7 (0.1–6.3)	22/6.1 (4.0–9.1)
Time 1	12/10 (5.7–16.8)	7/5.8 (2.7–11.8)	3/2.5 (0.5–7.4)	22/6.1 (4.0–9.1)
Time 2	17/14.2 (8.9–21.6)	22/18.3 (12.4–26.3)	11/9.2 (5.1–15.8)	50/13.9 (10.7–17.9)
Total	41/11.4 (8.5–15.1)	37/10.3 (7.5–13.9)	16/4.4 (2.7–7.2)	94/8.7 (7.2–10.5)

[a]Values are presented as count/percentage (95% CI) of positive cultures.

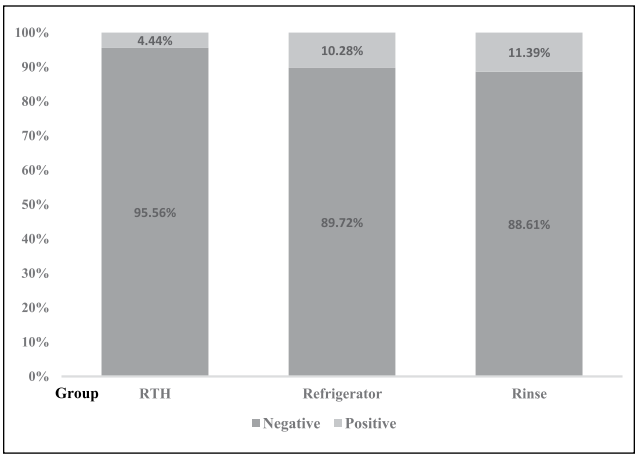

Figure 1. Comparison of positive cultures showing bacterial growth by intervention (overall, $P = .002$; rinsed vs ready to hang [RTH], $P = .0006$; refrigerated vs rinse, $P = .003$; refrigerated vs rinsed, P = NS).

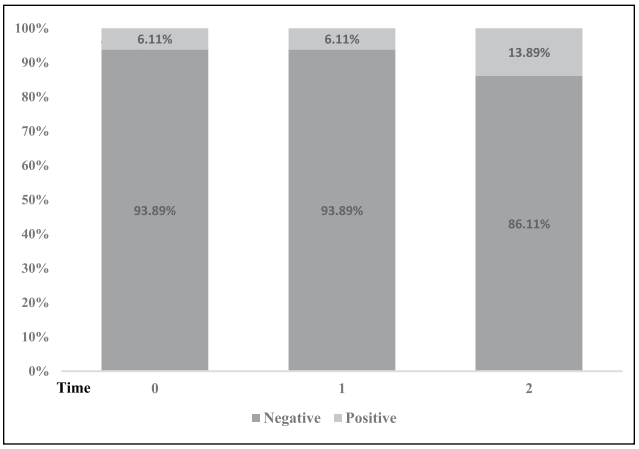

Figure 2. Comparison of positive cultures showing bacterial growth by collection time (overall, $P = .0001$; time 0 vs time 1, P = NS; time 0 vs time 2, $P = .0005$; time 1 vs time 2, $P = .0005$).

At baseline and time 1, the results of this study showed <1% of the cultures had unacceptable bacterial growth based on the 1995 FDA Dairy Food Safety Guidelines (Table 2). There was no statistically significant difference in acceptable growth among the 3 handling techniques. Of note, all the unacceptable growth was found at time 2, except for a mold that was obtained at time 1 in the RTH group. Table 3 summarizes the type of bacterial growth obtained during the study.

Supply Costs

The costs of supplies for each handling technique are summarized in Table 4. RTH feedings cost was $3.40 per day, while rinsing cost was $5.47 (including sterile water) and refrigeration cost $4.14 (including the zippered plastic bag). Over 1 month of tracking, there was an average of 7.5 patients per day on 1 nursing unit receiving intermittent enteral feedings.

Nursing Labor Costs

Twenty-four time-in-motion studies were done for each handling technique. Nursing time per EFS method was based on using the RTH method as the baseline, as it was the shortest time duration per feeding on an average of 31 minutes, 38 seconds. Table 4 summarizes those results. The time-in-motion studies for each formula handling method were determined using mean and standard deviation. We further compared the time among 3 handling methods using analysis of variance (ANOVA). Post hoc pairwise comparison between any 2 handling methods was performed with Tukey's adjustment. Statistical significance was claimed at the 95% confidence level. Statistical analysis was performed using SAS 9.4. The result of the ANOVA shows that there is a significant difference ($P < .0001$) for the time required to perform the 3 formula handling methods. The rinse method took the greatest amount of time (44.8 ± 2.7), refrigeration took an average of 35.8 ± 2.6 seconds, and the RTH method took the least amount of time (31.8 ± 0.6). All the differences are significant ($P < .0001$) (Figure 3).

Data from the time-in-motion studies were then used to calculate labor costs. Nursing salaries at this hospital average $28.02 per hour (range from $22.73–$33.30 per hour). It took nurses 13 minutes longer to administer enteral feedings by rinse method and 4 minutes longer by refrigeration method compared with administering RTH feedings (RTH = baseline). The labor costs of the rinse method by average nurse salary are an increase of $48.47/d from baseline. The labor costs of the refrigeration method by average nurse salary are an increase of $14.86/d from baseline.

Table 2. Unacceptable Bacterial Growth by Intervention and Collection Time.[a]

Collections	Rinsed Bags (120 Cultures/Time Period)	Refrigerated (120 Cultures/Time Period)	Ready to Hang (120 Cultures/Time Period)	Total
Time 0	0/0 (0–3.7)	0/0 (0–3.7)	0/0 (0–3.7)	0/0 (0–2.2)
Time 1	0/0 (0–3.7)	0/0 (0–3.7)	1/0.1 (0–5.0)	1/0.3 (0–1.7)
Time 2	2/1.7 (0.1–6.3)	2/1.7 (0.1–6.3)	2/1.7 (0.1–6.3)	6/1.7 (0.7–3.7)
Total	2/0.6 (0–3.1)	2/0.6 (0–3.1)	3/0.8 (0.2–2.5)	7/0.7 (0.3–1.4)

[a]Values are presented as count/percentage (95% CI) of positive cultures.

Table 3. Bacterial Species by Intervention and Collection Time.

Collection Time	Sterile Water Rinse	Refrigeration	Ready to Hang
Unacceptable bacterial growth	2	2	3
Total number of positive cultures	41	37	16
0	*Micrococcus luteus* (n = 4) *Micrococcus* sp. (n = 2) *Staphylococcus epidermidis* *Staphylococcus warneri* (n = 2) *Staphylococcus caprae* *Bacillus simplex* *Actinomyces bovis*	*Staphylococcus capitis* *Staphylococcus epidermidis* (n = 2) *Staphylococcus hominis* *Staphylococcus pasteuri* *Staphylococcus warneri* (n = 2) *Micrococcus luteus*	*Cornybacterium imitans* Micrococcus luteus
1	*Staphylococcus epidermidis* (n = 7) *Staphylococcus auricularis* (n = 2) *Deinococcus wulumuqiensis* *Micrococcus luteus* (n = 2)	*Staphylococcus auricularis* *Staphylococcus capitis* *Staphylococcus epidermidis* (n = 2) *Micrococcus luteus* (*n* = 2) *Streptococcus parasanguinis*	Mold[a] *Bacillus simplex* *Micrococcus luteus*
2	*Staphylococcus hominis* *Micrococcus luteus* (n = 3) *Staphylococcus epidermidis* (n = 6) *Delftia acidovorans*[a] (n = 2) *Staphylococcus warneri* *Staphylococcus pasteuri* (n = 2) *Streptococcus mitis* *Bacillus megaterium*	*Bacillus idriensis* *Cornybacertium tuberculostericum* *Staphylococcus aureus*[a] *Staphylococcus auricularis* (n = 2) *Staphylococcus caprae* *Staphylococcus capitis* *Staphylococcus epidermidis* (n = 8) *Staphylococcus hominis* *Staphylococcus pasteuri*[a] (n = 1) *Staphylococcus pasteuri* (n = 1) *Staphylococcus warneri* (n = 2) *Rothia dentocariosa Turicella otidis*	*Kocuria rhizophila* (n = 2) *Micrococcus luteus* *Neisseria macacae*[a] (n = 2) *Staphylococcus auricularis* (n = 2) *Staphylococcus caprae* *Staphylococcus warneri* *Turicella otitidis* (n = 2)

[a]Unacceptable bacterial growth.

Adding the costs of supplies to the labor cost equations, the sterile water rinse method costs were $53.94 more than RTH per day. The refrigeration method costs are $19.00 more per day than RTH. Therefore, the average rinse method costs $147,660.75 per year and refrigeration costs $52,012.50 more per year than RTH. The rinse method cost about $95,648.25 more per year than refrigeration on 1 patient unit.

Supplies Inventory

It is possible that nursing staff use more than 1 EFS per day or even per shift as the sterile water rinse method is considered time-consuming. To discern the magnitude of this overage, an inventory was conducted. Over 1 month, 275 EFS were used on 1 patient unit, although per patient population, the total that we expected to use was 182 sets. The difference of 93 EFS is almost 50% more than required and represents an additional EFS use every 24 hours. This resulted in a cost increase for the hospital unit of $219.48 for the month.

Discussion

It is important for pediatric clinicians to assess current enteral delivery systems for potential bacterial contamination as these

Table 4. Comparison of 3 Methods of Enteral Feedings by Supply Costs and RN Time/Salaries.

Supply	Rinse	Refrigeration	RTH
Formula cost (1 L)	$1.68	$1.68	$1.71
Bag and tubing cost	$2.36	$2.36	$1.69
Sterile water	$1.43	0	0
Plastic zippered bag	0	$0.10	0
Total cost	$5.47	$4.14	$3.40
RN time per feeding (average),[a] min	44.8	35.8	31.8
RN time difference from RTH (per feeding), min	13	4	0
RN time difference from RTH (per day), min (h)	104 (1.73)	32 (0.53)	Baseline
Additional RN salary ($28.04/h)	$48.47/d	$14.86/d	Baseline
Cost differences compared with RTH (additional time + supplies)	$53.94/d	$19.00/d	Baseline

RN, registered nurse; RTH, ready to hang.
[a]This includes the time of the whole feeding cycle, including maintenance of the feeding set.

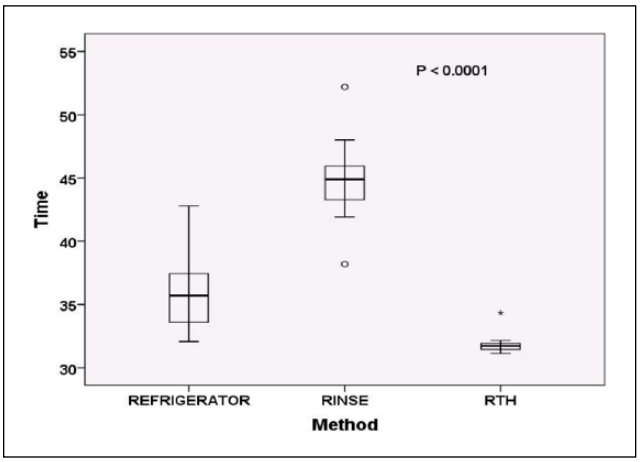

Figure 3. Box plot of time among 3 enteral feeding set handling methods. IQR, interquartile range; RTH, ready to hang; ○, represents outliers that are greater than 1.5 × IQR; *, represents extreme outliers that are greater than 2.1 × IQR.

systems change over time. The overall low growth seen in this study was much less than we premised given the increased manipulation of the EFS. This study design emulated a previous report by Beattie and Anderton[5] in 1998 where enteral feeding systems using both RTH and decanted formula were infused into a beaker with the tip of the EFS suspended above the fluid level to assess the impact of handling on bacterial growth. Investigators deliberately contaminated the hands of those who set up the initial EFS to determine the impact of bacterial contamination over time. They found the RTH formula had no bacterial growth during a 24-hour infusion and the other products using different designs of EFS did show growth. In our study, we did find low growth in the RTH group, but our study looked at intermittent use of the RTH set, which meant more manipulation. In both this older study and our study, using both RTH and decanted enteral formulas, more bacterial growth was seen toward the end of the 24-hour study period. However, the Beattie and Anderton study used EFS systems that required the tubing to be spiked into the enteral bag, which added a step that now does not exist as current EFS typically have the bag and tubing connected by the manufacturer.

A previous report by our group looked at this same EFS design and the same, sterile decanted formula hung for 12 hours.[23] In that study, lower than expected overall bacterial growth was also seen, but this was a clinical study using actual patients. Results from that study do mimic this newer study in that low levels of *Staphylococcus* species suggested touch contamination. We also saw more enteric pathogens, including *Enterobacter cloacae* and *Serratia marcescens* in the previous study, but this simulated investigation did not show that type of bacterial growth. Also differing from our earlier study where bacterial growth increased over time, our newer study did not demonstrate that trend. Instead, we saw low-level bacterial cultures at time 0 and time 1 with unacceptable bacterial growth at the end of the study period, indicating that each individual bolus feeding seemed independent of the previous ones.

Seventeen of the 24 species found in our study were skin or oral flora. *Delftia acidovorans* was isolated at 2 separate dates and pumps in the sterile water rinse group. This unacceptable bacterial growth is a gram-negative organism found in common household water supplies and plant life and, under normal conditions, is considered harmless.[24] *Staphylococcus pasteuri* (10^4 CFU/mL) was isolated from 1 EFS from the refrigeration group, which met the FDA criteria for unacceptable growth. It is associated with nosocomial infections.[25] The FDA criteria deem any culture growing *S aureus* to be unacceptable, and 1 culture from the refrigeration group grew that bacteria. *S aureus* is found on the skin, and approximately 30% of people will also have growth in the nares.[22]

As predicted, bacterial growth increased with the length of time the EFS was hanging. The time of the unacceptable growth occurred at the end of 24 hours with the exception of the mold found in time 1. The growth of mold was attributed to tubing coming disconnected and the tip coming into contact with the environment. The nursing unit where this study was being conducted was in the process of removing old carpet.

Of note was that there was even low growth in time 2 compared with time 0 and time 1. Time 0 was not always zero growth showing initial contamination at the time of setup. We did see <1% growth in time 0 plates. Using a new set and sterile formula suggests a break in technique in the beginning even though the initial setup was done by one of the investigators who had performed hand hygiene and wore clean gloves. These data confirm the findings by Bornemann et al[8] that strict adherence to sanitation practices must be followed in handling the EFS and that the EFS should be discarded after 24 hours.

Costs of supplies were low among the 3 methods, ranging from $3.40 for RTH to $5.47 for rinse methods. RTH is least expensive, but very few formulas used for children are available in RTH. From a cost perspective, refrigerating the whole set in a zippered plastic bag between feedings is the second best modality. The most substantial differences were observed in nursing time and labor costs (Figure 3). The defining factors that drive both nursing time and labor costs contained the greatest variables. Some of those variables included but were not limited to the following:

- differential pay compensation such as nighttime, weekend, specialty certification, and clinical advance ladder;
- level of skilled nursing permitted to administer the various methods of feedings; and
- fluctuations to the number of bolus feeds required in 24 hours.

Regardless of cost containment methods used, the fact that this study was done in a simulated setting does not take into account limitations that may indirectly increase nursing time and labor costs. Among those limitations are factors such as patient condition, room environment, access to patient-only refrigerators, parent preference, and unforeseen equipment malfunction. Some hospitals do not have in-room patient refrigerators, which would make the use of a zippered plastic bag method of EFS handling impractical as the EFS cannot be removed from the patient room.

Based on the results of this simulated study, nursing efficiency (time and costs) determined the largest difference among methods assuming safety from contamination was equivalent. Using RTH formula is the most efficacious in terms of contamination, costs, and labor and would be the best choice if available in many formulations. That stated, refrigerating the EFS between uses in the patient's refrigerator is the next safest and most cost-effective. This process could save patient care facilities an enormous amount of money and free nurses to concentrate on other expedient issues of patient care. Nursing costs amount to over 25% of hospital expenditures and about one-fourth of a trillion dollars per year in the United States.[26] Long-term nursing shortages are expected due to high attrition rates and a shortage of nursing faculty despite a shortage moratorium during the recession years.[27] Scott and colleagues[28] investigated the function of nurses in this century and found that patients assumed their nurses were competent in physical and technical skills but put a high value on psychosocial support. Many tasks took nurses away from the bedside, leaving them feeling short for time to deliver comfort care, educate families, and even surveil patients' safety. Even pediatric patients wanted their nurses to check on them frequently, give them medicine on time, and talk/listen to them.[29] Therefore, not only would using the most cost-efficient method of storing EFS between feedings lead to cost savings for hospitals, but it would also free up time for nurses to deliver patient-centered care instead of technology-centered tasks. Future studies should be nonsimulated and include laboratory analysis of formula specimens from actual patients and patient outcomes.

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Statement of Authorship

B. Lyman agrees to be accountable for all aspects of the work ensuring integrity and accuracy; contributed to the acquisition, analysis, or interpretation; and drafted the manuscript. M. Williams, J. Sollazzo, and P. Hensley contributed to the acquisition, analysis, or interpretation; and drafted the manuscript. A. Hayden contributed to the conception or design, and critically revised the manuscript. H. Dai contributed to the interpretation and critically revised the manuscript. C. Roberts critically revised the manuscript and gave final approval. All authors read and approved the final manuscript.

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Use of Blenderized Tube Feeding in Adult and Pediatric Home Enteral Nutrition Patients

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Abstract

Background: Long-term use of enteral nutrition (EN) continues to increase due to significant noted benefits. Patients also continue to express significant desire to pursue holistic and organic diets. Despite this, many nutrition providers are not well versed in assisting patients with blenderized tube feeding (BTF), and prevalence of its use is unknown. *Methods:* A validated survey was administered to Oley Foundation members or individuals with access to the Oley website to assess the prevalence of BTF. *Results:* A total of 216 participants took the survey, of whom 125 (57.8%) were pediatric patients with a mean age of 5.4 ± 3.5 years and 91 (42.2%) were adults with a mean age of 51.7 ± 19.5 years. Of pediatric patients, 112 (89.6%) used BTF for an average of 71% of their total daily nutrition intake; 93 (83%) reported that BTF comprised >50% of their daily EN, 12 (10.7%) reported it comprised 25%–50% of their daily enteral intake, and 7 (6.3%) reported BTF comprised < 25% of their daily intake. In the adult population, 60 (65.9%) used BTF for an average of 56% of total daily nutrition intake; 41 (68.4%) reported BTF comprised >50% of their daily nutrition intake, 11 (18.3%) reported it compromised 25%–50%, and 8 (13.3%) reported BTF comprised <25% of their daily intake. *Conclusions:* Most of the pediatric and adult patients surveyed use BTF as some portion of their enteral intake, making it essential that clinicians expand their knowledge related to BTF to appropriately care for this patient population. (*Nutr Clin Pract*. 2017;32:201-205)

Keywords

enteral nutrition; nutritional support; home care services; blenderized formulas; tube feeding formulas

A number of disease states such as cancer, chronic obstructive pulmonary disease (COPD), and cerebrovascular accidents are often associated with significant malnutrition and the inability to meet nutrition needs orally, leading to poor outcomes.[1–4] In fact, cachexia represents the cause of death in 10%–22% of all cancer deaths.[5] Enteral nutrition (EN) can be a safe and cost-effective way to provide nutrition support leading to improvement in quality of life and mortality.[5,6] Due to these benefits, long-term use of EN has increased significantly in the United States and worldwide.[7,8]

While commercial enteral formulas have been an available and convenient option for over 30 years, there has been an increased interest and shift toward providing whole foods via feeding tube.[9–13] Transitioning to a blenderized tube feeding (BTF) regimen allows the clinician and patient the ability to uniquely individualize EN intake, rather than relying on a commercial formula that can be difficult to modify to meet individual nutrition needs when multiple disease states are present.[7] Specifically, with an increase in food allergies and more complex diagnoses in the pediatric population, BTF allows parents the option to tailor a regimen that best fits their child's needs. There has been a cultural movement to include more natural, organic, and/or locally grown foods at the table, and BTF allows both adult and pediatric patients the opportunity to experience these foods and enjoy the diet of fellow family members. With this, registered dietitian nutritionists (RDNs) are reporting increased requests from patients and parents to provide BTF with the belief that BTF is healthier and a superiorly tolerated alternative to commercial formula.[7,13]

In the past 25 years of providing care in home EN (HEN), we hypothesized a significant component of both our adult and pediatric population was using BTF; however, it has been difficult to ascertain the percentage using BTF or the frequency, volume, and tolerance of this feeding method. To investigate this further, we had the opportunity to work with the Oley Foundation, a national, independent, nonprofit organization

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Conflicts of interest: Dr Ryan Hurt is a consultant for Nestlé. Lisa Epp is a consultant for Abbott.

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Table 1. Overall Prevalence of BTF Use and Baseline Demographics.[a]

Variable	Pediatric Group (Age <18 Years) (n = 125)	Adult Group (Age ≥18 Years) (n = 91)	*P* Value
Patients who have used BTF	112 (89.6)	60 (65.9)	<.0001
Male	74 (59.2)	39 (42.9)	.018
Age, mean ± SD, y	5.4 ± 3.5	51.7 ± 19.5	<.001
Work status	NA		
Full-time		14 (15.4)	
Part-time		13 (14.3)	
Do not work		64 (70.3)	
Duration of tube feeding			.004[b]
<1 month	0	0	
1–6 months	3 (2.4)	11 (12.1)	
6 months to 1 year	3 (2.4)	4 (4.4)	
1–5 years	76 (60.8)	37 (40.7)	
>5 years	43 (34.4)	39 (42.9)	

BTF, blenderized tube feeding; NA, not applicable.
[a]Values are presented as number (%) unless otherwise indicated.
[b]*P* value reflects significant difference between Pediatric and Adult groups.

with 16,300 registered members, of whom 3748 are on record as enteral patients. The Oley Foundation was founded in 1983 with a primary focus "to enrich the lives of patients dependent on home intravenous nutrition and tube feeding through education, advocacy, and networking."

Methods

This cross-sectional study and survey were approved by the institutional review board (IRB) of the authors' institution. The survey (Supplementary Figure S1) used in the current study was developed and validated for content by our multidisciplinary HEN team (which includes RDNs, nurses, midlevel providers, pharmacists, and nutrition support physicians), and the validation process has been outlined previously.[7] The inclusion criterion for the current study included any patient or family member who had not previously taken the study. Individuals who had previously taken the survey were excluded.

Following IRB approval, a link to the survey was published on the Oley Foundation website and remained live for 4 weeks. The online surveys were completely anonymous. No identifying information was collected from any patient. The surveys were collected using Adobe Form Central software (Adobe Systems, San Jose, CA). Statistical analysis was performed on all variables using JMP, version 10 (SAS Institute, Cary, NC). For the associations of categorical variables, we used the χ^2 test or Fisher's exact test (when frequency <5 within any of the cells). For matched pairs binary categorical data on the same patients, we used the McNemar test, which allowed us to see which method led to more weight loss for the participants.

Results

A total of 216 participants took the survey (Table 1), amounting to 5.8% of the Oley members registered as enteral patients. Of these, 125 (57.8%) were pediatric patients (<18 years old) and 91 (42.2%) were adults (≥18 years old). The mean age of the pediatric cohort was 5.4 ± 3.5 years, and the mean age of the adult cohort was 51.7 ± 19.5 years. Of the patients surveyed, 112 (89.6%) of pediatric patients used BTF for an average of 71% of their total daily nutrition intake. In the adult population, 60 (65.9%) used BTF for an average of 56% of total daily nutrition intake. Pediatric patients had a significantly higher tendency to use BTF ($P < .0001$).

In the pediatric population, 6 (4.8%) received HEN for <1 year, 76 (60.8%) had HEN for 1–5 years, and 43 (34.4%) received HEN >5 years. In the adult population, 15 (16.5%) had HEN for <1 year, 37 (40.7%) had HEN for 1–5 years, and 39 (42.9%) received HEN for > 5 years. In the adult cohort, 14 (15.4%) of the participants worked full-time, 13 (14.3%) worked part-time, and 64 (70.3%) did not work.

When comparing pediatric vs adult patients that use BTF, those who were younger were more likely to be compliant and consistent in using BTF, with 93.75% of pediatric patients administering BTF 7 days per week and 76.67% of adults administering BTF 7 days per week ($P = .0011$) (Table 2). In the pediatric patients who used BTF, 93 (83%) reported it comprised >50% of their daily EN feedings, 12 (10.7%) reported it comprised 25%–50% of their daily enteral intake, and 7 (6.3%) reported BTF comprised <25% of their daily food intake. In the adult population, 41 (68.4%) reported BTF comprised >50% of their daily nutrition intake, 11 (18.3%) reported it comprised 25%–50%, and 8 (13.3%) reported BTF comprised <25% of their daily intake. However, there was no significant association between age of the patient and the percentage of BTF that was consumed on a daily basis.

Most patients using BTF self-prepared their own blends at home, with 84 (75%) of the pediatric population self-preparing BTF and 40 (67%) of the adult population preparing their own BTF (Table 2). A total of 27 (24%) of the pediatric population

Table 2. Data for Patients Using BTF.

Variable	Pediatric Group (Age <18 Years) (n = 112), No. (%)	Adult Group (Age ≥18 Years) (n = 60), No. (%)	*P* Value[a]
Days per week of BTF use			.001
7	105 (93.8)	46 (76.7)	
<7	7 (6.3)	14 (23.3)	
What percentage of daily food comprises BTF?			.015
<25%	7 (6.3)	8 (13.3)	
25%–50%	12 (10.7)	11 (18.3)	
50%–75%	13 (11.6)	7 (11.7)	
75%–100%	80 (71.4)	34 (56.7)	
What type of BTF do you use?			.04
Commercial	1 (<1)	5 (8)	
Self-prepared	84 (75)	40 (67)	
Both	27 (24)	15 (25)	
Weight loss with enteral feeds			<.0001
No weight loss with BTF	101 (90.2)	51 (85)	
Weight loss with BTF	11 (9.8)	9 (15)	
No weight loss with commercial formula	66 (58.9)	31 (32.0)	
Weight loss with commercial formula	46 (41.1)	29 (48.3)	

BTF, blenderized tube feeding.
[a]*P* values reflect significant difference between Pediatric and Adult groups.

used a combination of self-prepared blends at home and commercial blended formulas (Compleat [Nestlé, Florham Park, NJ], Liquid Hope [Functional Formularies, Centerville, OH], and Real Food Blends [Real Food Blends, Chesterton, IN]). Only 1 (<1%) of the pediatric cohort used all commercial blended formula for their BTF intake. In the adult group, 15 (25%) used both their own self-prepared blends and commercial blended formula, while 5 (8%) used commercial blended formula alone. There was a significant association ($P = .0371$) between age of the patient and the type of BTF (self-prepared vs commercial) used, specifically showing those younger were more likely to self-prepare their own blends at home.

In the group of pediatric patients, 101 (90.2%) reported no weight loss when using BTF while 66 (58.9%) reported no weight loss when using commercial EN formulas (Table 2). In the adult population, 51 (85%) reported no weight loss when on BTF vs 31 (32%) reporting no weight loss with commercial enteral formulas. Results showed using commercial EN formula was more likely to lead to weight loss than using BTF ($P < .0001$).

Discussion

The present study is the first that we are aware of to compare BTF patterns of adult and pediatric patients and revealed that in a diverse population, there is significant prevalence of BTF use. Through self-reported surveys, 89.6% of pediatric patients and 65.9% of adult patients received some form of BTF. It is important to note that these surveys were offered through the Oley Foundation, which has as an active, involved, and educated group of HEN consumers, possibly making them more likely to seek out resources regarding BTF. This could explain why these prevalence rates were higher than we previously reported from a single-center adult cohort (55% reported BTF use).[7] Despite these differences, both studies do highlight that BTF use is present in most HEN patients surveyed. Further clinical support is essential to provide adequate education and resources for patients engaged in BTF to ensure successful clinical outcomes such as appropriate growth, development, and weight gain.

In the past, there have been many speculated disadvantages of BTF, including potential higher risk for microbial contamination, increased labor to prepare BTF, and lack of standardized recipes for BTF preparation.[14–19] The nutrition content of BTF has been demonstrated in some studies to be highly variable and inconsistent in nutrient composition, potentially leading more often to micronutrient deficiencies, underfeeding, and a resultant decline in weight.[20] In Sullivan et al,[16] nutrition quality of BTF samples was analyzed from 4 hospitals in the Philippines, finding a high degree of variability in the nutrition content, specifically the calorie composition along with a lower than expected measured value of nutrition content being present in BTF samples. However, of interest when reviewing results from our survey was that weight loss was actually less likely to occur in patients using BTF vs those using commercial enteral formulas.

Previous studies have reported improvements in vomiting and tolerance of gastric feedings and decreased symptoms of gagging and retching with BTF, allowing for pediatric patients to maintain adequate growth.[21,22] In Hurt et al,[7] patients surveyed had significantly less reported nausea, vomiting, bloating, diarrhea, and constipation on BTF, and 80% of adult patients using BTF reported maintaining goal body weight.

The BLEND (Blenderized Enteral Nutrition Diet) Study, a prospective, 6-month, feasibility study, looked at 14 pediatric patients who were transitioned to a blenderized diet receiving >75% of their nutrition via gastrostomy tube and found the energy and protein intakes were higher with their blenderized feeds than with commercial feedings.[23]

With proper training and education, RDNs can help standardize BTF recipes to provide consistent levels of macronutrients and micronutrients. To help support weight maintenance, it is vital for patients using BTF at home to have close follow-up and monitoring with an RDN. In Hurt et al,[7] only 16% of patients reported seeking out an RDN to help develop BTF recipes and monitor their nutrition. In the present survey, 46% of pediatric patients and 28.3% of adult patients reported the most common cause for not using BTF was not knowing how to prepare it. We strongly feel that an RDN with expertise in BTF should be following these patients to help with recipe development tailored to the patient and to regularly intervene and make adjustments should weight loss occur.

While it is important for patients to have close monitoring with an RDN, it is equally important that the RDN have the education and knowledge regarding recipe development, preparation, and administration of BTF. In Johnson et al,[13] RDNs were surveyed on their experience with BTF in their practice and noted that lack of time and ability to follow up with patients was one of the most frequently selected reasons for not using BTF in clinical practice. In the same study, 28% of RDNs surveyed also reported that while they were familiar with BTF, they wanted more information regarding it. Older RDNs reported less familiarity and use in practice. With our survey reporting high prevalence of use of BTF among both pediatric and adult patients, this only strengthens the importance of ensuring RDNs are adequately trained to manage those on BTF.

In the past, another consideration that may deter both patients and clinicians from using BTF is the time commitment and labor required for the preparation and administration of BTF. Compared with commercial formulas, preparation of BTF is more labor intensive and involves several steps, including grocery shopping, cooking and blending of foods, proper food storage, and food safety practices. The additional effort can potentially increase the burden on a patient or caregiver already dealing with other medical cares. However, while caregivers have reported finding the diet more time-consuming and more expensive compared with commercial formula, they were satisfied with BTF and planned to use it long term.[23]

The current study did have a number of limitations. The first and main limitation with generalizability of the results is the population surveyed. Although the exact number is uncertain, the number of patients in the United States receiving HEN has been estimated to be >150,000.[7,24] With this number, the population eligible for the current survey was ~2% of the HEN population. In addition, the population surveyed would tend to be biased toward individuals who are more active in terms of nutrition and thus perhaps more likely to use BTF. This could partially explain why the prevalence of BTF was even higher than we noted in our previous single-center survey.[7]

Another limitation is that the survey was designed and validated to apply to all patients receiving HEN regardless of age to allow comparisons. As such, questions regarding employment were present and may not apply fully to the pediatric population. Despite this limitation, we did note that in the adult population, 70.3% of patients using BTF did not work, whereas 29.7% of those reporting BTF use worked full-time or part-time. Those working and using BTF were more likely to use a commercially prepared blended formula as an alternative or backup option. In addition, the survey as an instrument focuses on self-reported data, which can also create inherent bias. As an example, respondents who have switched to BTF may be more likely to report more positive results, perhaps skewing reports of weight change or symptoms with BTF.

The questions also asked that if the patient was unable to fill out the survey, a family member could answer for the patient. This did require some careful interpretation of the responses as typically the pediatric group was too young to prepare the BTF themselves. Again, despite this limitation, we felt that important points were raised such as the survey revealing that 40.1% of pediatric patients and 21.6% of adult patients were preparing their blenderized food recipe one time per day and then refrigerating the blend for use throughout the day. A small percentage (9%) of pediatric patients was preparing blenderized foods multiple times per day (right before each meal) vs 28.3% of the adult population using this method. The time commitment required becomes a key barrier to implementing BTF and one that an RDN with expertise in the development and preparation of BTF recipes may be able to help the working patient overcome through appropriate education, resources, and a monitoring plan. In a recent publication from the Academy of Nutrition and Dietetics, steps are provided to implement a homemade tube feeding recipe, and a sample recipe is shown.[12] It may be helpful to have a national effort to share more BTF recipes between patients and providers in the future.

Conclusions

Most of the pediatric and adult patients surveyed use BTF as some portion of their enteral intake. With a high prevalence of use, it is vital that clinicians expand their knowledge related to BTF, and patients have access to RDNs with expertise in the area of BTF recipe development, preparation, and monitoring. Further resources, education, and research to ensure BTF safety will help ensure ongoing success for these patients.

Statement of Authorship

L. Epp and L. Lammert contributed to the acquisition of data and conception of the study and drafted the manuscript; N. Vallumsetla contributed to the acquisition of data and critically revised the manuscript; M. S. Mundi and R. T. Hurt contributed to the conception and design of study and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary Material

Supplementary Figure S1 is available with the article online at http://journals.sagepub.com/home/ncp.

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Ultrasound-Assessed Gastric Antral Area Correlates With Aspirated Tube Feed Volume in Enterally Fed Critically Ill Patients

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Abstract

Background: Enteral tube feed (ETF) intolerance occurs frequently in hospitalized patients and more so in critically ill patients. Most critical care nurses continue to assess gastric residual volume (GRV), especially among those with a history of ETF intolerance. We hypothesized that ultrasound assessment of GRV correlates directly with aspirated tube feed volume. *Methods:* This was a prospective cohort study of a convenience sample of critically ill mechanically ventilated patients admitted to an intensive care unit receiving ETF. The gastric antrum was imaged using the aorta and inferior vena cava (IVC) as landmarks concurrently and simultaneously using a curvilinear probe in the midline. All ultrasound measurements were performed at 30 degrees head up, in the supine position, and prior to the assessment of GRV by nursing staff blinding the ultrasonographer to gastric volume aspirated. Gastric antral area was determined by assessing anteroposterior (AP) and craniocaudal (CC) diameters of the gastric antrum. *Results:* Gastric cross-sectional area (CSA) using IVC as a landmark ($R^2 = 0.92$, $P < .0001$) and aorta as a landmark ($R^2 = 0.86$, $P < .0001$) correlated with aspirated volume. CC diameter of the stomach measured using the aorta as a landmark correlated with aspirated volume and increased linearly with increasing GRV ($R^2 = 0.78$, $P < .0001$). A CC diameter of <10 cm using the aorta as a landmark predicted a gastric volume of <500 mL. *Conclusions:* Ultrasound assessment provides accurate assessment of gastric volume in real-life settings, and the CC diameter of the gastric antrum provides a simple surrogate of GRV. (*Nutr Clin Pract*. 2017;32:206-211)

Keywords

ultrasonography; gastric volume; tube feeds; feed intolerance; critical care; enteral nutrition; nutritional support

Background

Recently published guidelines[1] recommend that critically ill patients be monitored for enteral tube feed (ETF) intolerance using some combination of radiologic studies, physical examination, or a history of absence of passage of flatus or stool. ETF intolerance manifested by high nasogastric output, abnormal radiographic studies, abdominal distension, or diarrhea occurs in up to one-third of hospitalized patients and has been associated with worse outcomes.[2] Physical examination and review of abdominal radiologic films are recommended as alternative strategies at institutions where routine assessment of gastric residual volume (GRV) is eliminated.[1,2] GRV assessment continues to be useful in the postoperative setting, in patients being aggressively bolus fed (defined variably as 200–400 mL over 15 minutes),[3] and in patients on vasopressor therapy or those in whom a large aspiration event may be harmful. GRV assessment also remains the only method to assess for gastric dysmotility.

Ultrasonographic assessment of gastric antral cross-sectional area (CSA) has been used to estimate gastric volume in the perioperative setting[4,5] to assess gastric emptying time[6] and in the peri-intubation period to assess whether the stomach is full and whether, therefore, there is a risk of aspiration during rapid sequence intubation.[7] A large national survey of critical care nurses based on >2200 responses concluded that most (>97%) would measure GRV with wide variation in interpretation of aspirated volume and possibly resulting in an unnecessary reduction in calories delivered.[8]

It is unclear whether gastric antral CSA determined by ultrasound correlates with aspirated tube feed volume. The goal of this pilot study of a convenience cohort of intensive care unit (ICU) patients was to assess gastric antral dimensions with ultrasound and correlations with volume of tube feeds aspirated with the intent of eliminating the need to assess GRV by aspirating tube feeds when indicated.

Methods

Thirty patients or their proxies were approached for enrollment in the study. Eleven declined to participate. A convenience

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sample of 19 patients admitted to the medical ICU at John H. Stroger Hospital of Cook County was enrolled. The study was reviewed and approved by the institutional review board, a requirement for a verbal consent narrative was approved, and written signed consent was waived given minimal risk to patients and the difficulty of obtaining consent in the ICU.

Inclusion criteria included critically ill patients of all races, both sexes, and aged 18–100 years who were admitted to the medical ICU with the following:

- Nasogastric or orogastric tube or percutaneous gastrostomy tube in place
- Tube feeds ongoing or planned to continue
- Tip of tube in stomach on most recent x-ray

Exclusion criteria were as follows:

- Feeds being delivered by nasojejunal tube
- Tip of gastric tube not in the stomach in most recent x-ray (at intake)
- Prisoners
- Intestinal obstruction
- Gastrointestinal perforation
- Plan to keep patients nil per os (NPO) for a prolonged duration for any reason
- GRVs not being monitored regularly by nurses for any reason
- Pregnant women
- Patient deemed inappropriate for study enrollment by either attending/registered nurse or investigator for any reason

A 2–5 MHz wide band convex-array transducer (GE LOGIQ e; General Electric Healthcare, Wauwatosa, WI) was used to acquire images of the gastric antrum in the sagittal plane in the epigastrium (Figure 1) using the aorta and the inferior vena cava (IVC)/superior mesenteric vein as landmarks concurrently and simultaneously. All scans were performed at 30 degrees head up in the supine position. Probe depth was set to 17 cm and adjusted as necessary. The index marker on the transducer pointed towards the patients head while the index marker on the screen was oriented to the left. A total of 57 attempts to image the antrum using the aorta as a landmark and 57 using the IVC as a landmark were documented. Measurements were obtained prior to routine tube feed aspiration by nursing staff, and after no further tube feeds were aspirated, the stomach was scanned again to ensure complete emptying. Three anteroposterior (AP) diameter ("1" in Figures 2–6) and craniocaudal (CC) diameter ("2" in Figures 2–6) measurements of the gastric antrum were performed at each site (the technique has been described previously),[4,5] and the average of each used to determine antral CSA as follows:

$$\text{Area} = 3.142 \times (\text{average AP diameter} \times \text{average CC diameter})/4.$$

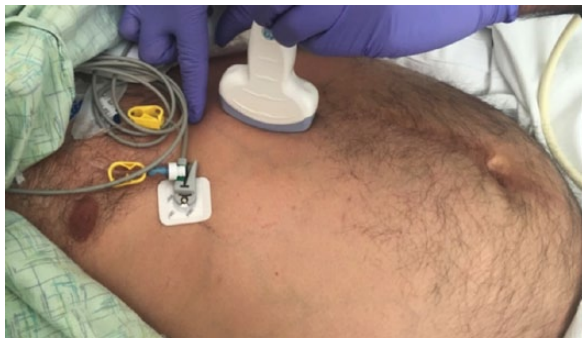

Figure 1. Gastric residual volume assessment technique. Curvilinear probe in the epigastrium.

Patients were scanned daily, up to 4 times a day (depending on sonographer availability), and before scheduled GRV check by nurses for at least 5 days or until the decision to remove the feeding tube was made and/or the patient began to eat or was transferred out of the medical ICU or died, whichever came first. At our institution, a GRV check is performed every 6 hours, as deemed necessary by the nursing staff. A 50-mL syringe is used to aspirate tube feeds until no feeds are aspirated and charted as "gastric residuals." Patient scenarios where tube feeds had been held for a procedure or potential extubation were included in the protocol to enable characterization of the empty stomach in the critically ill patient. A single sonographer (VS) with training in critical care ultrasound (American College of Chest Physicians Critical Care Ultrasound Certification) performed ultrasound assessments and measurements.

Previous studies in similar patient populations[9] have not shown significant associations between computed tomography–determined gastric volume and age, sex, body mass index, mechanical ventilation, or vasopressor infusion. We therefore performed simple linear regression analysis to assess correlations. Statistical analysis was performed and graphic displays generated using JMP version 7.0.1 software (SAS Institute, Cary, NC) with $P < .05$ accepted as indicating significant differences.

Results

Table 1 depicts demographics of the patients included in the study. Visualization of the gastric antrum (114 total attempts at imaging) was more frequent using the aorta as a landmark compared with the IVC (21% not visualized vs 42%), mostly due to overlying bowel gas or intragastric air. Typical images depicting various gastric volumes aspirated are shown in Figures 2–5. The largest GRV aspirated was >700 mL. An empty and collapsed stomach is depicted in Figure 6, and a typical image obtained when the stomach was not visible due to gas in the antrum is shown in Figure 7. When visualized easily, aortic and IVC gastric antrum CSA were correlated tightly and could be

Table 1. Demographics and Baseline Clinical Parameters.[a]

Variable	Value
Age, y	55 ± 12
Female sex	7 (37)
Charslon comorbidity index	4.2 ± 3
SAPS II	54 ± 17
Sepsis	12 (63)
Septic shock	3 (15)
Mechanical ventilation	19 (100)
Body mass index, median (IQR), kg/m^2	26 (17–41)
Height, median (range), cm	165 (127–178)
Weight, median (range), kg	74 (40–120)
Comorbidities	
CKD	6 (32)
CHF	4 (21)
COPD	5 (24)
Diabetes	7 (37)
Malignancy	7 (37)
Stroke	1 (5)
Ethnicity, No.	
Black	11
White	2
Hispanic	4
Other	2

CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score.
[a]Variables are presented as mean ± standard deviation or number (%) unless otherwise indicated. Comorbidities add up to more than 19 due to multiple comorbidities per patient.

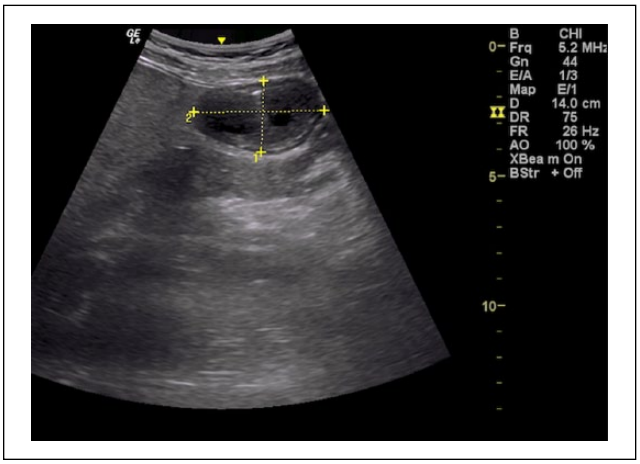

Figure 2. Gastric antrum ultrasound appearance of aspirated volume of 150 mL (aorta as landmark). 1, 2.7 cm; 2, 5.0 cm.

used interchangeably ($R^2 = 0.98$, $P < .0001$) (Figure 8). Gastric antral CSA using IVC as a landmark ($R^2 = 0.92$, $P < .0001$) and aorta as a landmark ($R^2 = 0.86$, $P < .0001$) correlated with aspirated volume. Craniocaudal diameter ("Average CC Diameter,

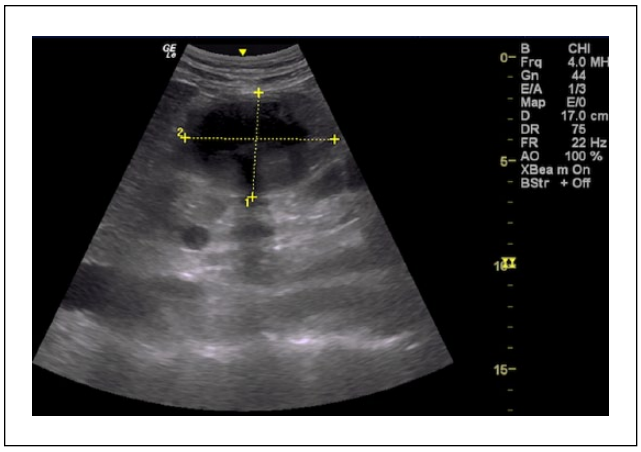

Figure 3. Gastric antrum ultrasound appearance of aspirated tube feed volume 315 mL (aorta as landmark). 1, 5.0 cm; 2, 7.2 cm.

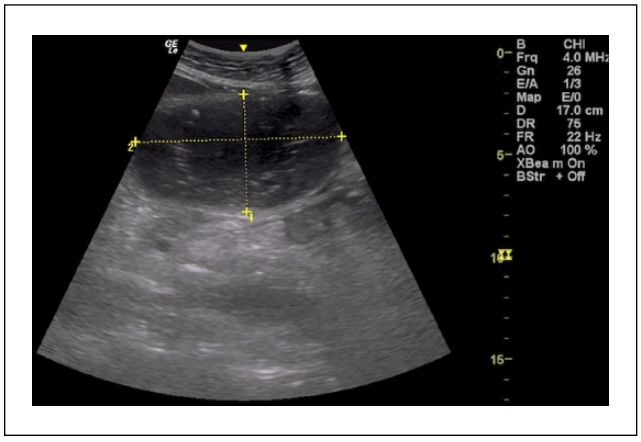

Figure 4. Gastric antrum ultrasound appearance of aspirated tube feed volume of 770 mL (aorta as landmark). 1, 5.7 cm; 2, 10.0 cm.

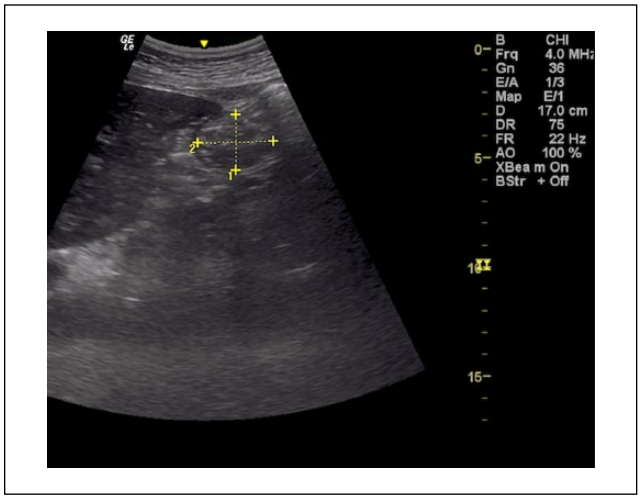

Figure 5. Gastric antrum ultrasound appearance of aspirated tube feed volume of 10 mL (aorta as landmark). 1, 2.5 cm; 2, 3.4 cm.

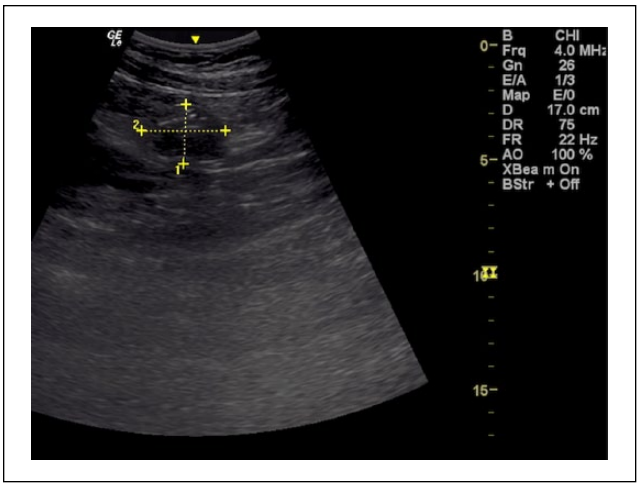

Figure 6. Gastric antrum ultrasound appearance of aspirated tube feed volume of 0 mL. 1, 2.6 cm; 2, 3.6 cm.

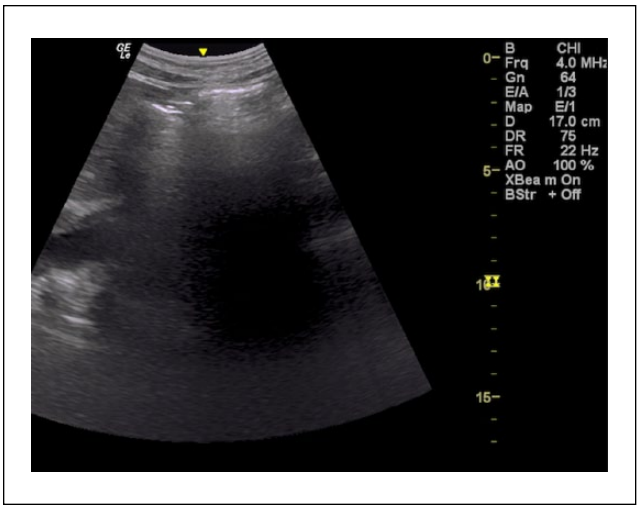

Figure 7. Gastric antrum not visualized due to gas in the stomach.

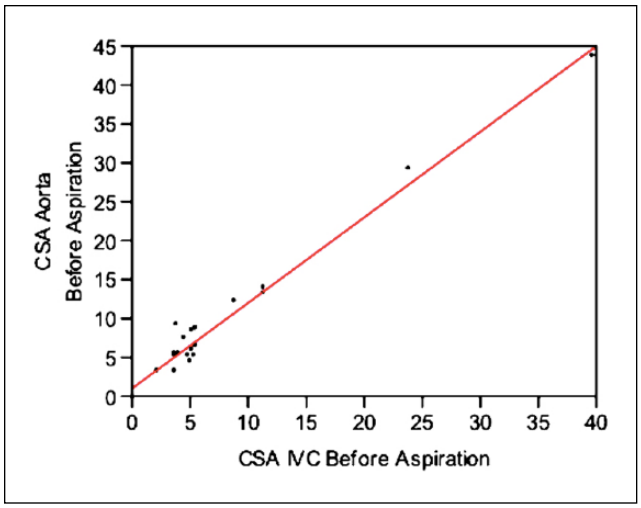

Figure 8. Correlation between antral cross-sectional area (CSA) using inferior vena cava (IVC) as a landmark and aorta as a landmark.

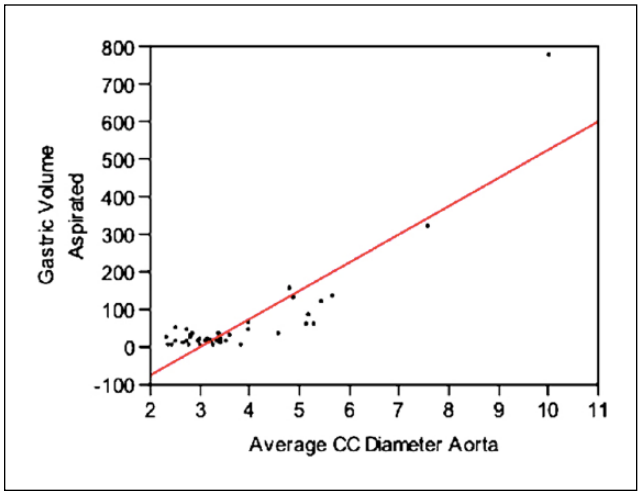

Figure 9. Correlation between aspirated gastric volume and antral craniocaudal (CC) diameter using aorta as a landmark.

Aorta," Figure 9) and CSA of the antrum of the stomach ("CSA Aorta," Figure 10) measured using the aorta as a landmark correlated with aspirated volume and increased linearly with increasing GRV. A craniocaudal diameter alone of <10 cm using the aorta as a landmark predicted a gastric volume of <500 mL and a craniocaudal diameter using the aorta as a landmark of <5 cm predicted GRV <150 mL. When imaging was possible, postaspiration antral CSA was identical to CSA obtained for patients in whom GRV was <10 mL.

Discussion

This is the first study (to our knowledge) that directly correlates ultrasound-derived measurements (specifically gastric antral CSA and craniocaudal [CC] diameter) with simultaneous and chronologically synchronously acquired aspirated tube feed volume. This study validates ultrasound assessments of GRV in patients fed enterally in the medical ICU setting. Previously published studies have assessed gastric contents (solid and liquid) with ultrasound in the setting of emergent or elective surgery by manipulating stomach contents (stomach massage and positional changes on the operating table),[4,6] with linear correlations being noted between assessment with ultrasound vs actual volumes aspirated in the right lateral decubitus position. Hamada et al[9] report a strong correlation between ultrasound and computed tomography–determined gastric volume in a population with a large proportion (49%) of trauma patients. In this study, a mean delay of 31 minutes between ultrasound and computed tomographic studies as well as the presence of

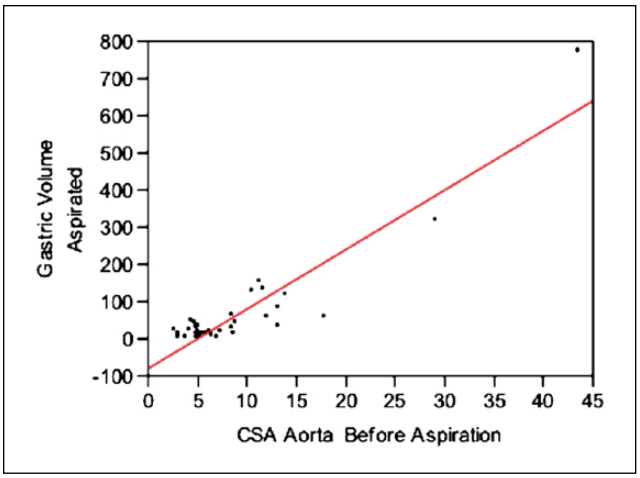

Figure 10. Correlation between aspirated gastric volume and antral cross-sectional area (CSA) using aorta as a landmark.

trauma-related pathology might have affected results.[10] ETF intolerance (defined as some combination of vomiting, regurgitation, abdominal distension, and large GRVs defined as ≥500 mL)[11] is more prevalent in critically ill patients and has been associated with increased mortality. Aggressive bolus feeds[3] may increase the risk of pneumonia,[12] and ultrasound-assessed GRV in this scenario may allow early detection of patients with gastric dysmotility. Recent guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN)[1] suggest that patients on vasopressor therapy receiving EN be monitored more closely for ETF intolerance. These guidelines recommend that increasing GRV, abdominal distension, and/or increasing nasogastric tube output be considered early signs of gut ischemia with recommendations to hold enteral nutrition (EN) until these symptoms abate. These guidelines also suggest that if the practice of routine GRV assessment is eliminated, alternative strategies, including physical examination and abdominal radiologic films, be used to monitor critically ill patients. We strongly believe, based on results of this study, that use of directed ultrasound can directly assess GRV, making additional radiation exposure unnecessary. Some experts call for a nuanced assessment of GRV to assess gastric function[13] and advocate for retention of GRV measurements, especially in surgical ICU patients and those patients who have a higher severity of illness.

Canadian Clinical Practice Guidelines (CCPG)[14] as well as published expert opinions[13,15] recommend variable thresholds for ETF intolerance with a threshold of 500 mL as a marker of optimal delivery of EN. The German Society for Nutritional Medicine recommends measurement of GRV among patients with abdominal surgery, suggesting a threshold of 200 mL as the cutoff for modification of ETF delivery rate as well as monitoring GRV every 4–6 hours in this group of patients. These guidelines also recommend that enteral delivery rates be reassessed and altered in the event that vomiting occurs.[13]

Medical students can learn basic ultrasound, including echocardiography, lung ultrasound trauma assessment, and vascular access with e-learning and a 4-hour didactic session.[16] Gastric ultrasound is easy to learn.[9] Gastric antral assessment requires simply placing the probe in the midline inferior to the xiphoid process with visualization of the aorta, and the antrum is usually visualized anterior to the aorta. Nurses routinely assess urinary bladder volume in the ICU with handheld devices, and the technique described here is similar.

A single linear measurement (gastric antral CC diameter) on gastric ultrasound performed by nursing staff may replace a cumbersome and time-consuming conventional GRV assessment or radiologic studies in patients suspected to have or be at risk for ETF intolerance. In addition, GRV assessment is impossible in those patients with a small-bore nasogastric tube in place, and in this setting, gastric ultrasound provides an easy way to assess gastric volume among patients with suspected ETF intolerance. While none of the patients in this study were being cared for in the surgical ICU, we feel strongly that this technique can be extended to assessment of ETF intolerance among surgical patients.

Limitations of this study include the inability to visualize a substantial proportion of gastric antrums. In our collective experience, the antrum is not as easy to visualize as has been reported in previous studies, mostly due to obscuration by intragastric air or air in the surrounding bowel lumen. However, since this is a prospective study with imaging attempts on each patient multiple times a day, we believe this is an accurate "real-world" representation of mechanically ventilated patients in the medical ICU. Another limitation is the small sample size, but 114 imaging attempts on these patients allow us to draw clinically relevant conclusions.

Conclusions

We show in this pilot study that, when necessary, gastric ultrasound can accurately estimate gastric volume among critically ill patients being enterally fed in a medical ICU setting. The ultrasound appearance of the empty or nearly empty stomach is defined, allowing for confident titration of feeds or institution of aggressive bolus feeding, especially when there is a "need to know" the gastric volume. Ultrasonographically assessed CC diameter of the gastric antrum <10 cm using the aorta as a landmark is a simple test to predict gastric volume <500 mL. Nursing staff may be able to use bedside ultrasound as an alternative to radiographic studies to assess gastric volume in patients with ETF intolerance.

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Statement of Authorship

V. Sharma conceived and designed the research study; J. Bailitz and R. Gueret contributed to the review of the initial study design;

V. Sharma acquired and analyzed the data; and D. Gudivada contributed to data entry and cross-checking accuracy of the numerical data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Computed Tomography–Guided Percutaneous Gastrostomy/Jejunostomy for Feeding and Decompression

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Abstract

Background: An effective method for long-term enteral feeding or stomach decompression is the use of a percutaneous gastrostomy (PEG) or sometimes jejunostomy (PEJ). Under certain circumstances (eg, inadequate transillumination), endoscopic placement of PEG/PEJ tubes is impossible. In these cases, computed tomography (CT)–guided PEG/PEJ may represent an alternative technique. In this study, we evaluate indications, results, and complications of CT-guided PEG/PEJ. *Materials and Methods:* A total of 102 consecutive referred patients were enrolled in the study. Patients came to the endoscopy unit of our department to undergo a CT-guided PEG/PEJ for long-term intragastric/intrajejunal feeding (n = 57) or decompression (n = 45). The majority (n = 98) received a pull-through PEG/PEJ with simultaneous gastroscopy/jejunoscopy. Dose length product and the effective dose for every patient were calculated. *Results:* PEG/PEJ tube placement was successful in 87.3% (89 of 102). Feeding PEG/PEJ tube placement was successfully completed in 91.2% (52 of 57); decompressive PEG/PEJ tube placement was likewise successfully completed in 82.2% (37 of 45). No procedure-related mortality was observed. Minor complications (eg, tube dysfunction, local bleeding, minimal leakage, local skin infection) were observed in 13 patients. The complication rate was similar between the feeding and decompression groups ($P = .9$). *Conclusions:* CT-guided PEG/PEJ is a feasible and safe method with a low procedure-related morbidity rate for patients where endoscopic placement via transillumination is not successful. Thus, the procedure is an attractive alternative to surgical tube placement. Long-term complications, mainly tube disturbances, can be treated easily. (*Nutr Clin Pract*. 2017;32:212-218)

Keywords

enteral nutrition; gastrostomy; jejunostomy; gastrointestinal endoscopy; computed tomography; radiology

Introduction

The most common access for long-term enteral feeding is a percutaneous endoscopic gastrostomy (PEG).[1,2] If simultaneous stomach decompression or small bowel feeding is preferred, a percutaneous endoscopic jejunostomy (PEJ) is used alone or in combination with the PEG. Reasons for the need of PEG/PEJ placement to ensure enteral food intake are, among others, dysphagia caused by neoplasia or neurologic disorders.[2] Reasons for the need of bowel or stomach decompression are mostly malignant obstructions.[3] In this context, PEG/PEJ tubes are placed in patients with poor performance status and not eligible for surgical treatment, in those who refuse to undergo surgery, and in patients with a limited life expectancy because of end-stage cancer.[4] PEG was first described by Gauderer et al[5] in 1980 and remains the standard procedure for long-term feeding access. In some cases, however, placement of PEG/PEJ tubes is not feasible due to previous (esophageal or gastric) surgery, obesity, hepatosplenomegaly, peritoneal carcinosis, inadequate transillumination, or obstructed passage.[6] PEG placement fails in up to 4% to 5% of the patients.[7,8] In these cases, computed tomography (CT)–guided PEG/PEJ may represent an alternative technique to enable feeding and/or decompression in patients in whom the endoscopic method cannot be used.

A combination of radiologic and endoscopic imaging is advantageous toward improvement of accuracy and visibility when endoscopy alone is not possible. The high success rate, coupled with low morbidity and mortality, makes the procedure an attractive alternative to surgical tube placement.[9] Furthermore, in some cases when the passage is blocked and endoscopic control is not feasible, a CT-guided direct puncture and air insufflation may be successful. The aim of this study was to evaluate indications, results, and complications of CT-guided PEG/PEJ. Another objective was to investigate the average amount of radiation received during the procedure.

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Table 1. Indications for Gastrostomy/Jejunostomy (n = 102).

Indication	No.	%
Feeding PEG/PEJ	57	100
Head and neck cancer	29	50.9
Neurologic disorders	12	21.1
Esophageal cancer	5	8.8
Sepsis/multiple-organ dysfunction syndrome	4	7.0
Gastric cancer	2	3.5
Cervical cancer	1	1.9
Lung cancer	1	1.9
Appendiceal cancer	1	1.9
Thyroid cancer	1	1.9
Paranasal sinus cancer	1	1.9
Decompression PEG/PEJ	45	100
Ovarian cancer	14	31.1
Gastric cancer	14	31.1
Cervical cancer	4	8.9
Breast cancer	4	8.9
Neurologic disorders	3	6.7
Colorectal cancer	2	4.5
Head and neck cancer	1	2.2
Pancreatic cancer	1	2.2
Appendiceal cancer	1	2.2
Esophageal cancer	1	2.2

PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

Materials and Methods

Between January 2008 and April 2015, 102 consecutive patients who were referred to the endoscopy unit of our department to undergo a CT-guided PEG/PEJ for long-term intragastric/intrajejunal feeding or decompression were enrolled in this study (Table 1). Initially, these patients were referred to the endoscopic unit of our department for PEG/PEJ placement, but endoscopic placement failed. Informed written consent was obtained from every patient or the patient's legal representative before any intervention. The study was conducted according to the Declaration of Helsinki and was approved by the local Ethics Committee at the University Hospital of Erlangen. All relevant patient records were reviewed to assess a primary diagnosis, complications occurring during PEG/PEJ placement, as well as complications associated with PEG/PEJ use. In addition, radiation exposure data and tube sizes were evaluated. The patient charts included patient demographics, follow-up information, and outcome.

The majority of the patients (n = 98) received a pull-through PEG/PEJ (Freka PEG Set Gastric 9F or 15F, Fresenius, Bad Homburg, Germany; NutriciaFlocare PEG 14F or 18F, Pfrimmer Nutricia GmbH, Erlangen, Germany). In this case, the stomach was first insufflated via endoscope. Before the puncture was performed, the skin at this site was cleaned carefully to prevent infection. Thereupon, a suitable puncture site was chosen under CT control, and the stomach or jejunum was punctured (Figures 1 and 2). Next, a scalpel was used to make a horizontal incision (0.5–1.0 cm wide, 2–3 mm deep) at the marked site. Then, the catheter over needle was passed through this incision into the stomach (Figures 1 and 2). The needle was withdrawn, and a thread was advanced through the catheter and secured with biopsy forceps. The endoscope and forceps grasping the thread were withdrawn from the mouth as a single unit. The gastrostomy tube was then connected to the looped end of the thread and the PEG tube-thread unit placed into the stomach by pulling the end of the thread exiting the skin incision, with the internal bumper remaining in the gastric lumen. An external bumper was subsequently passed over the external portion of the PEG tube to secure the PEG tube in place. Correct tube placement was confirmed by CT scan (Figures 1 and 2). After the operating room was set up, the time required to perform each procedure was between 15–30 minutes. Feeding could be started within 4 hours after the procedure. Decompression could be started immediately.

In 4 patients, a direct puncture gastrostomy with prior gastropexy was performed. In these cases, an Entuit Thrive Balloon Retention Gastrostomy Feeding Tube (14F or 18F; Cook Medical, Winston-Salem, NC) was used. In the placement process, first the stomach needed to be secured to the abdominal wall by use of adjustable suture anchors. Then, after a 5-mm incision of the skin between the anchors, a trocar with a plastic peel-away sheath was carefully introduced into the stomach through this incision by applying constant gentle pressure. The trocar was removed, and the PEG tube was introduced via the plastic peel-away sheath. Thereafter, the gastric balloon at the tip of the PEG tube was injected with sterile water and gently pulled against the stomach wall. The sheath was peeled away, and the retaining plate (external bumper) was placed without too much traction between the balloon and the external bumper of the PEG tube. Feeding could be started within 4 hours after the procedure. Decompression could be started immediately.

A senior attending physician in interventional radiology and a senior attending endoscopist or a resident under appropriate supervision always performed placement of PEG/PEJ tubes. Ten procedures were performed under general anesthesia in patients from intensive care units. The remaining patients received conscious sedation according to the available guidelines for sedation in gastrointestinal endoscopy.[10,11] When the placement of a PEJ tube was performed, N-butylscopolammonium bromide was occasionally used to reduce bowel activity. Blood pressure, heart rate, and oxygen saturation were continuously monitored during the procedure. In our study, no specific sedation-related severe adverse events that led to discontinuation of the procedure were noted, such as hypoxemia and hypotension (defined as hemoglobin oxygen saturation <90% and systolic blood pressure <90 mm Hg). Local cutaneous anesthesia was established by injection of lidocaine 1%. No routine antibiotic prophylaxis before PEG placement was used. In all patients, the

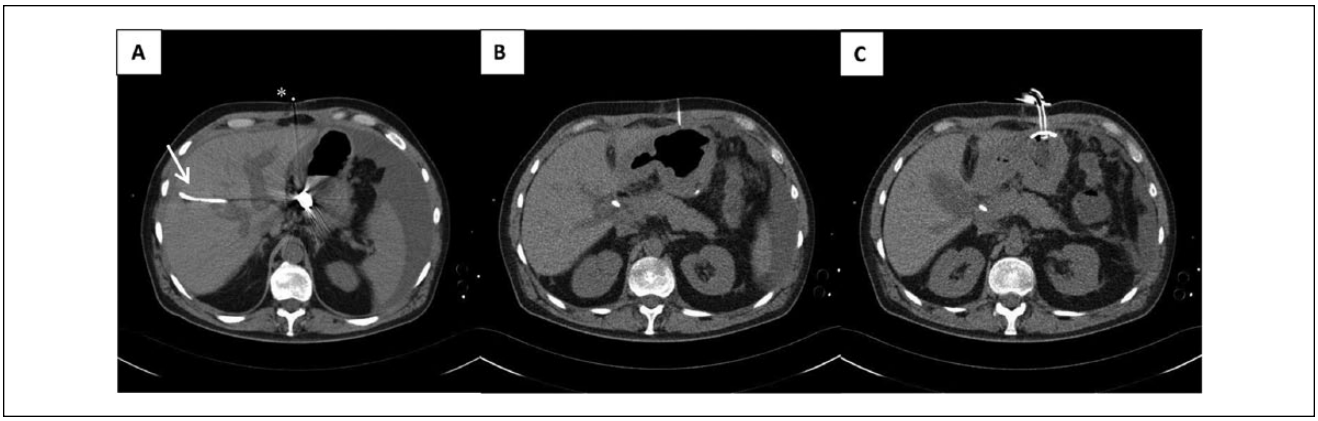

Figure 1. Fifty-three-year-old patient with a history of partial gastrectomy and gastroenterostomy because of gastric cancer was referred for decompression percutaneous gastrostomy. The patient presented with peritoneal carcinosis, and no adequate transillumination could be obtained during previous esophagogastroduodenoscopy. (A) Gastroscope is shown inside the stomach; note external biliary drainage tube because of obstructed bile duct (arrow) and external wire guide for orientation (asterisk). (B) Computed tomography–guided puncture of the stomach. (C) Image after placement of the tube (pull-through type) inside the stomach.

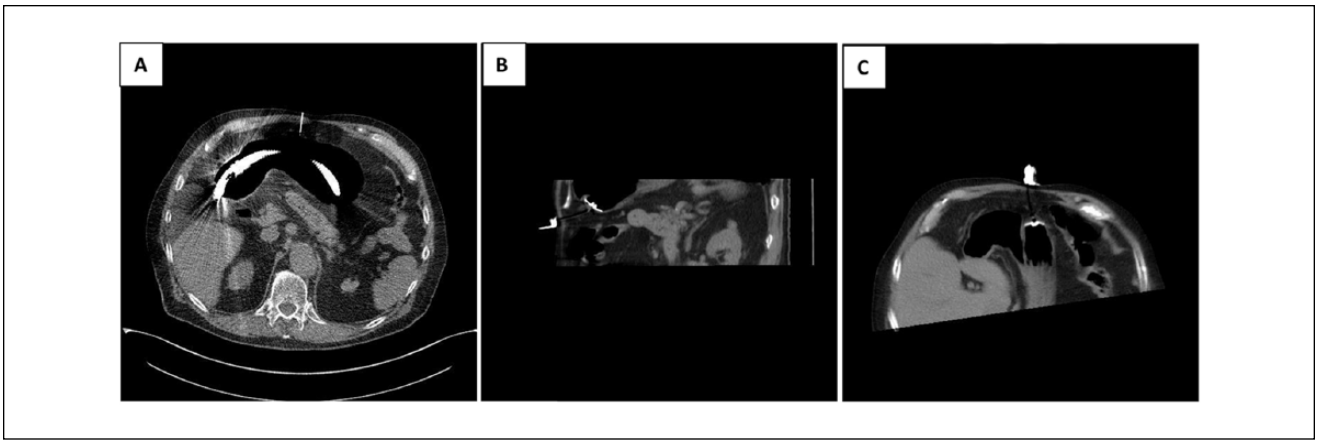

Figure 2. Seventy-eight-year-old patient with esophageal cancer was referred for feeding percutaneous gastrostomy prior to scheduled radiochemotherapy. No adequate transillumination could be obtained during previous esophagogastroduodenoscopy. (A) Gastroscope is shown inside the stomach (computed tomography–guided puncture of the stomach). (B–C) Images after placement of the tube (pull-through type) inside the stomach.

interventional procedure was performed with the following multidetector CT (MDCT) scanners: SOMATOM Sensation 10, SOMATOM Sensation 64, SOMATOM Definition AS+, and SOMATOM Definition Flash (Siemens, Forchheim, Germany). For each CT-guided PEG/PEJ procedure, the dose length product (DLP) values were retrospectively extracted from the dose report, documenting the complete CT examination in the PACS (picture archiving and communication system) of the local radiology department. In the present study, for the calculation of DLP to effective dose (expressed in mSv), a region-specific conversion factor (k factor) of 0.015 mSv/mGy × cm was utilized, which has been published according to the International Commission on Radiological Protection for the abdominal region in adults.[12] We used low-dose CT scans throughout the study with dose modulation.

Statistics

Descriptive statistics were used to analyze patient demographics. The results were expressed as the mean or median (range). The outcome of interest is a binary variable for each patient. Hence, we used Pearson's chi-square as a conservative way to test if there was a statistically significant association between the complication rate and the categorical variables for feeding or decompression tube placement. We used Spearman's rank correlation coefficient to test for an association between the complication rate and the PEG/PEJ tube sizes, which we treated as ordinally scaled. A 2-sided P value <.05 was considered to be significant. All statistical analyses were performed with the statistics package Stata/SE 13.1 (StataCorp LP, College Station, TX).

Table 2. Complications (Major and Minor) After PEG/PEJ Tube Placement (n = 102).

Complication	No.	%
Misplacement	2	1.9
Superficial mucosal bleeding	1	0.9
Peristomal leakage	2	1.9
Superficial skin infection	6	5.9
Tube dysfunction	4	3.9
Total	15	14.7

PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy.

Results

A total of 55 men (53.9%) and 47 women (46.1%) with a median age of 58 years (range, 26–92) were included in the study. The reason for PEG/PEJ tube placement was feeding/nutrition support in 57 of 102 patients (55.9%) and decompression in 45 of 102 patients (44.1%; see Table 1). The majority of the patients (n = 73) were referred for CT-guided PEG/PEJ because of inadequate transillumination. Other reasons for CT-guided gastrostomy were peritoneal carcinosis in 20 patients and obstructed passage in 9 patients. Upper GI endoscopy was generally attempted in all patients. Only patients with complete obstruction of the esophagus or an unsuccessful attempt to pass a pediatric endoscope did not receive endoscopy. In these cases, direct puncture gastrostomy with prior gastropexy was performed (n = 4).

Altogether, PEG/PEJ placement was successful in 87.3% of the patients (89 of 102). Feeding PEG of PEJ placement (52 of 57) and decompressive PEG of PEJ placement (37 of 45) were successful 91.2% and 82.2% of the time, respectively. Reasons the procedures failed or were aborted included the following: stomach or proximal jejunum covered by a dilated colon or left lobe of the liver (n = 11), intramural gastric abscess–preoperative diagnosis with CT (n = 1), and vomiting and aspiration during the intervention (n = 1). Importantly, reasons for placement failure were similar in both the decompression and feeding groups. In general, the tube diameter selected for the patient was dependent on the indication and estimated time that the tube was needed. For feeding support, mainly 9F (32 of 52 patients) gastrostomy tubes were used, whereas for decompression, 15F (21 of 37 patients) or 18F (7 of 37 patients) gastrostomy tubes were preferred.

Major and Minor Complication Rates

During the follow-up period (range, 1–62 months; median, 4 months), 2 patients were readmitted with complications. The first patient suffered from buried bumper syndrome (the internal bumper had migrated into the wall of the stomach) and required removal of the existing tube. Fortunately, a replacement PEG under endoscopy alone was successful. The second patient had the misplaced tube removed, and it was then determined that a replacement tube was not needed. No other major complications were observed, such as procedure-related death, bleeding requiring treatment, or need for further surgery or intensive care admission. Minor complications—such as tube dysfunction, local bleeding, minimal leakage, and local skin infection—were observed among 13 patients during the follow-up period. Individual complications (minor and major) are presented in Table 2. Tube blockage was successfully treated by replacing the tube with a new one. Peristomal leakage could be treated in one case by exchanging the catheter for a larger one. Superficial mucosal bleeding in 1 patient was self-limiting. Superficial skin infection was treated by local anti-infective treatment and systemic antibiotics if necessary. We did not administer prophylactic antibiotics prior to PEG/PEJ tube placement. Altogether, complication rates were low, and no difference was noted between tubes placed for feeding or decompression ($P = .9$). In addition, with a P value of .4, there was also no statistically significant difference in complication rates concerning the individual PEG/PEJ tube sizes.

Because the majority of the patients suffered from wasting malignant disease, 38 of 102 died during the follow-up period, 20 of them within the first 30 days after tube placement. Of these patients, 16 were referred to CT-guided PEG/PEJ tube placement for decompression (80%) in an advanced stage of malignant disease. All cases of death were disease related and not triggered by tube placement.

Radiation Exposure

The mean DLP in all patients was 478.5 mGy × cm (range, 108–5325 mGy × cm). The effective dose for each patient was calculated as 0.7177 mSv. During the initial CT scan and the CT-guided control of the correct needle placement after puncture, the radiologist and the interventional endoscopist were not present in the examination room, thus reducing the radiation exposure to them.

Discussion

PEG/PEJ tube placement is a safe procedure and an effective enteral feeding method in patients where oral feeding is not possible because of neoplasia or neurologic disorders.[1] The method allows the maintenance of the patient's nutrition status during treatment or the reversal of malnutrition,[13] and it has clearly been shown that PEG feeding is also effective to avoid hospitalization in this patient group.[14]

However, the main goal of decompression PEG/PEJ tube placement is to provide symptomatic relief of nausea and vomiting without the need for nasal intubation in patients with advanced malignant bowel obstruction.[6] Kawata et al reported successful symptom relief achieved in 96% of their patients with malignant bowel obstruction after placement of decompression PEG.[3] Furthermore, PEG/PEJ tube placement allows

most patients to have end-of-life care at home or in an inpatient hospice. It is highly recommended for patients who present with recurrent bowel obstruction and who have advanced incurable malignancy.[15] In this context, our results clearly demonstrate that CT-guided PEG/PEJ tube placement is a good option for those patients where endoscopic placement is not successful and symptom relief is needed (eg, in end-stage cancer patients).

Currently, gastrostomy is usually placed endoscopically (PEG) with a 95% success rate.[6] However, it is relatively contraindicated if adequate transillumination is not achievable because of risk of organ injury. Reasons why endoscopic PEG/PEJ tube placement is unsuccessful include previous operation (esophageal or gastric), obesity, hepatosplenomegaly, peritoneal carcinosis, ascites, or interposition of the colon between the stomach and the anterior abdominal wall. In addition, an obstructed passage may cause failure of endoscopic placement. In addition, patients with portal hypertension and gastric varices have an increased risk of peritoneal hemorrhage.[2] Thus, in this group of patients where endoscopic placement is not successful, alternative methods are needed to provide the possibility of PEG/PEJ tube placement. We demonstrate in our study that CT-guided PEG/PEJ is a relatively safe method with a high success rate for enabling PEG/PEJ in patients who have failed usual endoscopic attempts. CT guidance allows an excellent anatomic orientation and a rapid assessment of needle and tube placement. In general, the use of CT for the guidance of percutaneous interventional procedures has been established for many years.[16-18] Other interventional techniques for provision of enteral feeding include percutaneous radiologic gastrostomy under ultrasonographic and fluoroscopic guidance,[19-21] as well as cone beam CT-guided percutaneous radiologic gastrostomy,[22] but there is (to our knowledge) no prospective data available comparing these techniques. For example, data to clarify the role of bedside sonographic guidance for the positioning of enteral feeding tubes are still lacking.[23,24] Finally, some patients still require surgery because PEG/PEJ placement cannot be performed with the above-mentioned techniques.

In our study, we report the results and complications of 102 CT-guided PEG/PEJs. Our data demonstrate that PEG/PEJ placement is technically possible even in patients with peritoneal carcinosis, tumor coating the stomach, or previous abdominal or gastric surgery. Spelsberg et al reported comparable results in a series of CT fluoroscopy-guided PEG/PEJs for feeding support or stomach decompression.[6] In their work, CT fluoroscopy either alone or in combination with endoscopy for PEG tube placement is described. This is the advantage of the fluoroscopy approach—the need of only 1 physician. The authors conclude that CT fluoroscopically guided gastrostomy provides a high success rate with a low complication rate. However, high radiation exposure to patients and personnel during CT fluoroscopy remains a concern. In our study, no personnel or physician was present in the examination room during the CT scan, thus reducing radiation exposure to them. As far as radiation exposure of the patients is concerned, our results for the use of CT guidance for PEG/PEJ tube placement are comparable to the work of Gottschalk et al.[2] Our dosimetric analysis of patient radiation exposure due to CT scan during the PEG/PEJ placement and diagnostic CT performed after the intervention showed DLP values comparable to other published data.[6] According to the German Federal Office for Radiation Protection, the reference value of an abdominal CT scan would be 900 mGy × cm. This corresponds to an effective dose of 1.35 mSv per patient, compared to 0.7177 mSv in our study.

A combined approach (CT guidance and simultaneous endoscopy) was preferred whenever possible, and the pull-through technique was mostly used in our study. The combination of both procedures reduced the risk of tube misplacement. Direct puncture gastrostomy was performed only in patients in whom the endoscope could not be passed because of high-grade stenosis. Another important fact is that CT guidance allows a clear visualization of all anatomic structures (eg, the colon) lying in the way of puncture.

Gottschalk et al reported 83 patients in whom CT-guided percutaneous gastrostomy was performed, mostly in patients with malignancy of the upper respiratory or digestive tract.[2] While this group achieved a total success rate of 95.2% of all cases, there is no differentiation made between feeding PEG/PEJ tube and decompressive PEG/PEJ tube placement. In their study, the placement had to be aborted in 2 cases because of vomiting and problems with sedation. As far as placement of feeding PEG/PEJ tube is concerned, our results are comparable, with a total success rate of 91.2%, but placement of decompressive PEG/PEJ tubes could be accomplished only in 82.2% of the patients. This demonstrates again that in cases where decompression is needed, higher complication rates and lower success rates can be expected because most of these patients are in an advanced stage of the disease.

To our knowledge, there is no systematic evaluation concerning which sedatives and analgesics and how many should be used for CT-guided PEG/PEJ tube placement. However, the recommendations of the recent guidelines for sedation in gastrointestinal endoscopy were followed,[10] and the procedures could be conducted without specific sedation-related severe adverse events. N-butylscopolammonium bromide, an anticholinergic drug, can be given to decrease gastric or jejunal motility[25] and was used several times in our study. As recommended by the European Society of Parenteral and Enteral Nutrition, we did not use routine antibiotic prophylaxis.[26] Moreover, our results confirm this recommendation, with a low infection rate of 5.9% of superficial skin infection and no systemic infections, although our patients did not routinely receive periprocedural antibiotics.

CT guidance for the puncture of the stomach or jejunum also seems to be advantageous to avoid neighboring organs, such as the liver.[23] This point is of particular importance because transhepatic PEG/PEJ placement is a rare but potentially life-threatening complication.[27-29] Long-term minor

complications observed in our study were mostly due to tube disturbances rather than real complications. Indeed, most of these adverse events consisted of tube dysfunction and superficial skin infection, which did not produce unfavorable consequences. Furthermore, these adverse events were most often managed easily, either by local anti-infective treatment and systemic antibiotics, if necessary, or by exchanging or repositioning the tube via a guidewire. Kawata et al reported wound infection with or without stomal leakage in 4.7%–21% of patients with PEG/PEJ for decompression.[3] According to the results of Zopf et al, insertion of 9F PEG/PEJ tubes is related to lower complication rates and mortality risk.[30] Similar results concerning major or minor complications were reported by other groups.[6,31-33] In the literature, the incidence of major PEG complications has been reported at 1%–3% to as high as 9%; the incidence of minor complications is more widely varied, ranging from 16%–50%.[34] In our study, we report a total complication rate of 14.7% (major and minor complications). While all procedures were performed by experienced endoscopists (>200 PEG/PEJ tube placements), no statistically significant difference in the complication rates between the feeding and decompression groups or concerning the tube sizes could be observed. In our study, we noticed 1 case of buried bumper syndrome (migration of the internal bumper into the wall of the stomach), which represents a serious and potentially life-threatening complication of PEG tube insertion, occurring in 1.5%–1.9% of the patients.[35] Different techniques have been used to manage the buried bumper syndrome.[36] In our endoscopy unit, we could manage the problem without further complications. As described in the literature for the treatment of buried bumper syndrome, an endoscopic approach can be recommended as a minimally invasive and safe method.[35,36] In our study, none of the deaths were triggered by the PEG/PEJ tube placement but rather caused by the underlying malignant disease. This is in accordance with recent published data from Kawata et al reporting deaths related only to the patients' illnesses and not PEG.[3]

Potential limitations of our study should be acknowledged. First, only patients from a single endoscopy unit in a tertiary referral center in Germany were included. It may be speculated that results would be different if the study were performed in an international setting. To the best of our knowledge, our study reports the biggest number of patients with CT-guided PEG/PEJ placement. Second, the probability of selection biases due to the design of the study should be considered, and the results should be proven by prospective randomized studies comparing different methods of PEG/PEJ tube placement. Third, the rather small sample size increases the possibility of a type 2 statistical error concerning the complication rates. Fourth, the presented method for PEG/PEJ placement with the use of CT guidance requires a certain expertise of both the performing endoscopist and the radiologist and may therefore not be immediately available to all patients for whom endoscopic placement is not successful. Thus, the method should currently be reserved for those centers where this expertise is ensured.

Conclusions

In our experience, CT-guided PEG/PEJ placement—in combination with endoscopy if technically feasible—is a safe and minimally invasive endoscopic procedure associated with a low procedure-related morbidity rate for those patients where endoscopic placement is not successful. Compared with alternative methods, such as ultrasonographic and fluoroscopic guidance, CT-guided PEG/PEJ placement should be regarded as a good option and an attractive alternative to surgical tube placement. CT guidance provides durable access for enteral nutrition or decompression of the stomach, can help to prevent malnutrition, and reduces hospitalization in cancer patients. Long-term complications, which are mainly tube disturbances, can be treated easily. Nevertheless, we recommend regular follow-up visits by informed healthcare professionals to detect long-term problems and expertly determine when PEG/PEJ tube is to be changed or removed.

Statement of Authorship

H. Albrecht and J. Mudter contributed to the concept and design of the research and drafted the manuscript. A. F. Hagel, P. Schlechtweg, T. Foertsch, and M. F. Neurath contributed to the acquisition, analysis, and interpretation of the data. All authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the work, and read and approved the final manuscript.

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Differences in Durability, Dislodgement, and Other Complications With Use of Low-Profile Nonballoon Gastrostomy Tubes in Children

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Abstract

Background: Nonballoon low-profile gastrostomy tubes (GTs) are used for enteral nutrition support in a subset of pediatric patients with feeding difficulties when use of balloon GTs is problematic. Different nonballoon low-profile tube types are available, but comparative studies are lacking. *Materials and Methods:* This was a retrospective cohort study comparing complications and outcomes between different low-profile nonballoon GTs at a pediatric tertiary care center over 10 years. *Results:* We identified 43 patients with 160 tube placement procedures, including 93 (58%) BARD tubes (type A) and 67 (42%) Mini-ONE tubes (type B). Accidental tube dislodgment occurred exclusively with type B (33% vs 0%, $P < .0001$) with dislodgment occurring at a median of 54 days after placement. Type A GTs were more likely to be changed due to leakage (47% vs 8%, $P < .0001$). Minor gastrostomy site bleeding was more likely to be seen with type A tube changes (46% vs 7%, $P < .0001$). Patient sedation or site dilation was rarely needed in either group. Time to tube change was longer in the type B GTs (BARD) ($P = .016$) with a median tube survival in the type A and type B groups at 432 and 284 days, respectively, with a hazard ratio of 1.89 (95% confidence interval, 1.2–2.99), but once confounders were accounted for, the effect of tube type was no longer statistically significant. *Conclusion:* Our study shows that differences exist with use of various low-profile nonballoon GTs. This should be taken into consideration when counseling families about the most appropriate tube type for their children. (*Nutr Clin Pract*. 2017;32:219-224)

Keywords

gastrostomy tube; complications; enteral nutrition; tube feeding; pediatrics

Introduction

Enteral nutrition (EN) support through feeding tubes is well established in children who fail to achieve that adequately and safely via the oral route.[1,2] Establishing long-term nutrition support often requires endoscopic percutaneous endoscopic gastrostomy (PEG) tube or surgical tube placement, which is subsequently switched to low-profile or button tubes once the tract has matured.[3] Unlike PEG tubes, low-profile or skin-level gastrostomy tubes (GTs) extend only to the skin level without a long extension outside the abdominal wall. These more concealed enteral access devices have been associated with high caregiver satisfaction rates[4] and use balloons or bolsters as internal stabilizers.[5] Even though the cost can be up to 50% higher per tube than their balloon counterparts,[3] low-profile nonballoon GTs can be an attractive option for some patients and their families as they require fewer replacements as balloon ruptures are eliminated.[6] Due to their smaller internal bolster, nonballoon GTs may provide an advantage if concerns exist that an internal balloon bolster is anatomically causing partial gastric outlet obstruction. These nonballoon GTs are available with internal bolsters that are stretchable using special introducers or come with a collapsed encapsulated bolster that expands after placement. Disadvantages of low-profile nonballoon GTs include the need for a medical provider for the tube change as well as discomfort associated with tube changes as the size of the stretched bolster remains larger than deflated balloon bolsters. It is likely that families are offered certain feeding tube brands available within their local healthcare system. Comparative clinical studies among low-profile nonballoon GTs remain lacking but are important to aid physicians and care providers to choose among the multiple brands accessible on the national market. The aims of this study were to assess differences in complications and durability between low-profile nonballoon GTs used in children at our center.

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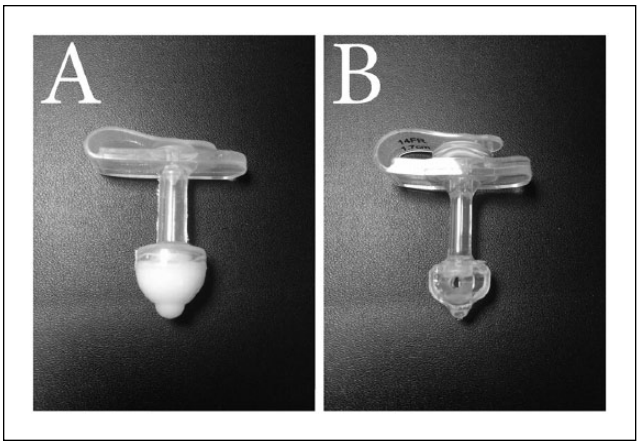

Figure 1. (A) BARD and (B) Mini-ONE nonballoon gastrostomy tube types.

Materials and Methods

Study Cohort

This was a retrospective cohort study of low-profile nonballoon GTs in patients followed in the Pediatric Gastroenterology Division at a pediatric tertiary care center over a 10-year period. Patients were identified through a procedural database and confirmed through billing records. The study procedures followed were in accordance with the ethical standards on human experimentation with approval granted by the institutional review board. The inclusion criteria were as follows:

1. Initial low-profile nonballoon GT placement at <18 years of age
2. GT placement and follow-up by the Pediatric Gastroenterology Division
3. Study duration from November 15, 2003, and November 15, 2013

Placement and Device Characteristics

For the purposes of this study, we defined the initial low-profile nonballoon GT placement as the first placement during the study period. All subsequent changes were considered replacements. Beginning of follow-up was defined as the time of initial successful GT placement within the study period. End of follow-up time was defined as the last documented clinic or phone encounter while using a nonballoon low-profile GT, patient death, or end of study period. Replacement indications were classified as accidental dislodgement, tube breakdown, valve malfunction, leakage, or switching to a balloon-type GT. The brands of nonballoon GTs tubes included the following:

1. Tube A: BARD tube (BARD Access Systems, Salt Lake City, UT; Figure 1A), which has a larger internal bolster
2. Tube B: Nonballoon Mini-ONE tube (Applied Medical Technology, Brecksville, OH; Figure 1B)

Nonballoon type A GTs (BARD type) were available at an earlier time on the U.S. market and within our center. In 2009, nonballoon-type B GTs (Mini-ONE) also became available at our center. The GT type used from 2009 onward was based on the discretion of the primary pediatric gastroenterologist in discussion with families. Elective scheduled GT changes were mostly offered on an annual basis.

Statistical Analysis

Categorical variables were described as percentages and proportions. Continuous variables were described using measures of central tendency and dispersion using mean and standard deviation for normally distributed data and median and interquartile range (IQR) for data with skewed distribution. Comparisons were made between the groups. Tests of significance included the Fisher exact test for categorical variables and Student *t* test and the Mann-Whitney-Wilcoxon test for continuous variables with normal and skewed distributions, respectively.

Univariate survival analysis for time to tube replacement (tube durability) was performed according to the Kaplan-Meier method. Survival time was defined as the time interval from GT placement to replacement with another tube, surgical intervention, patient death, or end of the follow-up. Events leading to GT changes were classified into censored and uncensored observations based on the information available at the time of change and whether the change could be related to a GT-related issue. Censored observations included events when the GT remained functional at the time of removal or end of follow-up (such as scheduled tube change or patient death). Uncensored observations included events leading to premature GT change (such as accidental dislodgement or tube breakdown). A 2-tailed log-rank test was applied to determine statistically significant differences. A probability value <.05 was considered significant.

Logistic regression was performed to calculate the odds ratio (OR) point estimates and confidence intervals (CIs) for tube type with regard to reasons for tube replacement. In cases of separation,[7,8] where small sample bias leads to a zero frequency cell in the 2 × 2 table relating the predictor and outcome, Firth's bias correction was used to prevent OR estimates infinite in value. Variables in Tables 1 and 2 that had statistically significant differences between the tube type groups (age, weight, neurologic disorder, cardiac defect, accidental dislodgement, leakage, mild bleeding) were considered in the model as potential confounders. Cox proportional hazards (PH) modeling[9] was performed to assess the impact of tube type and other control variables on the time to GT replacement. With the proportional hazards assumptions satisfied, this

Table 1. Cohort Characteristics.

Characteristic	All (N = 43)	Type A GT (BARD Group) (n = 23)	Type B GT (Mini-ONE Group) (n = 23)	*P* Value
Sex, No. (%) male	26 (60)	15 (65)	12 (52)	NS
Age at first nonballoon GT placement, median (IQR), mo	42.9 (98.4)	79.8 (127.9)	28.1 (34.7)	<.0001
Weight at time of nonballoon GT placement, median (IQR), kg	15.3 (20.5)	21.8 (23.8)	11.8 (7.0)	<.0001
Underlying diagnosis, No. (%)				
Neurologic disorder	25 (58)	20 (87)	8 (35)	.0003
Genetic/metabolic disorder	11 (26)	4 (17)	8 (35)	NS
Cardiac defect	7 (16)	0	7 (30)	.004
Prematurity	6 (14)	2 (9)	4 (17)	NS
Eosinophilic esophagitis	2 (5)	0	2 (9)	NS
Chronic lung disease	4 (9)	1 (4)	3 (13)	NS
Chronic renal disease	4 (9)	0	4 (17)	NS
Oncology diagnosis	2 (5)	1 (4)	1 (4)	NS
Cystic fibrosis	1 (2)	0	1 (4)	NS
Immune deficiency	1 (2)	0	1 (4)	NS
Oral/facial abnormality	3 (7)	3 (13)	0	NS

GT, gastrostomy tube; IQR, interquartile range; NS, not significant.

Table 2. Tube Replacements and Complications.

Characteristic	All, No. (%)	Type A GT (BARD Group), No. (%)	Type B GT (Mini-ONE Group), No. (%)	*P* Value
Reason for tube replacement	n = 148	n = 87	n = 61	
Accidental dislodgement	20 (14)	0	20 (33)	<.0001
Valve leakage	22 (15)	20 (23)	2 (3)	.0009
Leaking around GT site	24 (16)	21 (24)	3 (5)	.0018
All leaking combined	46 (31)	41 (47)	5 (8)	<.0001
Tube breakdown	16 (11)	8 (9)	8 (13)	NS
Elective scheduled change	22 (15)	15 (17)	7 (11)	NS
Miscellaneous				
Loose access port	2 (1)	0	2 (3)	NS
Unspecified tube malfunction	1 (1)	0	1 (2)	NS
Switch to balloon-type tube	11 (7)	8 (9)	3 (5)	NS
Bleeding at the site	2 (1)	1 (1)	1 (2)	NS
GT shaft too long	2 (1)	1 (1)	1 (2)	NS
GT shaft too short	3 (2)	3 (3)	0	NS
Infection at GT site	1 (1)	1 (1)	0	NS
Procedural complication	n = 156	n = 89	n = 67	
Failure of placement	1 (0.6)	0	1 (1.5)	NS
Significant bleeding at site	0	0	0	NS
Mild bleeding at site	46 (29)	41 (46)	5 (7)	<.0001
Site dilation needed	13 (8)	7 (8)	6 (9)	NS

GT, gastrostomy tube; NS, not significant.

modeling framework is most favorable for time-to-event data with censoring. To determine the most appropriate set of covariates that explains the time to GT replacement or censoring, we iteratively fit Cox PH models with all subsets of the predictor variables. The model with the smallest Akaike[10,11] information criterion (AIC) was determined to best represent

the data, leading us to our optimal predictor set. AIC takes into account how well a given model fits the data, while adding a penalty term proportional to the size of the predictor set, balancing goodness of fit and parsimony. Comparing tube type–only models to the model determined best by AIC illustrated the confounding nature of additional predictors by the change in tube type estimates and their significance.

Results

Cohort Characteristics

The cohort included 43 patients with a median age of 3.6 years (IQR, 8.2) at study inclusion and a median weight of 15.3 kg (IQR, 20.5) at time of GT placement. Sixty percent of patients were male. Other cohort characteristics are shown in Table 1. The indication for initial feeding tube placement was inadequate oral intake in all patients. The most common underlying diagnoses were neurologic disorders and genetic/metabolic disorders. Patients using type A GTs were more likely to have an underlying neurologic disorder, were older at time of study inclusion, and had a higher weight at the time of GT placements. Patients using type B GTs were more likely to have underlying cardiac defects.

Device Characteristics

The cohort included 23 patients who used type A GTs and 23 patients in the other group. All patients exclusively used only one GT type during the study period except for 2 patients who used both tube types at different times. A total of 160 GT placement procedures were documented involving 93 (58%) type A and 67 (42%) type B GTs. The diameter of type A GTs used was 18 French (98%) and 24 French (2%) while the other type had exclusively a 14 French diameter. Among type B GT users, the most common design was the encapsulated design in 87% (referred to as Mini-ONE capsule tube design, which includes a collapsed internal bolster that expands after placement).

Procedure Characteristics

Dilation of the gastrostomy site with metal Hegar dilators was reported in a small subset in each group, 8% with type A and 9% with type B GTs ($P = .8$). Minor bleeding at the gastrostomy site was more commonly documented with type A GT placements (46% vs 7%, $P < .0001$). Bleeding was described as transient and did not require further intervention beyond applying gauze/dressing to the site. The most common methods used to confirm proper tube position after placement were checking gastric residual and auscultation. Imaging and endoscopy were rarely used to confirm proper position, at 2% and 6%, respectively. Only 1 tube placement failure was documented in an attempt to place a type B tube. No placement failures were noted with the other GT type.

Most GTs (88%) were placed without any sedation irrespective of tube type. Twelve percent of cases received some form of sedation, including midazolam only, morphine only, or deep conscious sedation. Tube placement under deep conscious sedation was often performed in combination with other procedures such as endoscopy.

Tube Replacements and Durability

The indications for GT replacements were documented in 148 (93%) placement procedures and are summarized in Table 2. The main nonelective replacement indications included accidental tube dislodgement, leakage, or broken tube component in 14%, 31%, and 11% of cases, respectively. In 15% of cases, an elective GT change (typically on annual basis) was the main reason noted. Comparison based on tube type showed statistical differences in certain indications for tube changes, specifically accidental tube dislodgement and leakage.

Accidental tube dislodgment was more common with type B GTs (33% of 61 replacements) compared with none (0% of 87 replacements) with the other type. The odds of accidental tube dislodgement for type B was 85.45 times the odds for the other type (95% confidence interval [CI], 5.02–1488.91). When accounting for age, weight, neurologic disorder, and cardiac defect, which yielded a minimum AIC, the OR was 123.1 (95% CI, 7.48–2017.18), indicating that the additional variables did not confound the significant relationship between accidental tube dislodgement and tube type. Accidental dislodgment of type B GTs occurred in 12 patients at a median of 54 days (IQR, 127) after tube placement. In this cohort of patients with accidental dislodgment, 2 patients had 4 replacements each, 2 patients had 2 replacements each, and the remaining 8 patients had 1 replacement each (range, 1–4 dislodgements per patient). Participation of a trainee (typically a fellow) during the GT placement procedure was not associated with increased rate of subsequent tube dislodgment.

Type A GTs were more likely to be changed due to leakage (including valve leakage and leakage at the gastrostomy site), which was documented in 47.1% of 87 replacements compared with 8.2% of 61 replacements in the other type. The odds of leakage for type A was 9.98 times the odds for the other type (95% CI, 3.65–27.33). When accounting for age, weight, neurologic disorder, and cardiac defect, which yielded a minimum AIC, the OR was 31.57 (95% CI, 5.86–170.20) indicating that the additional variables did not confound the significant relationship between leakage and tube type.

Time to tube change was evaluated by the Kaplan-Meier analysis (Figure 2). Log-rank statistics showed a significantly longer time to tube change in type A GTs ($P = .016$) with a median tube survival in type A and type B GTs at 432 and 284 days, respectively.

The hazard ratio of the type B vs type A was 1.89 (95% CI, 1.2–2.99) in the tube type–only Cox model, indicating that there is evidence of different hazard functions of time to

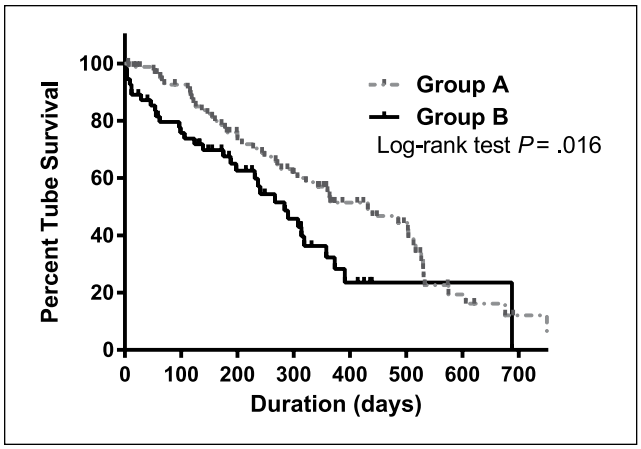

Figure 2. Gastrostomy tube durability.

replacement for the tube types; specifically, type A tends to have a longer survival time. The model with the minimum AIC included the variables age at study inclusion and weight at GT replacement. In this model, the hazard ratio of type B vs type A GTs was 1.13 (95% CI, 0.64–1.98). This suggested that there was not sufficient evidence of different hazard functions for time to replacement between the tube types once potential confounders were accounted for. There was a similar lack of tube type significance for models including only age at study inclusion or weight at GT replacement, showing that these variables confound the relationship between tube type and survival time.

Discussion

EN support through a variety of feeding devices has been shown to be safe and effective for proper nutrition, medication intake, and decompression in pediatric patients.[12–14] Our patient cohort requiring GTs was similar to those previously published with regard to the indications for tube placement and existing underlying diagnoses.[6,15,16] This mostly constitutes patients with neurologic impairment and associated feeding difficulties. The durability of the type A GT (BARD) in our cohort was 432 days, relatively comparable to a prior report of 379 days.[6] To our knowledge, this is the first study in children to report on the durability of low-profile nonballoon type B GT (Mini-ONE) at 284 days. As mentioned above, the difference in GT durability seemed to be affected by other confounders besides tube type.

Designs of enteral GTs have advanced since their introduction and include low-profile options with balloon and nonballoon internal retainer mechanisms.[5] The most common indication for replacing a balloon-type GT is balloon rupture.[15,16] Advantages of nonballoon GTs include smaller internal bolster size, which can relieve partial gastric outlet obstruction from GT balloons in addition to eliminating risk for balloon rupture, leading to superior tube durability.[6] Nonballoon GTs have disadvantages, including the need for specialized healthcare providers for tube changes in addition to pain/discomfort associated with tube changes due to insufficient collapse of the internal bolster.[17] The smaller internal bolster of certain brands, especially with the collapsed encapsulated design, may reduce trauma and pain associated with tube replacement, but as shown in our study, this may reduce tube stability, leading to increased dislodgement. Accidental tube dislodgement was significantly higher with type B GTs even after correcting for potential confounders and occurred at a median of 54 days after placement. We hypothesize that dislodgement is not likely to be related to the encapsulated design as the encapsulating cap detaches quickly after proper deployment. This may be due to the smaller bolster size, but other potential factors include differences in tube diameter and stiffness. Accidental tube dislodgement may be avoided through family education and emphasis on proper precautions at the time of placement. To limit emergency room (ER) visits and interruption to enteral feeding and medication intake due to dislodgement, providing backup temporary alternatives (Foley-like catheter or balloon tube) to maintain gastrocutaneous tract patency should be considered. Once gastrocutaneous tract patency is addressed at home or in the community, patients can present electively to the specialized outpatient clinic for nonballoon GT replacement. This may have significant financial and health utilization implications as tube dislodgement is one of the most frequent complaints for pediatric GT-related ER visits.[18] Recurrent tube dislodgment may also be addressed by switching to the other tube type, which showed better stability in our study. As stated, this may be related to the larger internal bolster, but further study is needed to substantiate that.

Leakage was seen more often with type A GTs, which may be related to the different valve system employed in each tube design. Switching to the other tube type may be considered in cases of significant leakage.

Our analysis showed that tube survival was superior with type A GT (BARD), but this difference was affected by other confounders. Our patient populations using the 2 tube designs were different in age at study inclusion and weight at GT placements, with the type A users being older at inclusion and weighing more at replacements. At our center, these differences in cohort characteristics are related to the earlier introduction of that tube to the market.

Conclusion

Our study shows that differences in complications exist between various low-profile nonballoon GTs. Differences in dislodgement rates may be related to the tube bolster design, but it is clear that other factors may have contributed to this, including dissimilarities in patient characteristics and tube diameter. The current differences noted highlight the importance of counseling and educating families about potential risks for GT-related complications and survival in a shared decision-making process to decide on the GT that best matches

the family's needs and preferences. A prospective study with more comparable patient groups may still provide further input on tube and patient outcomes as well as medical provider comfort with GT placement and lead to tube design advancements to better serve pediatric patients.

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Statement of Authorship

R. Rahhal and T. Hajjat contributed to the conception and design of the research as well as to the acquisition, analysis, and interpretation of the data; and R. Rahhal drafted the manuscript while T. Hajjat critically revised it. Both authors read and approved the final manuscript, and agree to be fully accountable for ensuring the integrity and accuracy of the work.

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Indicators for Enteral Nutrition Use and Prophylactic Percutaneous Endoscopic Gastrostomy Placement in Patients With Head and Neck Cancer Undergoing Chemoradiotherapy

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Abstract

Background: Chemoradiotherapy (CRT) is a major risk factor for malnutrition and dehydration in patients with head and neck cancer. Enteral support is often needed, and a percutaneous endoscopic gastrostomy (PEG) is frequently placed. Specific indicators for PEG placement remain unclear. This study retrospectively determined which factors contributed to enteral nutrition (EN) use and PEG placement in a large patient group to gain insight on potential indicators for PEG placement protocol creation. *Methods:* A retrospective chart review of 240 patients with head and neck cancer who underwent CRT in 2012–2015 was conducted. Lifestyle, oncological, treatment, and nutrition outcome characteristics were examined and compared between patients who used EN and those who did not, as well as between patients who received a PEG and those who did not. *Results:* In total, 195 patients used EN (via PEG or nasogastric tube). Multivariate analysis showed that nodal disease presence (P = .01) and bilateral neck irradiation (P = .01) were significantly related to EN use while increased age (P = .01), nodal disease presence (P = .02), reconstruction extent other than primary closure (P = .02), bilateral neck irradiation (P < .01), and an adapted intake consistency prior to treatment (P = .03) were significantly related to PEG placement. *Conclusion:* Important factors for EN usage and PEG placement consideration include nodal disease and planned bilateral neck irradiation. Results from this study in combination with existing literature can be taken into consideration in the design of a PEG placement protocol. A better understanding of predictive indicators to PEG placement should be explored in further prospective studies. (*Nutr Clin Pract*. 2017;32:225-232)

Keywords

head and neck cancer; enteral nutrition; nutritional support; gastrostomy; PEG tube; chemoradiotherapy

Head and neck cancer (HNC) encompasses mainly carcinomas of the oral cavity, oropharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands and are most often of squamous cell origin.[1] In the Netherlands, the incidence of HNC is rising,[2] and worldwide, roughly 550,000 new cases are diagnosed each year, making HNC the sixth most common cancer.[1,3,4] HNC is seen more frequently in males, with a male to female ratio ranging from 2:1 to 4:1 depending on tumor location.[1,4,5] Alcohol use, smoking, and human papillomavirus (HPV) are the most important risk factors,[1,6] while fruit and vegetable intake has been associated with a reduced risk of HNC.[7] Concurrent chemotherapy and radiotherapy, chemoradiotherapy (CRT), given as primary or adjuvant treatment, is a frequently used treatment regimen in patients with locally advanced squamous cell carcinoma of the head and neck.[8,9]

Common acute side effects of CRT include mucositis, xerostomia, odynophagia, dysphagia, nausea, vomiting, fatigue, and sensory changes. These side effects often reduce nutrition intake, thus inadvertently causing weight loss, dehydration, and malnutrition.[10–12] Dysphagia is present in 5%–52% of patients with advanced HNC prior to receiving CRT, depending on tumor location[13] or prior surgery. In addition, patients may already be malnourished when commencing CRT due to tumor-related dysphagia.[14,15] Lean body mass loss in

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these patients is associated with a decreased functional capacity and a reduced survival rate.[15] Nutrition counseling and intervention are therefore crucial in this patient population, and it has become accepted to use enteral feeding via a percutaneous endoscopic gastrostomy (PEG).[16–18] PEG placement and enteral feeding in patients with advanced stage head and neck cancer receiving CRT is found to be beneficial, safe, and effective in providing nutrition and hydration and allows for minimal interruptions to treatment course.[19,20] Discrepancies remain between studies whether PEG placement increases the risk of long-term dysphagia and feeding tube dependence.[21,22]

Previous studies have identified predictive factors for the necessity of PEG placement following radiation therapy, with or without concurrent chemotherapy, and include male sex, lower body mass index (BMI; <25 kg/m^2), advanced tumor stage, pretreatment swallowing difficulties, increased age (>60 years), concurrent chemotherapy (cisplatin dose ≥200 mg/m^2), and previous surgery.[23–25] To our knowledge, only a few hospitals use decision charts to determine whether a PEG should be placed as indicators for placement remain unclear. Within our institution, physicians decide prior to treatment initiation whether a PEG should be placed based on the condition of the patient and personal experience. This decision is subjective and not yet formalized in a protocol. To see whether more objective indicators could be defined for PEG placement, this study retrospectively determined which factors contributed to PEG placement and enteral nutrition (EN) use in a large patient group. Gaining further insight into these data helps to improve clinical decision making and provides clarity on indicators that could be used in the creation of prophylactic PEG placement protocols for patients with HNC receiving CRT.

Methods

Study Design

A retrospective chart review was conducted using electronic patient medical records at the University Medical Center Utrecht (UMCU) in Utrecht, The Netherlands. Ethical approval was obtained and procedures were followed in accordance to national and institutional ethical standards.

Study Population

All patients with locally advanced squamous cell carcinoma of the head and neck who commenced primary or adjuvant CRT in 2012–2015 at UMCU were included (n = 242). Patients receiving cetuximab (antibody directed against epidermal growth factor receptor) in combination with radiation instead of standard chemotherapy were not included. Two patients died prior to completion of CRT and were excluded. The total study population consisted of 240 patients.

Standard CRT consisted of chemotherapy (cisplatin 100 mg/m^2) administered intravenously on days 1, 22, and 43 and 35 fractions of radiotherapy in 7 weeks, 5 times weekly. Detailed treatment information has been described previously.[26] Cisplatin was initially administered and could be replaced by carboplatin if nephrotoxicity, ototoxicity, or neurotoxicity occurred.

Lifestyle Characteristics

Age was determined at the time of CRT initiation. Smoking history was defined as currently smoking or having a history of smoking while alcohol abuse (past or present) was noted when recorded by physician in the patient's medical chart.

PEG Placement and EN

Patients received a prophylactic PEG as deemed necessary. This decision was made by the HNC tumor board. Prophylactic PEG placement is defined as the decision to place the PEG prior to treatment and includes placement of a push PEG, pull PEG, percutaneous radiologic gastrostomy (PRG), or other (surgically placed PEG, percutaneous endoscopic, percutaneous endoscopic jejunostomy [PEJ]). The actual placement could occur prior to or in the early phases of treatment (during hospitalization for chemotherapy). EN is defined as nutrition support via PEG or nasogastric (NG) tube.

Nutrition Status

Patients were counseled weekly by a dietitian during CRT treatment. Percentage of weight loss during treatment was determined using weight at first and last consultation by the dietitian during treatment.

Statistical Analysis

Statistical data analysis was carried out using SPSS version 21 (SPSS, Inc, an IBM Company, Chicago, IL) with a significance level of .05. Normality was assessed visually and using the Kolmogorov-Smirnov test. The Student independent sample *t* test was used to analyze continuous variables while Pearson χ^2 and Fisher exact tests were used to compare categorical variables. Nonnormally distributed continuous variables were compared using the Mann-Whitney *U* test. Variables that were significant factors to PEG placement and EN use in univariate analysis were then selected for multivariate logistic regression analysis to assess contribution impact on PEG placement. Selected model variables were also tested for multicollinearity using a variance inflation factor (VIF) >10.

Results

Patient, Oncological, and Treatment Characteristics

A total of 240 patients were included. Demographic, tumor-related, and treatment characteristics are shown in Table 1. The median (interquartile range [IQR]) population age was 60

Table 1. Patient, Oncological, and Treatment Characteristics: A Comparison Between PEG Placement and EN Use Groups.[a]

Parameter	All Patients (N = 240)	PEG Placement			EN Use		
		Placed (n = 202)	Not Placed (n = 38)	*P* Value	Used (n = 195)	Not Used (n = 45)	*P* Value
Patient/lifestyle							
Age, median (IQR), y	60 (55–65)	61 (56.5–65.5)	55.5 (48.5–62.5)	**.02**	61 (57–66)	57 (51–64)	.10
Sex, male	158 (65.8)	134 (66.3)	24 (63.2)	.70	126 (64.6)	32 (71.1)	.49
Social status, married/cohabitate	149 (62.1)	125 (61.9)	24 (63.2)	.88	120 (61.5)	29 (64.4)	.87
Smoking history (n = 220)	184 (83.6)	156 (83.9)	28 (82.4)	.83	150 (83.8)	34 (83.8)	1.0
Alcohol abuse history (n = 206)	47 (22.8)	42 (24.0)	5 (16.1)	.34	43 (25.4)	4 (10.8)	.08
Oncological							
Primary tumor site				**<.01**			**<.01**
Oral cavity	93 (38.8)	76 (37.6)	17 (44.7)		71 (36.4)	22 (48.9)	
Pharynx	107 (44.6)	96 (47.5)	11 (28.9)		92 (47.2)	15 (33.3)	
Nose, inner ear, paranasal sinus	10 (4.2)	4 (2.0)	6 (15.8)		4 (2.1)	6 (13.3)	
Larynx	14 (5.8)	12 (5.9)	2 (5.3)		12 (6.2)	2 (4.4)	
Neck recurrence	4 (1.7)	3 (1.5)	1 (2.6)		4 (2.1)	0 (0.0)	
Unknown primary tumor	12 (5.0)	11 (5.4)	1 (2.6)		12 (6.2)	0 (0.0)	
Synchronous tumors present	10 (4.2)	9 (4.5)	1 (2.6)	1.0	10 (5.1)	0 (0.0)	.22
Tumor stage (n = 237)				.12			.23
T0–T2	85 (35.9)	68 (33.8)	17 (47.2)		65 (33.9)	20 (44.4)	
T3–T4	125 (64.1)	133 (66.2)	19 (52.8)		127 (66.1)	25 (55.6)	
Node stage (n = 239)				**<.01**			**<.01**
N0	54 (22.6)	34 (16.8)	20 (54.1)		33 (17.0)	21 (46.7)	
N1	33 (13.8)	31 (15.3)	2 (5.4)		27 (13.9)	6 (13.3)	
N2	144 (60.3)	130 (64.4)	14 (37.8)		127 (65.5)	17 (37.8)	
N3	8 (3.3)	7 (3.5)	1 (2.7)		7 (3.6)	1 (2.2)	
Primary surgery	108 (45.0)	85 (42.1)	23 (60.5)	**.04**	83 (42.6)	25 (55.6)	.13
Reconstruction (n = 108)				**.02**			.10
Primary closure	56 (51.9)	38 (44.7)	18 (78.3)		38 (45.8)	18 (72.0)	
Pedicled flap	6 (5.6)	6 (7.1)	0 (0.00)		6 (7.2)	0 (0.0)	
Free vascularized transfer	37 (34.3)	34 (40.0)	3 (13.0)		32 (38.6)	5 (20.0)	
Bone transfer	9 (8.3)	7 (8.2)	2 (8.7)		7 (8.4)	2 (8.0)	
Chemotherapy							
All (3) dosages received (cisplatin or carboplatin)	208 (86.7)	178 (88.1)	30 (78.9)	.13	166 (85.1)	45 (93.3)	.22
Switched to carboplatin				**<.01**			**.01**
Did not switch	174 (72.5)	150 (74.3)	24 (63.2)		143 (73.3)	31 (68.9)	
From dosage 1	9 (3.8)	3 (1.5)	6 (15.8)		5 (11.1)	4 (2.1)	
From dosage 2	29 (12.1)	27 (13.4)	2 (5.3)		27 (13.8)	2 (4.4)	
Last dosage	28 (11.7)	22 (10.9)	6 (15.8)		21 (10.8)	7 (15.6)	
Radiation							
Primary tumor (location) irradiated	205 (85.4)	177 (87.6)	28 (73.7)	**.03**	171 (87.7)	34 (75.6)	.06
Neck nodes irradiated (n = 195)				**<.01**			**<.01**
Unilateral	32 (16.4)	25 (14.1)	7 (38.9)		28 (14.4)	17 (37.8)	
Bilateral	163 (83.6)	152 (85.9)	11 (61.1)		167 (85.6)	28 (62.2)	

EN, enteral nutrition; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy.
[a]Values are presented as number (%) unless otherwise indicated. Statistically significant values ($P < .05$) are given in bold. N = 240, unless otherwise stated.

(55–65) years, with 158 (65.8%) male patients. Most of the population (184; 83.6%) were current smokers or had a history of smoking, and in 47 (22.8%) patients, an alcohol abuse history (past or present) was noted. Of these patient characteristics, only age was significantly different between the PEG placement groups, as patients with a PEG placed were about 5 years older ($P = .02$).

Primary tumors of the pharynx (44.6%) and oral cavity (38.8%) were most frequently present. Tumor site significantly differed ($P < .01$) between both the PEG placement and EN use (via PEG or NG tube) groups. Patients with pharynx or larynx tumors more often received a PEG and/or more often needed EN. Most patients displayed stage T3 and T4 primary tumors, but tumor stage did not significantly differ between PEG

Table 2. Nutrition-Related Characteristics: Comparison Between PEG Placement and EN Use Groups.[a]

Parameter	All Patients (N = 240)	PEG Placement			EN Use		
		PEG Placed (n = 202)	PEG Not Placed (n = 38)	*P* Value	Used (n = 195)	Not Used (n = 45)	*P* Value
Adapted intake consistency prior to CRT[b]	96 (40.0)	87 (43.1)	9 (23.7)	**.03**	83 (42.6)	13 (28.9)	.13
EN used during CRT	195 (81.3)	183 (90.6)	12 (31.6)	**<.01**	195 (100.0)	0 (0.0)	—
Days of EN (n = 126), median (IQR)	86 (44–130)	90 (46–133)	63 (35–91)	**.01**	86 (44–128)	0 (0.0)	—
Weight loss % prior to CRT (n = 235), mean (SD)	5.1 (6.6)	5.3 (6.7)	4.3 (5.9)	.41	5.3 (6.6)	4.4 (6.9)	.46
Weight loss % class prior to CRT (n = 199)				.15			.91
<5%	101 (50.8)	86 (50.9)	15 (50.0)		83 (43.0)	18 (42.9)	
5%–10%	56 (28.1)	44 (26.0)	12 (40.0)		45 (23.3)	11 (26.2)	
>10%	42 (21.1)	39 (23.1)	3 (10.0)		36 (18.7)	6 (14.3)	
Weight loss % during CRT, mean (SD)	2.9 (5.7)	2.7 (4.8)	3.1 (4.7)	.62	2.8 (4.7)	2.4 (4.9)	.55
Weight loss % class during CRT (n = 176)				.93			.14
<5%	107 (60.8)	91 (60.7)	16 (61.5)		87 (58.8)	20 (71.4)	
5%–10%	58 (33.0)	50 (33.3)	8 (30.8)		49 (35.5)	1 (8.3)	
>10%	11 (6.3)	9 (6.0)	2 (7.7)		8 (5.4)	3 (10.7)	

CRT, chemoradiotherapy; EN, enteral nutrition; IQR, interquartile range; PEG, percutaneous endoscopic gastrostomy; —, indicates no *P* value available.
[a]Values are presented as number (%) unless otherwise indicated. Statistically significant values ($P < .05$) are given in bold. N = 240, unless otherwise stated.
[b]Adapted intake consistency prior to treatment includes ground, minced, liquid, or nil per os.

groups ($P = .12$) and EN use groups ($P = .23$). Higher nodal stage was associated with PEG placement ($P < .01$) and EN use ($P < .01$).

In total, 108 (45.0%) patients received surgery before CRT, 85 (42.1%) with a PEG in situ and 23 (60.5%) without. Patients with primary closure less often received a PEG (78.3% vs 44.7%), while patients with more extensive reconstruction techniques more frequently received a PEG (Table 1). Most (208; 86.7%) patients completed chemotherapy and received all 3 dosages of either cisplatin or carboplatin. If and when a patient switched to carboplatin during CRT were significantly different ($P < .01$) between PEG placement groups as more patients switched to carboplatin in the non-PEG placement group. This was also reflected between the EN use groups ($P = .01$), as less patients switched to carboplatin when EN was used. A total of 205 (85.4%) patients received radiation to the primary tumor or, in the case of adjuvant therapy, to the primary tumor site. This differed significantly ($P = .03$) between PEG placement groups since in patients in whom a PEG was placed, a larger number of patients receiving radiation to the primary tumor site were seen (87.6% vs 73.7%). In addition, significant differences ($P < .01$) were shown in whether or not the neck nodes received radiation and if this radiation was unilateral or bilateral. Patients in whom a PEG was placed more often received radiation to the neck nodes as well as significantly more ($P < .01$) bilateral neck node radiations (85.9% vs 61.1%). Patients who used EN during treatment also received significantly more radiation to the neck nodes ($P < .01$) and more bilateral neck node radiations (85.6% vs 62.2%).

PEG Placement Characteristics

In patients in whom a PEG/gastrostomy was placed (n = 202), most (148; 76.7%) received a pull PEG. Thirty-six (18.7%) received a push PEG, 6 (3.1%) a PRG, and 3 (1.5%) other. The average (median [IQR]) number of days of PEG in situ was 166 (107–226) with 49 (24.5%) patients who received a PEG prior to initiation of CRT. At the time of data collection, 120 (60.0%) patients had the PEG removed, while 38 (66.7%) of the deceased patients (n = 57) died with the PEG in situ. Therefore, in 17% of the patients alive at last follow-up, a PEG-tube was used.

Nutrition-Related Characteristics

Weight, EN, and other nutrition-related characteristics are detailed in Table 2. Eighty-seven (43.1%) of the patients with a PEG in situ had used foods and drinks with a consistency that had been adapted to their needs prior to initiation of CRT in comparison to 9 (23.7%) patients without a PEG tube ($P = .03$). A total of 195 (81.3%) patients needed and used EN during the course of CRT with an average (median [IQR]) of 86

Table 3. Multivariate Analysis: Baseline, Oncological, and Nutrition-Related Characteristics and Contribution to PEG Placement.[a]

	PEG Placement (N = 240, Placed = 202)	
Multivariate Parameter	Estimate[b] (95% CI)	*P* Value
Age, y	1.04 (0.99–1.09)	**.01**
Primary tumor site, pharynx (yes vs no)	1.08 (0.42–2.77)	.87
Primary tumor site, larynx (yes vs no)	2.03 (0.32–12.82)	.45
Node stage (vs N0)	2.94 (1.17–7.37)	**.02**
Reconstruction (other than primary closure)	2.89 (1.19–7.01)	**.02**
Bilateral neck node radiation (yes vs no)	5.27 (2.23–12.43)	**<.01**
Adapted intake consistency prior to CRT[c]	2.72 (1.08–6.83)	**.03**

CRT, chemoradiotherapy; PEG, percutaneous endoscopic gastrostomy.
[a]Statistically significant values ($P < .05$) are given in bold. N = 240, unless otherwise stated.
[b]Estimate described in terms of odds ratio.
[c]Adapted intake consistency prior to treatment includes ground, minced, liquid, or nil per os.

(44–128) days. EN use and average days of EN were significantly different ($P < .01$ and $P = .1$, respectively) between patients who had a PEG placed and those who did not. Nineteen patients (9.4%) who received a PEG did not use EN. A total of 195 (81.3%) patients needed EN either through PEG or via NG tube during treatment. No significant differences were seen between patients who used EN and those who did not. The average percentage weight loss and categorized weight loss prior to and during CRT did not differ between both PEG placement and EN use groups.

Multivariate Analysis

The PEG placement multivariate analysis (Table 3) showed that increased age, node stage (N1–N3), reconstruction extent other than primary closure, bilateral neck node radiation, and an adapted intake consistency prior to treatment were significantly related to PEG placement. Bilateral neck node radiation increased the odds of PEG tube placement by 5-fold with an odds ratio (OR; 95% confidence interval [CI]) of 5.27 (2.23–12.43; $P < .01$). Multivariate analysis of EN use (Table 4) showed that node stage (N1–N3) and bilateral neck node radiation were significantly related to EN use.

Discussion

To our knowledge, this is the largest retrospective study to date to examine exclusively CRT patients with HNC. This chart review of 240 patients with HNC undergoing CRT showed that patients who had a PEG tube placed were significantly older, more often had pharyngeal or laryngeal tumors, had a higher nodal stage, underwent less primary surgery, had more extensive reconstruction, less often switched to carboplatin, received radiation to the primary tumor site, and more often received bilateral neck node radiation. Patients who received a PEG also used foods and drinks with a consistency that had been adapted to their needs significantly more often and had a more frequent and longer EN duration. Patients who used EN during treatment more often had pharyngeal or laryngeal tumors, had a higher nodal stage, less often switched to carboplatin, and more often received bilateral neck node radiation.

Table 4. Multivariate Analysis: Baseline, Oncological, and Nutrition-Related Characteristics and Contribution to EN Use.[a]

	EN Use (N = 240, Used = 195)	
Multivariate Parameter	Estimate[b] (95% CI)	*P* Value
Primary tumor site, pharynx (yes vs no)	1.10 (0.50–2.44)	.81
Primary tumor site, larynx (yes vs no)	2.16 (0.40–11.88)	.45
Node stage (vs N0)	2.83 (1.26–6.34)	**.01**
Bilateral neck node radiation (yes vs no)	2.61 (1.23–5.52)	**.01**

EN, enteral nutrition.
[a]Statistically significant values ($P < .05$) are given in bold. N = 240, unless otherwise stated.
[b]Estimate described in terms of odds ratio.

Univariate analysis results suggest that older age, tumor location (pharyngeal and laryngeal), node stage (N2–N3), reconstruction extent, radiation field, and an adapted intake consistency (as an indicator of swallowing or chewing problems upon presentation) may have played a role in the decision making of PEG placement. Tumor location (pharyngeal and laryngeal), node stage, and radiation field may influence need for EN during treatment. Independent variables for PEG placement found through multivariate analysis include a higher age, presence of nodes, extensive reconstruction surgery, bilateral neck node radiation, and an adapted intake consistency prior to treatment.

Interestingly, primary surgery was found significantly more often in patients without PEG placement. Similar results were found in a recent study by Yang et al[25] in a population of 192 patients with HNC. These results may be influenced by tumor stage, as patients with locally advanced tumors and/or nodal disease are frequently irresectable and therefore receive CRT as the primary treatment.[26]

In line with previous research comparing PEG placement in patients with HNC,[25] tumor location (especially pharynx) was shown to be significantly different between the PEG placement groups. This was not reflected in the multivariate analysis. This may be caused by the fact that in patients with oral cancer,

surgery is usually the primary treatment while CRT is mainly used as adjuvant treatment through which these patients will frequently have the morbidity of 3 treatment modalities, including previous (extensive) surgery when CRT is indicated. An increased nodal stage was found in patients in whom a PEG was placed and in patients who used EN. An advanced tumor stage has previously been found related to PEG placement and EN need,[25] but this was not reflected within the present cohort. This may be because only CRT patients were assessed, who typically have a higher tumor stage or more advanced disease state in comparison to patients with HNC receiving surgery or radiation alone.[26] The variation in tumor stage was in turn smaller than that in comparable studies, potentially leading to the nonsignificant difference found.

To our knowledge, reconstruction after primary surgery and switch of chemotherapy type have not been assessed in previous studies. Results suggest that more invasive reconstruction surgeries (ie, pediculed and free vascularized flaps or bone transfer) contribute to PEG placement when adjuvant CRT is indicated based on adverse outcomes of histopathological examination of the surgical specimen. This may be explained by the fact that more extensive reconstructions have a larger impact on swallowing function and efficacy.[27] This is associated with a higher need for nutrition support due to dysphagia and an increased adapted intake consistency at the start of CRT.[28] Typically, more extensive surgeries require more extensive reconstructions and are associated with a larger tumor size. This is again previously shown to be associated with a higher rate of PEG placement.[25]

Patients with a PEG in situ and patients who used EN seem to switch less often to the chemotherapy carboplatin. This suggests that patients using EN are more likely to complete planned treatment. It cannot be concluded in the present cohort that patients with a PEG or using EN were better nourished, as a significant difference in weight loss was not observed. Current literature does show this trend and suggests that minimizing weight loss during CRT may improve treatment tolerance and completion rate.[29,30] On the other hand, it can be anticipated that due to feeding via a PEG, patients maintain weight equally well in comparison to patients not anticipated to need EN and therefore not selected for PEG placement. This may suggest that the multidisciplinary team accurately selected patients for PEG placement.

Results show that significantly more patients with a PEG in situ had radiation to the primary tumor or original primary tumor site when CRT was used as adjuvant treatment. Significantly more of these patients also received radiation to the neck nodes, especially bilaterally. A prominent side effect of radiation therapy is dysphagia, as radiation to the neck region causes damage to the soft tissue. This damage is increased if the radiation to the neck nodes occurs bilaterally, therefore putting patients at a higher risk for needing nutrition support or EN.[31]

More patients with a PEG in situ had an adapted intake consistency prior to CRT, meaning consumption of a ground or liquid diet upon presentation. This may indicate pretreatment dysphagia or chewing complications due to the nature of disease or prior surgery, which seems to contribute to PEG placement.[25] The significant differences found in EN use during CRT and length of EN use (in patients in whom a PEG was placed) can be explained by the fact that the PEG placement group may have had a higher chance of receiving EN due to the PEG in situ. In terms of EN use during CRT, results show discrepancies between physician recommendation regarding placement and actual patient need. Nineteen patients had a PEG placed but did not use EN, while 12 patients who did not have a PEG placed needed EN.

These results do raise questions regarding the risks and costs of unnecessary PEG placement and reinforce the fact that concrete protocols using indications for PEG placement need to be implemented. Although feeding via an NG or PEG tube has been found equally effective in limiting short-term weight loss,[32] each feeding route comes with advantages and disadvantages. Literature shows that patients with HNC with a PEG in place have significantly less weight loss than those without. On the other hand, it has been suggested that PEG tube use increases the risk of long-term dysphagia and feeding tube dependence, but discrepancies remain.[21,22] Evidence does show that PEG placement provides a better quality of life to patients, decreases hospital admissions, and minimizes treatment interruptions.[19,20,22,32] Information regarding PEG complications was not collected in the present study, and therefore specific conclusions regarding reasons for unused PEGs cannot be made.

Weight loss, especially lean body mass loss, is very common in patients with HNC undergoing CRT, as previous research has demonstrated that 55% of patients with HNC lose 10% body weight or more.[16,33] Critical weight loss is associated with increased complications, decreased tolerance to surgery and CRT, and a poorer prognosis, clinical outcome, and quality of life.[34] Published research typically shows that patients with a PEG in situ have significantly less weight loss during CRT than those without.[30,35] The present analysis did not show a significant difference in weight loss between PEG groups, as mean weight loss during CRT was 2.7% in patients with a PEG in situ and 3.1% in patients without a PEG. On the other hand, this similar weight loss between groups suggests that patients were appropriately selected for PEG placement in our institution. The weight loss shown in this cohort is much smaller than the weight loss during treatment demonstrated in comparable studies for patients with and without PEG placement, as Chen et al[35] found significant weight losses of 8% and 14%, respectively, and Lewis et al[30] had figures of 4.3% and 10.5%, respectively. The small percentage of weight lost in both groups may also be due to the frequent dietitian counseling that patients received, as significantly less therapy-related weight loss has been shown when dietary counseling is involved.[36–38] Dietitian counseling in comparable studies was not reported. Previous research within our institution examining outcomes

and toxicity of CRT did find that starting EN with use of a PEG in the early phases of treatment seemed to lead to significantly less weight loss.[26] From 1998–2002, the median weight loss during treatment was 8.5% (reactive PEG placement),[26] while 4.3% (prophylactic PEG placement) was reported from 2008–2010.[39] This study found an average weight loss during treatment of 2.9%, which suggests an improvement in practices regarding feeding.

Strengths of this study include the large population size and the fact that radiation to the neck nodes (bilateral vs unilateral) and switch to carboplatin was assessed, which is unique in comparison to similar studies. Limitations include the retrospective design of the study, which can lead to selection bias and inter-healthcare provider recording bias. EN use may also present bias as patients with a PEG may have received EN sooner than those without. Information regarding tumor recurrence or previous cancer therapy was not collected, and therefore nutrition intake complications associated with prior tumor or treatment were not taken into consideration and may increase the need for PEG placement. In addition, weight loss post-CRT was not assessed; therefore, long-term weight consequences of PEG placement could not be evaluated.

The aim of this retrospective chart review was to determine which factors contribute to the selection of PEG placement to provide insight and clarity on indicators that could contribute to a PEG placement protocol within our institution. Significant results between PEG placement and EN use groups reflect what was done within the present patient cohort.

The existing Royal Brisbane and Women's Hospital Swallowing and Nutrition Management Guidelines for patients with HNC define a high-risk group for PEG placement and need.[40] The guidelines are based on evidence and expert opinion and experience from the in-hospital head and neck clinic multidisciplinary team.[41] The indicators used to define high-risk patients include oral/oropharyngeal tumors and bilateral CRT, nasopharyngeal/hypopharyngeal/unknown primary tumor and CRT, or severe malnutrition at presentation, defined as weight loss of 10% in 6 months or a BMI <20 kg/m^2 with unintentional weight loss of 5%–10% in 6 months. Using these validated high-risk indicators on our population sample, 75.8% would require placement of a PEG, which is less than the actual 84.2% who received a PEG. This shows the need for a balance between indicators found in the present study and existing literature.

Based on the contributing factors to EN usage and PEG placement found in this study, in combination with existing literature, it is suggested that the following indicators be taken into consideration in the creation of PEG placement protocols:

Advanced tumor (T3–T4) and node (N2–N3) stage in combination with expected or planned treatment (CRT and bilateral neck node radiation field)
Dysphagia or chewing complications (adapted intake consistency) prior to start of CRT
Severe pretreatment malnutrition

Age of patient could also be taken into consideration as older patients (>60 years) may have a higher chance of needing nutrition support during therapy.

As research clearly demonstrates beneficial effects of prophylactic PEG tube placement in selected patients with HNC,[18,30,35,42,43] this study provides insights into protocol development of indicators for prophylactic placement decision making, based on current PEG tube use. Further research is needed to gain a better understanding of prediction criteria to EN use and PEG placement to validate and support concrete indicator creation, as well as to examine the sensitivity and specificity of proposed indicators. A prospective study within our institute is anticipated.

Statement of Authorship

N. C. van der Linden, A. Kok, and M. J. Leermakers-Vermeer contributed to the conception and design of the research; N. M. de Roos contributed to the design of the research; N. C. van der Linden, A. Kok, and M. J. Leermakers-Vermeer contributed to the acquisition, analysis, and interpretation of the data; N. M. de Roos and C. H. J. Terhaard contributed to the analysis and interpretation of the data; and R. de Bree and H. van Cruijsen contributed to the interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Transpyloric Feeding Tube Placement Using Electromagnetic Placement Device in Children

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Abstract

Background: Transpyloric feeding tubes (TPT) are often recommended in critically ill children. Blind tube placement, however, can be difficult, be time-consuming, and incur multiple radiation exposures. An electromagnetic device (EMD) is available for confirmation of successful placement of TPTs. We conducted a retrospective cohort study to evaluate the efficacy of an EMD for TPT placement in children and determine its impact on placement success, radiation exposure, confirmation time, and cost for tube placement compared with traditional blind TPT placement. *Materials and Methods:* Retrospective data were collected in patients receiving a TPT before (pre-EMD group) and after implementation of an EMD (EMD group). *Results:* Need for radiographic exposure decreased significantly in the EMD group (n = 40) compared with the pre-EMD group (n = 38) (0.6 vs 1.6 x-rays, $P < .001$). TPTs were placed and confirmed without abdominal x-ray in 21 of 40 patients in the EMD group. There were no serious adverse events such as misplacement into the lung or pneumothorax or perforation injury of the stomach. Successful tube confirmation took a significantly shorter time in the EMD group than in the pre-EMD group (1.45 vs 4.59 hours, $P < .0001$). There was an estimated cost savings of $245.10 per placement associated with decreased x-ray and fluoroscopy. *Conclusion:* The use of an EMD in children significantly decreased radiation exposure and confirmation time while maintaining TPT placement success. The use of an EMD can potentially offer large cost savings. Elimination of abdominal x-ray with EMD during TPT placement was achieved without any serious complications in approximately half of the children. (*Nutr Clin Pract*. 2017;32:233-237)

Keywords

enteral nutrition; feeding tube; feeding tube placement; x-rays; pediatrics; child

Introduction

Enteral nutrition (EN) support is the preferred route of feeding for patients unable to eat by mouth with a functional gastrointestinal (GI) tract.[1] Early EN has been shown to decrease time on the ventilator[2] and intensive care unit (ICU) length of stay[3] while maintaining the intestinal immune system and achieving positive nitrogen balance.[4–6] Often, a transpyloric tube (TPT) is recommended as the route for EN for reasons including delayed gastric emptying, inability to tolerate gastric feedings, impaired intestinal motility, pancreatitis, and ability to achieve nutrition goals sooner than with a nasogastric tube.[7–9] Traditional blind bedside placement of a TPT is completed by trained nurses and is reliant on clinical intuition, patient placement, and peristalsis, with an abdominal x-ray for final confirmation.[10] Blind bedside placement of a TPT can be challenging and time-consuming, involves multiple feeding tube manipulations, is costly, and exposes the patient to avoidable radiation.[11]

The purpose of this study was to evaluate the efficacy of the use of an electromagnetic device (EMD) for TPT placement in children and to determine whether EMD use affects placement success, radiation exposure, overall placement confirmation time, and cost for tube placement compared with traditional blind TPT placement.

Methods

The electromagnetic placement system (Cortrak EAS 2; CORPAK Med Systems, Buffalo Grove, IL) was introduced at a tertiary care children's hospital in July 2014. A retrospective cohort study was conducted in October 2015 after approval by the institutional review board for pediatric patients receiving a TPT from January 2013 to July 2015.

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Blind bedside placement by trained pediatric ICU nurses was the standard approach before EMD implementation in July 2014. An EMD was not available at the hospital during this time period (pre-EMD group). The blind procedure typically included a nurse placing a small-bore feeding tube and advancing it past the measurement for standard gastric placement. The patient was subsequently placed in a right lateral position to allow the feeding tube to migrate into the small bowel with the help of peristalsis. Nurses used their clinical judgment and preference for tube type, with or without a stylet, for blind TPT placement. Many nurses employed variable, described placement techniques to aid in transpyloric placement, including air insufflation and prokinetic agents (metoclopramide).[12] Per hospital policy, an abdominal x-ray was obtained for all patients receiving a blind TPT for confirmation prior to initiating EN. Patient data for pre-EMD group were collected retrospectively on all patients with an order for a TPT during the 1-year time period. Data collected included the number of abdominal x-rays received after initial TPT placement until the x-ray report indicated transpyloric placement or no additional attempts (the placement was considered unsuccessful if the radiologist report did not indicate transpyloric placement and no additional attempts were made), successful placement of the transpyloric feeding tube, and length of time until confirmation, in hours, defined as time from the initial insertion attempt of the feeding tube documented by the nurse in the electronic medical record up to the time the final abdominal x-ray was taken showing confirmation of its successful placement, since feeding is unable to be initiated until tube placement is confirmed.

Data for the "EMD group" were collected after the EMD was implemented as the standard of practice hospital-wide for use with TPT placement in patients who were able to receive either a size 8 French or 10 French feeding tube. Prior to data collection and implementation of the EMD, a team of 15 pediatric ICU (PICU) nurses was trained in use of the device. As recommended by the device company and other hospitals,[13] a team of trained nurses were the sole users of the EMD to ensure competence in machine use. A team of nurses provided 24/7 TPT placement service using the EMD for all patients who were able to tolerate either an 8 French or a 10 French tube.

Hospital guidelines for the use of the device were developed before implementation. These guidelines allowed the nurse to use clinical judgment when determining if the patient was large enough to tolerate an 8 French feeding tube and if an x-ray was needed to confirm placement. An x-ray for placement verification was requested if the nurse was not confident in the feeding tube track shown on the EMD screen. Data were collected on all patients who received a feeding tube placed with the aid of the EMD from the date of implementation. Retrospective data collected included the number of abdominal x-rays required to confirm transpyloric placement, successful placement of the TPT, and length of confirmation time, in hours, from initial insertion of the feeding tube documented by the nurse in the electronic medical record until the feeding tube was confirmed transpyloric, either by the nurse from the feeding tube track or the bedside physician from the abdominal x-ray.

Any documented complications from the placements were also collected. Patients in the pre-EMD group were excluded if there was not an order for a TPT or if an abdominal x-ray was not used to confirm placement. Patients who received a TPT after EMD implementation requiring a tube smaller than 8 French were excluded, as the EMD device was not used. The estimated cost for tube placement was compared per patient using the hospital cost for an abdominal x-ray ($215), a fluoroscopy ($600), a Cortrak feeding tube ($32.10), and a standard feeding tube with stylet ($8). EMD machine cost ($30,000) was not included as the machine was obtained by a usage contract and pricing may vary across institutions based on suppliers or usage contracts.

Data were analyzed using the Student *t* test for geographic data, radiation exposure, and time of feeding tube placement; Mann-Whitney test for time for placement attempt; and χ^2 test for success rate. The level of significance used was $P = .05$. The statistical analysis was performed using SPSS version 20 (SPSS, Inc, an IBM Company, Chicago, IL).

Results

There were a total of 38 patients in the pre-EMD group and 40 in the EMD group. Among the pre-EMD group, 60.5% (23/38) of the patients were in an ICU setting compared with 55% (22/40) in the EMD group. The pre-EMD group used a greater variety of feeding tubes ranging from 5–10 French, with 6 French being the most common size (22/38). The EMD group primarily used 8 French as this is the smallest Cortrak tube available (34/40). The patient population in the pre-EMD group was younger than the patients in the EMD group (26.6 ± 44.4 vs 56.2 ± 80.7 months, 2-tailed *t* test, $P = .047$; Table 1). There were 1.63 ± 0.75 abdominal x-rays per tube placement attempt in the pre-EMD group vs 0.6 ± 0.74 in the EMD group ($P < .0001$, Figure 1). Only 19 of the 40 patients from the EMD group received radiation exposure for confirmation of TPT placement. Few patients in both groups were difficult placements and received more than 2 abdominal x-rays, 6 in the pre-EMD group and 1 in the EMD group. Three TPT placement attempts using blind placement techniques were unsuccessful and required fluoroscopy guidance for tube placement. Twelve patients were excluded from the pre-EMD group; 8 were excluded as they did not have a TPT order, and 4 were excluded since an x-ray was not used to evaluate tube placement. There was 1 incident in the EMD group where the tube coiled, knotted during placement, and was replaced with a smaller bore feeding tube without using the EMD. Two additional patients were excluded from the EMD group after unsuccessful placement with the EMD and nurse preference to switch to a smaller bore feeding tube for better patient tolerance. One patient was excluded from the EMD group who did not have a TPT order. There were no other complications associated with the feeding tube placement during the study such as inadvertent placement into the airway or GI perforation with the tubes in either group.

There was an estimated cost savings of $245.10 per placement associated with decreased abdominal x-ray and fluoroscopy, not including nursing time spent during placement or the

Table 1. Age, Location, and Feeding Tube Size of Patients.[a]

	Age						Location		Feeding Tube Size			
Patient Group	0–5 mo	6–12 mo	1–3 y	4–9 y	10+ y	Mean ± SD, mo	ICU	Non-ICU	5 French	6 French	8 French	10 French
Pre-EMD (n = 38)	21	4	6	3	4	26.6 ± 44.4	23	15	5	22	8	3
EMD (n = 40)	17	7	5	1	10	56 ± 80.7	22	18	0	0	34	6

EMD, electromagnetic device; ICU, intensive care unit.
[a]Patients were older in the EMD group ($P = .047$, 2-tailed t test). The size of feeding tube was smaller in the pre-EMD group ($P < .001$, 2-tailed t test).

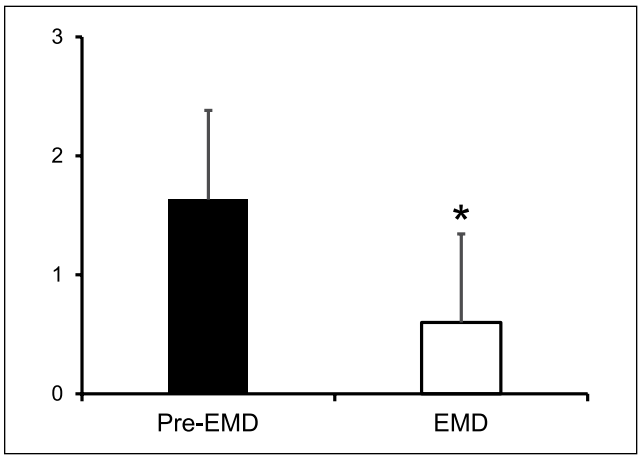

Figure 1. The number of x-rays per a transpyloric tube placement. The usage of an electromagnetic device (EMD, n = 40) significantly decreased the number of x-rays per tube placement. The tube was placed blindly in the pre-EMD group (n = 38). Data are expressed as mean and SD (1-tailed t test, $*P < .0001$).

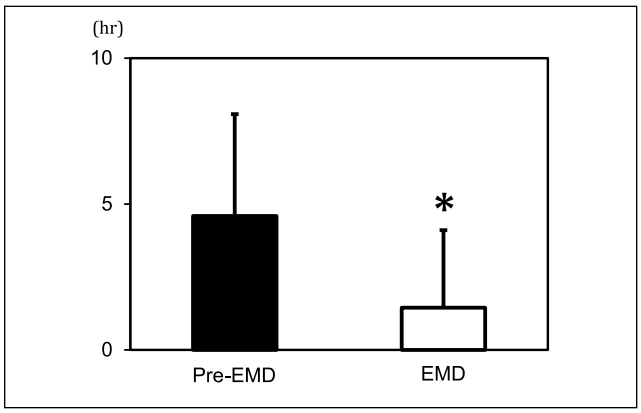

Figure 2. Time for successful placement. The electromagnetic device (EMD) significantly decreased the time (2-tailed Student t test, $*P < .0001$). Data are expressed as mean and SD.

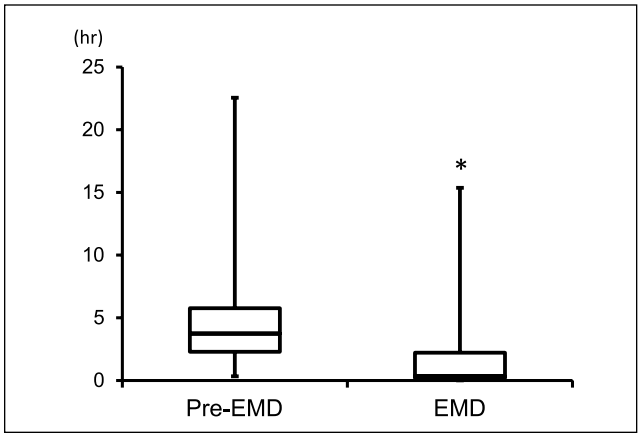

Figure 3. Time for placement attempt. The electromagnetic device (EMD) significantly decreased the time for placement attempt (pre-EMD, n = 38; EMD, n = 40; 2-tailed Mann-Whitney, $*P < .05$). Data are expressed as median and interquartile range.

cost of the actual Cortrak EAS2 machine as the hospital received a machine as part of a usage contract. If we had purchased the machine at a cost of $30,000 and continued using the machine for 40 patients per year, the estimated cost saving would be used for paying off the machine cost for approximately 3 years or 122 procedures.

Successful blind TPT placement confirmation took an average of 4.6 ± 3.5 hours, and successful EMD placement confirmation took an average of 1.5 ± 2.7 hours ($P < .0001$, Figure 2), while total (successful and unsuccessful) tube placements took an average of 5.29 ± 5.15 hours for blind placement and 1.73 ± 3.00 hours for the EMD (Figure 3).

Success rate was 76.3% for the pre-EMD group and 87.5% for the EMD group. The EMD group was further divided into 2 groups, the first 20 placements and the last 20 placements, to evaluate any potential significance in success rate over continued use of and greater experience with the machine (Figure 4). Transpyloric tubes were successfully placed in all of the last 20 patients with EMD. However, there were no significant differences between the 3 groups (χ^2 test, $P = .052$). Furthermore, we conducted a subgroup analysis to compare the success rate in patients who received x-rays between the groups. There was no statistically significant difference in success rate between the groups (pre-EMD 76.3% vs EMD with x-ray 84.2%, $P = .49$, χ^2 test).

Discussion

This cohort study demonstrated that the use of the EMD decreased radiation exposure per patient to 0.6 ± 0.74 ($P < .0001$), shortened tube placement confirmation time to 1.5 ± 2.7 hours ($P < .0001$), and decreased medical cost by $245.10 per placement. Previous evaluations of the EMD in critically ill children showed a significant decrease in radiation exposure to

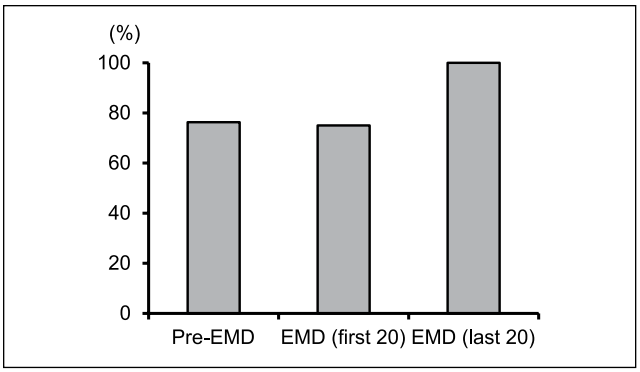

Figure 4. Success rate. Despite no significant differences, there was a trend to an increase in the success rate over time (χ^2 test, $P = .052$). EMD, electromagnetic device.

1.2 per patient,[14] an increase in the success rate to 64.3%,[14] a decrease in placement time to 1.7 hours,[15] and a decrease in cost per tube placement by $132.05.[14] Comparatively, 1 pediatric study found that the EMD use increased time of placement[16] while another study found slightly higher cost with EMD.[17] The cost of the Cortrak EAS2 and Cortrak feeding tubes for our hospital may have been less than other hospitals due to a contract. Similar results are seen with evaluations in an adult population: significant reduction (50%) in radiation exposure,[18] 1.07 x-rays per patient,[13] and an increase in the success rate (83.9%).[13]

The reported safety events and Food and Drug Administration (FDA) approval were reviewed prior to implementation of the device to the institution. Since the Cortrak EAS 2 device is FDA approved for tube placement confirmation, the hospital guidelines for use permitted the trained nurses to obtain an abdominal x-ray only if they were not confident in the location of the feeding tube based on the track shown on the device screen. This cohort study showed a lower rate of radiation exposure per patient (<1 x-ray per placement), including 21 patients without x-ray, and shorter TPT placement confirmation time with application of the EMD. Cumulative radiation exposure poses risks to patients with chronic diseases, and excess, potentially unnecessary, radiation should be avoided.[19] In addition, no adverse events, such as pneumothorax, misplacement into the lung, or perforation of the GI tract, were seen with the EMD group. In adults, 1 study safely eliminated x-ray for TPT placements in most cases (only 7.7% required x-ray).[20] Our study is the first study that safely and efficiently eliminated x-rays for TPT placement confirmation in children. However, medical device reports in the FDA Manufacturer and User Facility Device Experience (MAUDE) Database show reports of inadvertent lung placement and tube malfunction.[21] The National Health Service (England) issued a patient safety alert in 2013 regarding misplacement of feeding tubes with the aid of a placement device.[22] Patient safety remains our highest priority, and we should continue to monitor the safety alarm recommendations from the FDA and other agencies.

We hypothesize that the EMD made the nurses feel more confident in the tube placement location (in more than half of the patients, the nurse did not request an abdominal x-ray) because they could actually see the tube track, including depth tracking, to help them determine the placement of the tube. In this study, 1 patient in the EMD group had the feeding tube knot after coiling in his stomach. In this case, the nurse noticed the tube was coiling and attempted to pull back the stylet a few inches and replace in an effort to remove the coil. During this time, the tube knotted and the stylet was unable to be replaced; the feeding tube was removed uneventfully. However, this could have occurred with any feeding tube with a stylet; the EMD allowed the nurse to identify the coil before obtaining an x-ray compared with blind placement.

TPT placement confirmation time in the EMD group was significantly shorter when comparing successful patients. Hypoglycemia is commonly observed in critically ill children and associated with neurological morbidity and mortality.[23,24] Therefore, initiating enteral feeding quicker would be beneficial to avoid hypoglycemia and its complications. The confirmation time reduction is likely due to the omission of the abdominal x-ray, as patients can wait an average of 3.4 hours for an x-ray with a radiologist reading.[25] In contrast to the FDA-approved Cortrak EAS 2 and abdominal x-ray, confirmation of feeding tubes may not be as accurate from other methods, including pH, capnography, appearance of aspirate, or auscultation.[26] Comfort of the nurse with placing TPTs and machine use can contribute to time of tube placement. One study reported slightly increased procedure time of TPT placement with the EMD (median, 9.5 vs 5.0 minutes, EMD vs blind).[16] However, their practitioners had significant experience placing TPTs blindly, and the EMD group had 100% success rate in the study.[16] Also, their study did not mention the time waiting for x-rays.[16,23] In our institution, all PICU nurses placed blind TPTs for the entire hospital compared with only a select group (the charge/lead nurses) of the PICU nurses who were trained to use the EMD. Typically, charge/lead nurses have more experience and could potentially place a TPT faster than other nurses. This could have contributed to the blind group having a longer average time per patient. However, nurses who are very skilled in blind TPT placement can be delayed with the use of technology as they may doubt their skills and become too concerned with use of the machine.[16] During blind placement, nurses were also given the autonomy to choose their preferred tube, with or without stylet, for use compared with the EMD, which requires a feeding tube with a stylet. This may contribute additional variance in length of time to place the tube as a tube with a stylet may be more successful.[16]

There are some limitations in this study. This is a retrospective cohort study, and the patients were not randomized for the group. The skills of the nurses between the groups might be different as only charge/lead nurses, typically with more experience, were on the EMD-trained team and the non-EMD group included all PICU nurses. Order of x-ray in the EMD group is dependent on comfort levels of each nurse and may have varied across trained nurses. Time the x-ray was taken instead of time of the radiologist report was used for calculating placement confirmation time as attending physicians may view the image to determine placement before the radiologist reads the image. Procedural nursing time was not evaluated between the groups. As this was a retrospective study, the

tube insertion time is only documented in the electronic medical record and not the total nursing time spent inserting the tube. Actual procedural time for the EMD group can potentially be longer because the nurse is able to see if the tube coils or is not advancing to the small intestine in real time and adjust accordingly, potentially spending more time on the initial insertion. With blind placement, nurses cannot immediately tell if the tube is coiled or has remained in the gastric position until the abdominal x-ray, where they would need to spend additional procedural time to adjust the tube after the initial insertion. The smallest Cortrak tube available is 8 French. This may have contributed to increased placement confirmation time and x-ray use in the EMD group in younger patients who received an 8 French tube since the nurse may have preferred to use a smaller tube if it were available. In other studies including critically ill pediatric patients using only 8 French and 10 French feeding tubes, patient size was not associated with placement success.[15,16] Also, due to tube size limitations, patients requiring smaller than 8 French were not included in the EMD study group. This may have contributed to the younger age for the pre-EMD group and may have altered placement confirmation time and radiation exposure, as these patients were included in the pre-EMD group.

Conclusion

Radiation exposure and the length of time for TPT placement confirmation significantly decreased with the assistance of an EMD in children. The use of an EMD can potentially offer large cost savings associated with decreased x-ray and fluoroscopy. Need for abdominal x-rays during TPT placement was reduced by ~50% without any serious complications, further attesting to the safety of this technique.

Statement of Authorship

All authors contributed to the conception and design of the research; S. Pickard and M. Goggans contributed to the acquisition of data; A. N. West, S. Shah, and D. Kimura contributed to the analysis and interpretation of data; and M. Goggans and D. Kimura drafted the manuscript. All authors critically revised the manuscript, gave final approval, and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Effect of Time and Temperature on Thickened Infant Formula

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Abstract

Background: Unlike adult populations, who primarily depend on liquids for hydration alone, infants rely on liquids to provide them with hydration and nutrition. Speech-language pathologists working within pediatric medical settings often identify dysphagia in patients and subsequently recommend thickened liquids to reduce aspiration risk. Caregivers frequently report difficulty attempting to prepare infant formula to the prescribed thickness. *Materials and Methods:* This study was designed to determine (1) the relationship between consistencies in modified barium swallow studies and thickened infant formulas and (2) the effects of time and temperature on the resulting thickness of infant formula. Prepackaged barium consistencies and 1 standard infant formula that was thickened with rice cereal and with 2 commercially available thickening agents were studied. Thickness was determined via a line spread test after various time and temperature conditions were met. *Results:* There were significant differences between the thickened formula and barium test consistencies. Formula thickened with rice cereal separated over time into thin liquid and solid residue. Formula thickened with a starch-based thickening agent was thicker than the desired consistency immediately after mixing, and it continued to thicken over time. The data from this project suggest that nectar-thick and honey-thick infant formulas undergo significant changes in flow rates within 30 minutes of preparation or if refrigerated and then reheated after 3 hours. *Conclusions:* Additional empirical evidence is warranted to determine the most reliable methods and safest products for thickening infant formula when necessary for effective dysphagia management. (*Nutr Clin Pract*. 2017;32:238-244)

Keywords

thickened liquids; dysphagia; deglutition disorders; pediatrics; infant; infant formula

Background

With medical advancements in neonatal and pediatric medicine, there has been a notable improvement in the survival rate of infants and children born with complex medical conditions. The improved survival rate of these children has contributed to a significant increase in the prevalence of pediatric feeding and swallowing disorders. The current estimated prevalence of dysphagia in the general population is just 1%,[1] and in pediatric populations with developmental disorders, it has been reported to be as high as 80%.[2] Many underlying conditions—including neurologic disorders, prematurity and its resulting sequelae, craniofacial anomalies, and pulmonary disorders/diseases—may result in at least transient dysphagia in pediatric populations.[2,3] Despite the lifesaving advances in medicine, the options for treating the common symptoms of dysphagia, laryngeal penetration, and aspiration remain limited for pediatric populations.

Dysphagia treatment options fall into 2 distinct categories: direct and indirect. Direct strategies involve exercises in which the patient must participate to improve swallowing function. Direct strategies rely on the patient's ability to follow directions and competently perform the tasks as instructed by the clinician or caregiver. In contrast, indirect strategies involve manipulation of the food substances or environment by caregivers to help facilitate safe swallowing. Indirect strategies are most commonly employed for the pediatric patient due to neurologic and physical immaturity. Increasing the viscosity or thickness of liquid, more commonly known as "thickening liquids," is one of the most frequently used indirect strategies for adult and pediatric populations.[4,5]

The appeal of providing thickened liquids is its theoretical simplicity. By following the directions provided on the package, caregivers can mix liquids to (presumably) desired

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thickness, and patients with dysphagia can safely consume the liquid. However, its clinical application provides more practical challenges, which have been documented with standard liquids that adults drink for hydration, such as water, coffee, and juice. The thickness of a liquid mixed with commercially available thickening agents depends on many variables (eg, type of thickening agent and stand time of liquid after mixing), but the effects of both time and temperature on the thickness of liquids mixed with commercially available thickening agents have been well documented.[6-8]

Garcia et al reported that viscosity (thickness) measurements of nectar-thick and honey-thick liquids are dependent on the type of thickening agent used, the type of liquid being thickened, and the amount of time that it was allowed to thicken. The authors provided a valuable discussion on the influence of the type of liquid to be thickened, as liquids with higher concentrations of ions, minerals, proteins, acids, and pectin produced significantly different results from more neutral liquids.[6] While the authors did not specifically draw attention to infant formulas in their study, infant formulas are nutritionally complete and are therefore significantly different from less nutrient-dense fluids commonly thickened for adults. Dewar and Joyce compared the characteristics of 2 types of starch-based thickening agents: maize-based and maltodextrin-based thickening agents. They reported that maltodextrin-based thickening agents produce a viscosity that is more stable over time than the maize-based equivalent in filtered water.[7] Garcia et al looked at the influence of temperature on the viscosity of liquids in a follow-up project. In the subsequent project, they used both starch-based and gum-based thickening agents to mix with refrigerated (water, juice, and milk) or hot (coffee) beverages, and they found that temperature was another significant variable on the thickness of the liquid.[8] The previous body of work has established that providing thickened liquids that are at the desired therapeutic thickness of either nectar or honey is far from simple and depends on multifactorial interactions of liquid type, thickening agent type, amount of time that elapses from preparation to consumption, and the serving temperature of the liquid.

The necessity of liquid intake in infants for appropriate nutrition and hydration adds a new layer of complexity to the considerations of providing thickened liquids to this population. In adult populations, there are reports of thickened liquid modifications being associated with dehydration due to patient refusal.[9] This phenomenon has not been explicitly investigated in pediatric populations; however, there have been recent speculations and anecdotal reports that thickening liquids may lead to dehydration and other adverse effects, such as malnutrition, diarrhea, malabsorption, necrotizing enterocolitis, and, in some cases, death in pediatric populations.[4] The questionable safety of thickening feeds was raised in a journal letter describing the acute onset of ultimately fatal necrotizing enterocolitis in 2 premature infants who received thickened enteral feeds.[10] Thickened liquids should be prescribed only when their effectiveness for improving the safety of a patient's swallow has been established, owing to the potential risks associated with the use of thickened liquids in pediatric populations.

Preparing infant formula to the desired thickness of either nectar-thick or honey-thick consistency is challenging. We know from previous work with commonly consumed adult liquids that the viscosity (thickness) depends on liquid type, thickening agent type, amount of time that elapses from preparation to consumption, and the serving temperature of the liquid.[6-8,11] Infant formula is a nutrient-dense liquid with adequate protein, fat, and carbohydrates to meet the full nutrition requirements of infants and is therefore characteristically different from previously studied adult fluids. The standard caloric density of infant formula is 20 calories per ounce (much higher than most adult dietary fluids); however, it is often manipulated to ≥24 calories per ounce based on the caloric needs of the medically fragile infant that it supports. Furthermore, no commercially available thickening agent in the United States provides instructions for how to mix formula or expressed breast milk to nectar-thick or honey-thick consistency.

Overseas research using thickening agents not available in the United States suggests that instructions provided for thickening infant formula often do not produce the desired thickness when mixed with different types of infant formula.[12] Other pediatric-specific issues related to thickening liquids include the fact that breast milk and infant formula are typically served at body temperature (98.6°F, 37°C), which is different from the serving temperature of most liquids consumed by adults, creating potential for variation in response to thickening agents. In addition, thickened liquids must be consumed through a bottle with a nipple, and the small nipple opening creates the potential for greater susceptibility to variations in thickness.

Given the variability of thickness present in commonly consumed adult liquids thickened with standard thickening agents, as well as the growing concern about the potentially harmful side effects of using thickened feeds with infants, there is an immediate need for clinicians to have a complete understanding of the variables affecting accurate preparation of infant formula into nectar-thick and honey-thick categories. This project sought to determine if barium test consistencies had equivalent flow rates to thickened formula, and it investigated the effects of time and temperature on the thickness of infant formula thickened with agents commonly used in pediatric practice in the United States.

Materials and Methods

This study was designed to determine (1) the relationship between barium test consistencies used during modified barium swallow studies and the subsequently provided thickened infant formulas and (2) the effects of time and temperature on the resulting thickness of the infant formula. Varibar (Bracco Diagnostics Inc, Monroe Township, NJ) prepackaged bariums were chosen as the liquids for comparison—including thin liquid barium (target viscosity: 4 cP, viscosity range: <15 cP),

nectar-thick liquid barium (target viscosity: 300 cP, viscosity range: 150–450 cP), and honey-thick liquid barium (target viscosity: 1500 cP, viscosity range: 800–1800 cP). One standard cow's milk–based infant formula, Good Start (Nestlé, Fremont, MI), was chosen as the formula to thicken with various thickening agents. Good Start is a formula composed of partially hydrolyzed whey protein, which is in contrast to other infant formulas in this category that contain intake cow's milk protein with a modified whey:casein ratio of 50:50 or 60:40. A single-grain rice cereal (Gerber; Nestlé), a thickening agent made from modified cornstarch (Resource ThickenUp Instant Food Thickener; Nestlé Health Care Nutrition Inc, Florham Park, NJ), and gum-based thickening agent made from xanthan gum (SimplyThick; SimplyThick, LLC, St Louis, MO) were chosen as representative samples of agents available to thicken infant formulas in clinical settings.

The formula was thickened with all 3 thickening agents to both the nectar-thick and honey-thick consistencies following the package directions. For rice cereal–thickened formula, nectar-thick consistency was prepared by mixing 1 tsp of rice cereal (from the package, not pulverized) with each ounce of formula, and honey-thick consistency was prepared by mixing 1 tbsp of rice cereal (from the package, not pulverized) with each ounce of formula. The ratios for rice cereal to formula for creating nectar-thick and honey-thick consistencies were based on clinical standards established by the speech therapy and nutrition departments at LeBonheur Children's Hospital, following confirmation of fluid categorization based on flow rate of infant formula mixed with rice cereal in the above ratios (we acknowledge that there is considerable variability among ratios for thickening formula with rice cereal across institutions). All thickening agents were mixed with 4 oz (120 mL) of formula at a time. The formula was prepared from powder following the instructions provided by the manufacturer. For heated samples, the formula was mixed, heated, and then the thickening agent was added. Elapsed time was measured from the time that the thickening agent was added. The refrigerated samples were prepared as previously described, without heating, and then allowed to rest in the refrigerator for 3 hours before being heated to body temperature and then sampled for this project.

The Mini-Temp FS Infrared Thermometer (Raytek Corporation, Santa Cruz, CA) was utilized to provide measures of liquid temperature. Liquids, when heated, were warmed with a commercially available bottle warmer to 98.6°F ± 2°F. Formula was mixed in Gerber 9-oz clear plastic bottles. The thickening agent was also mixed with the formula in the Gerber bottles. All formula and thickening preparations were performed in a room with a constant temperature of 78°F (25.56°C).

Bolus flow was measured with a standard line spread test.[11,13-16] Line spread test results have been found to distinguish therapeutically relevant categories of thickened liquids (ie, nectar and honey thick)[15] and, in some reports, to correlate with viscosity.[14,16] Line spread test measures most likely represent a combination of rheologic properties that affect the thickness of liquids, including viscosity, yield stress, and density.[15] A line spread test is made from a template of premeasured concentric circles spaced 1 cm apart, with a plexiglass overlay on top of the template. Line spread tests were performed on a countertop confirmed as level with use of a carpenter's level.

Liquids were prepared as described above and measured via graduated syringe into 50-mL boluses. The boluses of prepared fluid were plunged into a PVC pipe cylinder placed over the central circle of the line spread test. The cylinder was lifted, and the bolus was allowed to spread for 1 minute. At the end of 1 minute, the spread (in centimeters) was determined for each of the 4 quadrants on the line spread test. The mean of these 4 measures was then calculated as a measure of bolus flow. This process was completed 10 times for each formula thickness at each time interval (5 and 30 minutes postmixing and 3 hours of refrigeration) to determine the mean spread for each time. In between samples, the bolus was wiped off the plexiglass overlay with a slightly dampened cloth. No chemicals or soap were used in the cleaning of the plexiglass overlay.

Results

Table 1 presents the means for all liquids under all conditions of this project.

Significant variations in flow rates were evident when nectar-thick and honey-thick consistency bariums were compared with nectar-thick and honey-thick consistency formulas as prepared with rice cereal, starch, and gum-based thickening agents. As can be seen in Table 2, immediately after preparation, the nectar-thick formula samples thickened with starch and gum were significantly thinner than the nectar-thick barium test consistency, and the honey-thick formula samples thickened with rice cereal and starch were significantly thicker than the honey-thick barium test consistency.

Significant differences were also seen when thickened formula samples were compared after 5 minutes of stand time and after 30 minutes of stand time. Within samples of nectar-thick and honey-thick formulas, those thickened with rice cereal were significantly thinner after 30 minutes of stand time as compared with 5 minutes of stand time. Alternatively, nectar-thick and honey-thick formula samples thickened with starch-based and gum-based thickening agents were significantly thicker after 30 minutes of stand time as compared with 5 minutes of stand time. Mean flow rate values of each thickened consistency organized by stand time can be seen in Table 3.

Variation in flow rates were also demonstrated when thickened formula samples were compared after 5 minutes of stand time and after 3-hour refrigerated stand time and reheating. Nectar-thick and honey-thick formula samples thickened with rice cereal were found to be significantly thinner following a refrigerated stand time of 3 hours and reheating as compared with thickness at 5 minutes of stand time. Nectar-thick and honey-thick formula samples thickened with the starch-based

Table 1. Mean Flow Rates of All Tested Fluids for Each Condition of Project.[a]

Liquid: Thickener, Elapsed Time	Mean Flow Rate, cm		
	Thin	Nectar[b]	Honey[b]
Standard formula	7.98	—	—
Barium	8.01	4.12 (0.30)	3.51 (0.14)
Formula, rice			
5 min		4.45 (0.45)	2.18 (0.12)
30 min		5.91 (0.91)	3.99 (0.18)
3 h		5.93 (1.24)	3.65 (0.33)
Formula, starch			
5 min		5.13 (0.34)	2.81 (0.58)
30 min		4.09 (0.19)	0.88 (0.08)
3 h		3.56 (0.33)	0.18 (0.06)
Formula, gum			
5 min		5.50 (0.37)	3.63 (0.18)
30 min		4.16 (0.20)	3.33 (0.16)
3 h		4.14 (0.20)	3.95 (0.34)

[a]Formula was heated to body temperature, then mixed with thickener and run on the line spread test at 5 and 30 minutes postmixing with thickener. Samples run on line spread test after 3 hours were mixed and placed in the refrigerator without first heating them to body temperature. Refrigerated samples were heated to body temperature after 3 hours in the refrigerator prior to being run on the line spread test.
[b]Standard deviation in parentheses.

Table 2. Comparison of Mean Flow Rates of Barium and Thickened Infant Formulas for Nectar and Honey Consistencies.

Consistency	Mean Flow Rate, cm			
	Barium	Formula + RC	Formula + Starch	Formula + Gum
Nectar	4.12	4.45	5.13[a]	5.50[a]
Honey	3.51	2.18[a]	2.81[a]	3.63

Gum, Simply Thick; RC, rice cereal; starch, ThickenUp.
[a]$P < .01$ (vs barium in row).

Table 3. Comparison of Flow Rates of Thickened Infant Formulas for Nectar and Honey Consistencies by Stand Time.[a]

Consistency	Mean Flow Rate, cm	
	5 min	30 min[b]
Nectar formula		
RC	4.45	5.91
Starch	5.13	4.09
Gum	5.50	4.16
Honey formula		
RC	2.18	3.99
Starch	2.81	0.88
Gum	3.63	3.33

Gum, Simply Thick; RC, rice cereal; starch, ThickenUp.
[a]Formula was heated to body temperature, then mixed with thickener and run on the line spread test at 5 and 30 minutes postmixing with thickener.
[b]Each value in the column is significant at $P < .01$.

thickening agent were found to be significantly thicker following a refrigerated stand time of 3 hours and reheating as compared with thickness at 5 minutes stand time. Formula samples thickened to the honey-thick consistency with gum-based thickening agent were found to be significantly thicker following a refrigerated stand time of 3 hours and reheating as compared with thickness at 5 minutes of stand time. However, the honey-thick formula samples thickened with the gum-based thickening agent showed no significant differences following a refrigerated stand time of 3 hours and reheating as compared with thickness at 5 minutes stand time. These results are summarized in Table 4.

For the reported variability of nectar-thick and honey-thick formula preparations, see Figure 1. Formula thickened with rice cereal to both the nectar-thick and honey-thick consistencies got thinner over time, as evidenced by higher flow rates, likely because the rice cereal tended to separate over time into a thin liquid (formula) and solid residue (rice cereal). Additionally, there was wide variability observed with the resulting thickness of both nectar-thick and honey-thick preparations with standard infant formula. The formula mixed with a starch-based thickening agent to create a nectar-thick

Table 4. Comparison of Mean Flow Rates of Thickened Infant Formulas for Nectar and Honey Consistencies by Refrigeration, Reheating, and Stand Time.[a]

	Mean Flow Rate, cm	
Consistency	5 min	3 h
Nectar formula		
RC	4.45	5.91[b]
Starch	5.13	4.09[b]
Gum	5.50	4.16[b]
Honey formula		
RC	2.18	3.99[b]
Starch	2.81	0.88[b]
Gum	3.63	3.33

Gum, Simply Thick; RC, rice cereal; starch, ThickenUp.
[a]Formula was heated to body temperature, then mixed with thickener and run on the line spread test at 5 minutes. Samples run on the line spread test after 3 hours were mixed and placed in the refrigerator without first heating them to body temperature. Refrigerated samples were heated to body temperature after 3 hours in refrigerator prior to being run on the line spread test.
[b]$P < .01$.

consistency was closest to the test consistency of nectar-thick barium after a 30-minute stand time. In contrast, formula mixed with a starch-based thickening agent to create a honey-thick consistency was too thick after the initial 5-minute stand time, and it continued to thicken over time. The gum-based thickening agent produced formula samples at the nectar-thick consistency that were closest to the nectar-thick barium test consistency after 30 minutes of stand time or, if refrigerated and then reheated, after 3 hours of stand time. Honey-thick formula samples prepared with the gum-based thickening agent were closest to the honey-thick barium test consistency after 5 or 30 minutes of stand time (see Figure 1).

Discussion

This study brings attention to the complexity of successfully carrying out the recommendation to provide thickened liquids for infants with dysphagia. The results of this study reveal that none of the available thickening agents easily approximated the barium test consistencies when mixed with a standard cow's milk infant formula. These results confirm earlier work overseas that also found significant differences in the rheologic and material properties of the barium liquids used for testing and the thickened and unthickened infant formulas.[12]

In the current study, when the formula was mixed with rice cereal to both a nectar thickness and a honey thickness, the mixture separated into thin liquid with a solid residue over time, and there was large variability in flow rates. Infant formula mixed to the manufacturer's instructions for nectar-thick consistency with the starch-based thickening agent most closely approximated the nectar-thick barium test consistency after a 30-minute rest period. The manufacturer's instructions for honey-thick consistency with the starch-based thickening agent produced formula that was thicker than the honey-thick barium test consistency, which continued to thicken over time. Infant formula mixed with the gum-based thickening agent for nectar-thick consistency was closest to the nectar-thick barium test consistency after 30 minutes of rest or if refrigerated for 3 hours and then reheated. The gum-based thickening agents that were mixed following the manufacturer's instructions for the honey-thick consistency most closely approximated the honey-thick barium test consistency after resting for 5 or 30 minutes. These results highlight how difficult it is to reproduce the flow rate of nectar-thick and honey-thick barium test consistencies in a standard infant formula with common thickening agents. Currently, thickening agents come with standard instructions that do not take into account the individual makeup of the specific types of fluids with which they may be mixed. The results of this study bring about important considerations for clinicians who are treating dysphagia with a thickened liquid compensation in pediatric populations. These considerations include the need to confirm the appropriate thickness of formula after mixing with a thickening agent before serving to a patient, to adapt thickener:formula ratios as necessary to achieve the desired thickness, and to evaluate the impact of premixing daily batches of thickened formula for use in hospitals (due to the effect of time on the thickness of the formula).

A recent systematic review confirmed the popularity of thickened fluids as a clinical intervention and highlighted the limited knowledge available regarding the physiologic benefit and effects of utilizing thickened liquids in populations with dysphagia.[17] Thickened infant formula that is thinner than the test consistency may not be thick enough to prevent aspiration. Aspiration is a known contributor for poor pulmonary outcomes in pediatric populations. The opposite of this condition would be formula that is too thick. Overly thick formula may result in excessive effort expenditure by the infant during feeding, potentially causing fatigue and reduction in total volume of intake, which would contribute to malnutrition and dehydration. Thickening agents that do not mix well with infant formula may also block the nipple and prevent effective feed transfer. Additionally, formula that is perceived by caregivers to be too thick or lumpy may contribute to noncompliance with recommendations.

The results from this research project show that, when mixed with infant formula, common thickening agents may result in liquid that is thinner or thicker than test consistencies. Clinicians must be aware of these potential thickness differences and be available to problem solve with caregivers when atypical thickening results arise. It is advisable to schedule follow-up appointments with families who have received recommendations to thicken an infant's formula to ensure that they are able to replicate the desired thickness with the formula and thickening agent. Additionally, the infant's home bottle-and-nipple system must be examined to ensure that it is an appropriate size to allow a sufficient flow rate to permit the passage of thickened liquids without excessive sucking effort.

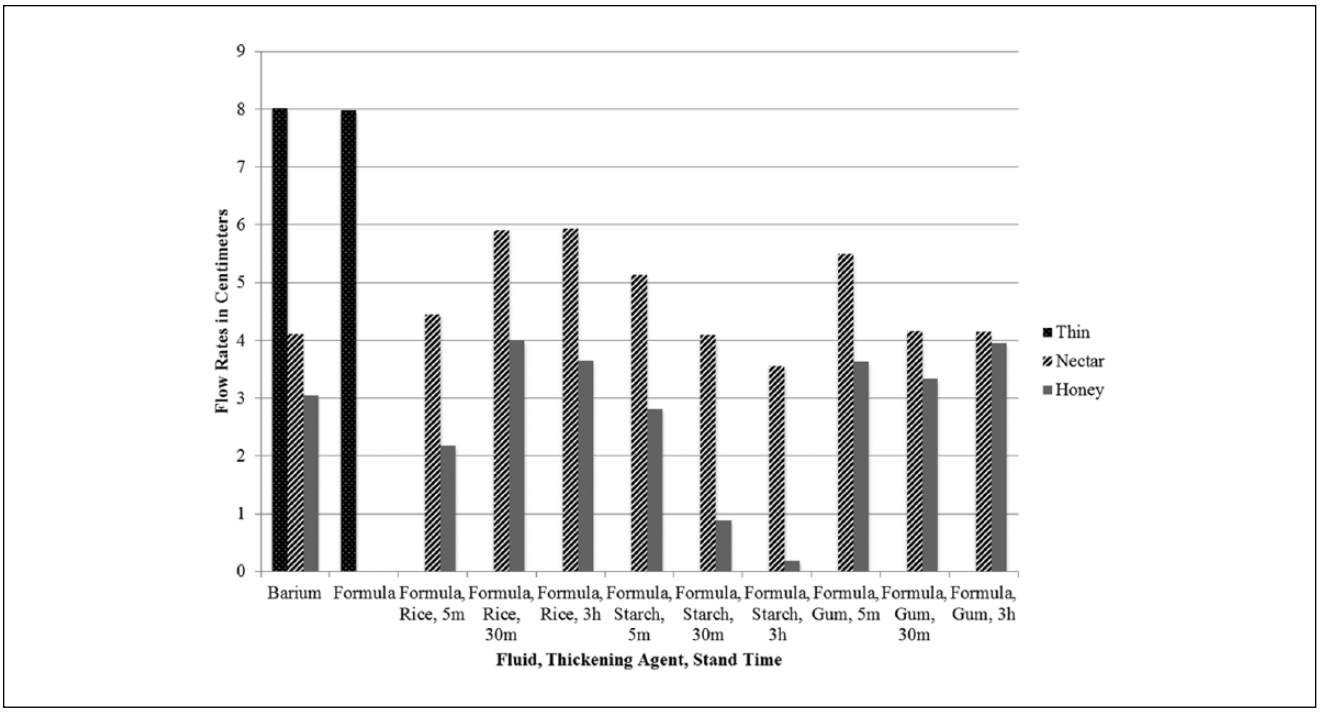

Figure 1. Flow rates of all test consistencies. 5m, 5 minutes; 30m, 30 minutes; 3h, 3 hours.

This study, like all research projects, is not without limitations. It is based on a standard infant formula (20 calorie per ounce) commonly consumed in the United States. A number of infant formulas are available, and they have different ratios of micronutrients and macronutrients that can affect how they react with the available thickening agents. Additionally, formulas that are concentrated to higher caloric contents or have a different protein base (soy vs cow's milk protein vs elemental formulas) may react differently to the various thickening agents, due to the reduced volume of water and nutritional base of the formula. The choice of a popular standard cow's milk formula for the base liquid in this research study potentially limits the generalizability to other formula varieties.

Three common thickening agents were chosen to mix with infant formula: rice cereal, 1 starch-based thickening agent, and 1 xanthan gum–based thickening agent. The proportions of ingredients in each brand of thickening agent are proprietary; therefore, there is no guarantee that a different brand of rice cereal, starch-based thickening agent, or gum-based thickening agent (or thickening agents that incorporate a mix of these) will replicate the findings of this research project. We do not promote the use of the products utilized in this research project; they were chosen due to their popularity and availability at the time that the research was undertaken. Ultimately, the results reveal the need for clinicians to make individualized treatment recommendations and confirm that the infant's specific formula and chosen thickening method result in a treatment consistency that is not significantly thinner or thicker than the test consistency.

This study utilized a line spread test to measure thickness. Other methods are available for measuring thickness, but this measure was chosen because of its reliability and clinical availability.[11,13-16] It should be noted that similar trends were found in an overseas study utilizing a viscometer to measure thickness.[12] Future research is necessary to further understand the ways that thickened liquids change in the in vivo environment. Initial data suggest that salivary amylase (in combination with changes in bolus temperature from being in the oral cavity) can have an immediate and significant effect on the flow rates of thickened boluses in adult populations.[18] It will also be of interest to understand what, if any, effect sucking pressure and rate have on characteristics of boluses as they move through the restricted opening in the bottle nipple. Additional research is necessary to understand the change in macronutrient distribution and dilution of micronutrients with the use of any thickening agent in infant formula. Future research should replicate this methodology with additional formula, expressed breast milk, and thickening types to provide further generalizability of these results.

Conclusions

The results of this study demonstrate the need for clinicians to be aware of potential variation in the thickness of thickened infant formulas. Clinicians need to know that infants with recommendations for thickened liquids may be consuming liquids that are thicker or thinner than the test consistencies that resulted in the recommendation for thickened liquids. Pediatric

clinicians must be alert to clinical signs of fatigue and aspiration that may be demonstrated during feeding, which will alert them to the fact that the infant that is consuming liquid that is too thick or too thin to be effective in dysphagia management. In addition, family members should be taught to recognize these signs, which likely indicate that the feed being offered is not of an appropriate thickness for the infant. We propose that it is unacceptable to recommend thickened liquids following imaging studies and not clinically follow up with caregivers to confirm that the infant is able to manage the recommended thickened liquids with successful amelioration of dysphagia signs and symptoms while maintaining adequate oral intake to support growth and development during infancy.

Authors' Note

Results from this project were presented at the annual convention of the American Speech-Language-Hearing Association (ASHA) in 2015 in Denver, Colorado.

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Statement of Authorship

M. M. Gosa and P. Dodrill equally contributed to the conception and design of the research and to the acquisition, analysis, and interpretation of the data; and M. M. Gosa drafted the manuscript. Both authors critically reviewed and revised the manuscript; read and gave final approval of the completed, revised manuscript; and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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An Institutional Change in Continuous Renal Replacement Therapy: Nutrition Support Team Resolves Resultant Severe Hypophosphatemia

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Abstract

Background: Critically ill patients with acute kidney injury may require parenteral nutrition (PN) and continuous renal replacement therapy (CRRT). Introduction of a phosphate-free premixed renal replacement fluid without system-wide education in May 2011 resulted in increased incidence of hypophosphatemia, necessitating change in practice. Changes included (1) maximizing phosphate in PN, (2) modifying the CRRT order set, and (3) developing a CRRT competency evaluation for nutrition support team members. This study evaluates the effect of these changes on the incidence of hypophosphatemia. *Methods:* Phosphate levels and predicated probability of hypophosphatemia were evaluated for patients receiving PN and CRRT over 3 time periods: prior to implementing the changes (preimplementation), during change implementation (intermediate), and following implementation (postimplementation). Hypophosphatemia was defined as a serum phosphate level <2.5 mg/dL. Generalized linear mixed models were applied for statistical analysis. *Results:* The retrospective study includes 336 measures from 49 patients. Patients in the intermediate and postimplementation periods were not significantly different from each other and had significantly higher mean phosphate levels than patients in the preimplementation period ($P < .0001$). They were also less likely to develop hypophosphatemia compared with preimplementation patients (intermediate: odds ratio [OR], 0.07; 95% confidence interval [CI], 0.03–0.18, $P < .0001$; postimplementation: OR, 0.09; 95% CI, 0.03–0.27, $P < .0001$). *Conclusions:* Modifications in phosphate dosing together with CRRT education reduced the incidence of hypophosphatemia in PN patients receiving CRRT. Communication of significant changes in clinical care should be shared with all services prior to implementation. Communication and planning between services caring for complex patients are necessary to prevent systems-based problems. (*Nutr Clin Pract*. 2017;32:245-251)

Keywords

parenteral nutrition; renal replacement therapy; phosphate; hypophosphatemia; renal replacement fluids

Background

Acute kidney injury (AKI) due to shock, sepsis, and often preexisting kidney dysfunction complicates the management of critically ill patients. AKI aggravates fluid, electrolyte, and acid-base homeostasis in these hypercatabolic patients.[1,2] Appropriate nutrition support is vital to recovery. While enteral feeding is preferable, clinical circumstances frequently necessitate nutrition delivery as parenteral nutrition (PN). Continuous renal replacement therapy (CRRT) allows delivery of appropriate PN to patients with hemodynamic instability and total fluid overload while supporting them through AKI.[3,4]

Several forms of CRRT are available for clinical use, including continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVHF or CVVH), and continuous venovenous hemodiafiltration (CVVHDF) as recently reviewed.[3] Each technique requires simultaneous administration of renal replacement fluids to account for fluid and electrolyte removal in the effluent. Concurrent administration of PN and CRRT requires cooperation and coordination of nutrition support and nephrology services to ensure fluid and electrolyte balance. Our institution employs a formal nutrition support team (NST) that oversees all PN prescriptions while our nephrology service dictates all CRRT prescriptions.

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Table 1. Example of Composition of Individually Compounded Renal Replacement Fluids Administered at Our Institution Prior to the Introduction of Premixed Renal Replacement Fluids.[a]

Bag	Sodium, mEq/L	Potassium, mEq/L	Calcium, mEq/L	Bicarbonate, mEq/L	Magnesium, mEq/L	Chloride, mEq/L	Glucose, mg/dL	Phosphate, mmol/L
A	155	5.5	0	0	0	170	0	1
B	125	0	0	125	0	0	0	0
C	78	5.5	0	0	0	82	0	1

[a]Renal replacement fluids were administered as a combination of the following 3 bags in addition to other supplements.

Table 2. Electrolyte Composition of Typical Parenteral Nutrition Prescription for Patients on Continuous Renal Replacement Therapy During the Preimplementation, Intermediate, and Postimplementation Periods.

Electrolyte	Preimplementation	Intermediate and Postimplementation
Sodium, mEq/L	130	40
Potassium, mEq/L	12	14
Calcium, mEq/L	0	6
Magnesium, mEq/L	4	4
Phosphate, mmol/L	3	30

For more than a decade prior to 2011, our pharmacy prepared custom renal replacement fluids based on the prescription of nephrology (Table 1). These fluids routinely infuse at rates ranging from 2000–3000 mL/h. Nephrology determined custom renal replacement fluid composition for each patient by measuring serum electrolytes every 4 hours for the first 24–48 hours after starting CRRT until a stable regimen was defined and every 8 hours thereafter. In particular, nephrology managed phosphate levels with replacement fluids, so the NST minimized phosphate in PN during CRRT (Table 2). Nationwide electrolyte shortages disrupted this system in 2011.[5]

Our institution introduced a commercially premixed renal replacement fluid (NxStage PureFlow dialysate solutions RFP: 401, 402, 453, 454; NxStage Medical, Lawrence, MA) in May 2011 in an effort to cope with these electrolyte shortages. However, no commercial replacement fluids contain phosphate,[1] representing a significant change from the individualized renal replacement fluids (Table 3). Unfortunately, this system-based change was not universally communicated to clinicians. An investigation into a precipitous increase in episodes of severe hypophosphatemia among PN patients demonstrated CRRT to be a common factor. Further examination revealed the source of these significant electrolyte abnormalities to be the change in renal replacement fluids. Since severe hypophosphatemia can produce significant complications in critically ill patients,[6,7] this pharmacy change mandated a response by the NST and nephrologists that included increased phosphate dosing in PN (Table 2), modification of the CRRT order set, and development and deployment of an education tool for CRRT competency for all NST members. This retrospective study describes these responses during the transition from the custom-mixed to premixed renal replacement fluids in critically ill patients requiring PN and CRRT.

Methods

Adult patients receiving simultaneous PN and CRRT between January 2, 2012, and June 21, 2013, were considered eligible for analysis. CRRT is only administered in our intensive care units (ICUs). This timeframe captures 3 specific time periods: (1) the preimplementation period represents a baseline for study following the introduction of premixed renal replacement fluids prior to consistent phosphate supplementation (January 2, 2012, to May 19, 2012), (2) the intermediate period during which 3 system-based interventions were implemented (May 20, 2012, to October 14, 2012), and (3) the postimplementation period (October 15, 2012, to June 21, 2013). This study was deemed exempt by the Minimal Risk Institutional Review Board of the University of Wisconsin–Madison, and a waiver of authorization and consent was granted (protocol 2013-1232).

During the intermediate period, 3 system-based interventions were sequentially implemented. First, in May 2012, the NST formally altered prescription practice for CRRT patients to include maximum quantities of phosphate (30 mmol/L) in PN as the standard of care.[8] This practice differed as PN traditionally provided minimal phosphate (3 mmol/L) for CRRT patients since phosphate was adjusted in the replacement fluids frequently. Second, in August 2012, a scheduled order for 15 mmol of intravenous (IV) sodium phosphate every 8 hours or 2 packets (8 mmol/packet) of oral sodium and potassium phosphate replacement 4 times per day was added as a default order for CRRT patients in the CRRT order set. A contingency order for phosphate supplementation previously existed, but there was not always a laboratory draw to supplement against. Third, by October 2012, a formal education and CRRT competency training program was developed at our institution and required of all NST members. The objectives were to (1) review CRRT methods, indications, and solutions; (2) describe macronutrient, micronutrient, fluid, and electrolyte requirements for patients on CRRT; and (3) integrate understanding of CRRT therapy and PN prescription. A written test covering these

Table 3. Composition of Premixed NxStage PureFlow Dialysate Fluids Administered at Our Institution During All Time Periods.[a]

Bag	Sodium, mEq/L	Potassium, mEq/L	Calcium, mEq/L	Bicarbonate, mEq/L	Magnesium, mEq/L	Chloride, mEq/L	Glucose, mg/dL	Phosphate, mmol/L
A	140	4	3	35	1	113	100	0
B	140	0	3	35	1	109	100	0
C	130	2	0	25	1.5	108.5	100	0
D	130	4	0	25	1.5	110.5	100	0

[a]Renal replacement fluids are administered as a combination of the 4 products in addition to other supplements.

objectives was required of all clinicians writing PN orders for CRRT patients.

Serum phosphate level and predicted probability of hypophosphatemia were determined for all patients in each time period. Serum phosphate level was measured by blood chemistry drawn per standard CRRT orders, and hypophosphatemia was defined as a serum phosphate level <2.5 mg/dL (per our institution during this particular time of national phosphate shortage). For patients with >1 value in a day, the lowest value obtained was used for that day. The group difference of hypophosphatemia and potentially influencing factors were evaluated across the 3 time periods (preimplementation, intermediate, and postimplementation). Analysis of variance (ANOVA) was used to test the group difference demographics, including patient age in years, number of ICU days, number of ICU days prior to PN initiation, and number of days of PN and CRRT. Linear mixed models were applied to test group difference in amount of dextrose, lipid, and phosphate prescribed in PN, as well as total supplemental phosphate administered. Generalized linear mixed models were adopted to test the group difference in the probability of developing hypophosphatemia determined by the minimal phosphate level. Generalized linear mixed models were applied for statistical analysis to account for the clustered data structure when multiple measurements were taken from the same patient.

In addition, a multiple-predictor mixed model was applied to test the effects of the serum phosphate level and the probability of hypophosphatemia based on phosphate administered via PN and as supplemental phosphate while parsing out the effects of potential covariates, including age, PN-administered dextrose, PN-administered lipid, and the serum phosphate measured the previous day. The application of mixed models was again to account for the clustered data structure as multiple measures were taken from the same patients. The Tukey-Kramer test was used to control for the inflation of the type I error rate associated with multiple comparisons of group difference. A P value <.05 was considered statistically significant.

Results

During our time periods, 49 adult patients received PN during CRRT administration with a cumulative total of 336 serum phosphate measurements. Sixteen patients were evaluated during the preimplementation period (81 measurements), 14 patients during the intermediate period (129 measurements), and 21 patients during the postimplementation period (126 measurements). Two patients received PN and CRRT during both the preimplementation and intermediate periods. Of note, there were no burn or palliative patients in our study.

General demographics regarding patient care team, diagnosis, complicating diagnoses, and care withdrawal/death at the time of PN and CRRT therapy are listed in Table 4. Patient-specific demographics, including patient age, ICU days, ICU days prior to NST consultation, and days of PN and CRRT treatment, are listed in Table 4. The only significant difference was in days of simultaneous PN and CRRT treatment between preimplementation and intermediate groups (P = .02), which was driven by 2 patients requiring therapy for >20 days.

PN components, including dextrose, lipid, and phosphate, were evaluated in addition to phosphate administered as either IV or oral supplements (Figures 1 and 2). The intermediate group had significantly more phosphate administered in PN than the preimplementation group (P = .004), although there were no differences between either of these groups and the postimplementation group. When summed, the total amount of phosphate received daily significantly differed between the postimplementation and the preimplementation groups (P = .037), and the overall difference between total phosphate among groups was also significant (P = .047). There were no significant differences in glucose or lipid in PN between groups for the overall test or any ad hoc pairwise comparison.

Mean phosphate levels during the intermediate and postimplementation periods remained significantly higher than those of patients in the preimplementation period (Figure 3). No significant differences in mean phosphate levels occurred between the intermediate and postimplementation periods (P = .99).

During the preimplementation period, there were 42 episodes of hypophosphatemia with 3 of those being severe episodes (serum phosphate ≤1.0 mg/dL). Nine and 12 episodes of hypophosphatemia occurred during the intermediate and postimplementation periods, respectively, with no severe episodes during either period.

Table 4. Patient Demographics.[a]

Demographics	Preimplementation	Intermediate	Postimplementation	Analysis of Variance
Age, y	55.6 ± 14.2	57.8 ± 12.2	57.8 ± 14.7	NS
ICU days	18.5 ± 9.7	24.9 ± 17.8	20.8 ± 11.4	NS
ICU days prior to NST consultation	1.8 ± 14.6	2.4 ± 10.4	6.9 ± 9.9	NS
Days of PN + CRRT	4.9 ± 3.2	9.4 ± 3.9[b]	6.2 ± 3.9	NS
Service, No.				
Medical ICU	13	10	8	
Surgical ICU	2	3	10	
Cardiothoracic ICU	1	1	3	
Admitting diagnosis, No.				
Sepsis	6	5	6	
ESLD	2	4	6	
Heart failure	0	2	3	
Respiratory failure	2	1	2	
Trauma	1	0	0	
Other	5	2	4	
Complicating diagnosis, No.				
Alcoholism	2	1	2	
Malnutrition	1	1	1	
Traumatic brain injury	0	0	0	
Burn	0	0	0	
Care withdrawn/mortality	8/16	6/14	8/21	

CRRT, continuous renal replacement therapy; ESLD, end-stage liver disease; ICU, intensive care unit; NS, not significant ($P > .05$ for overall test); NST, nutrition support team; PN, parenteral nutrition.

[a]Service refers to team caring for patient at the time of PN and CRRT. Admitting diagnosis represents primary diagnosis at the time of ICU admission. Complicating diagnoses were selected based on known influence on serum phosphate level. Care withdrawn/mortality represent death immediately following PN and CRRT therapy only. Values are presented as mean ± SD unless otherwise indicated.

[b]$P < .05$ between preimplementation and intermediate groups.

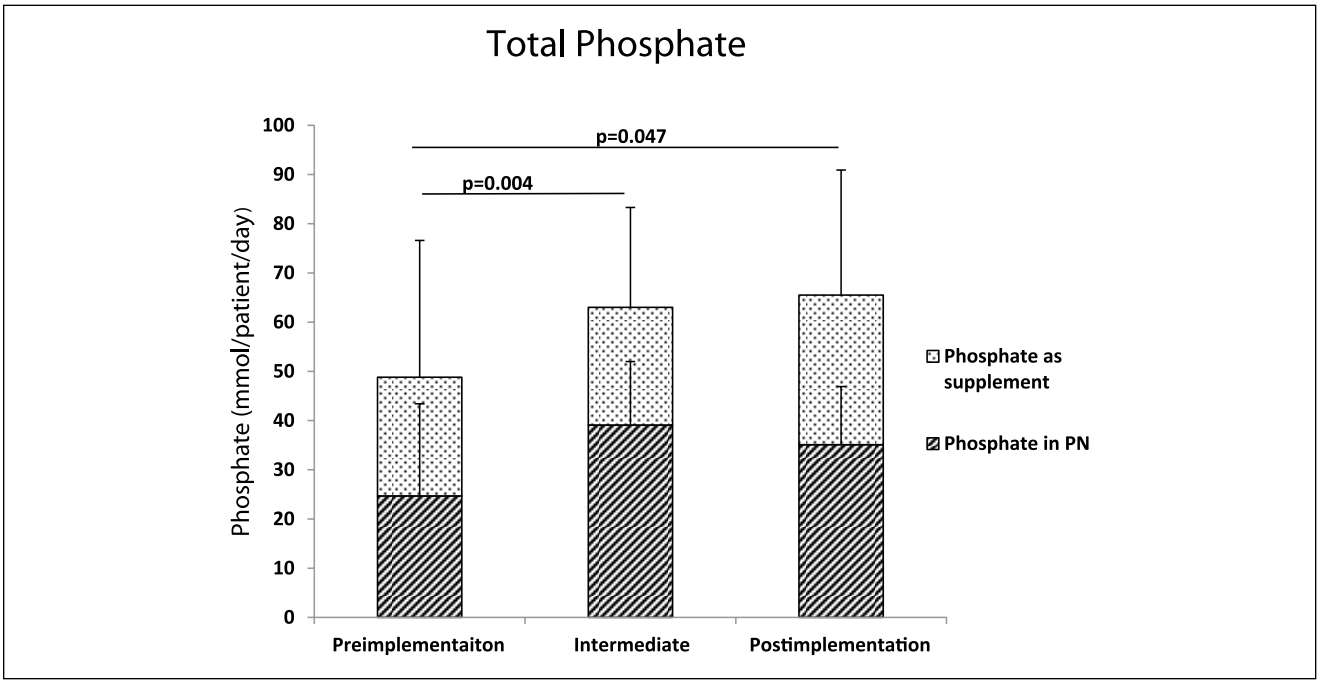

Figure 1. Quantity of phosphate administered in PN and quantity of sodium or potassium phosphate administered as a supplement per patient per day. Values are presented ± standard error of the mean. PN, parenteral nutrition.

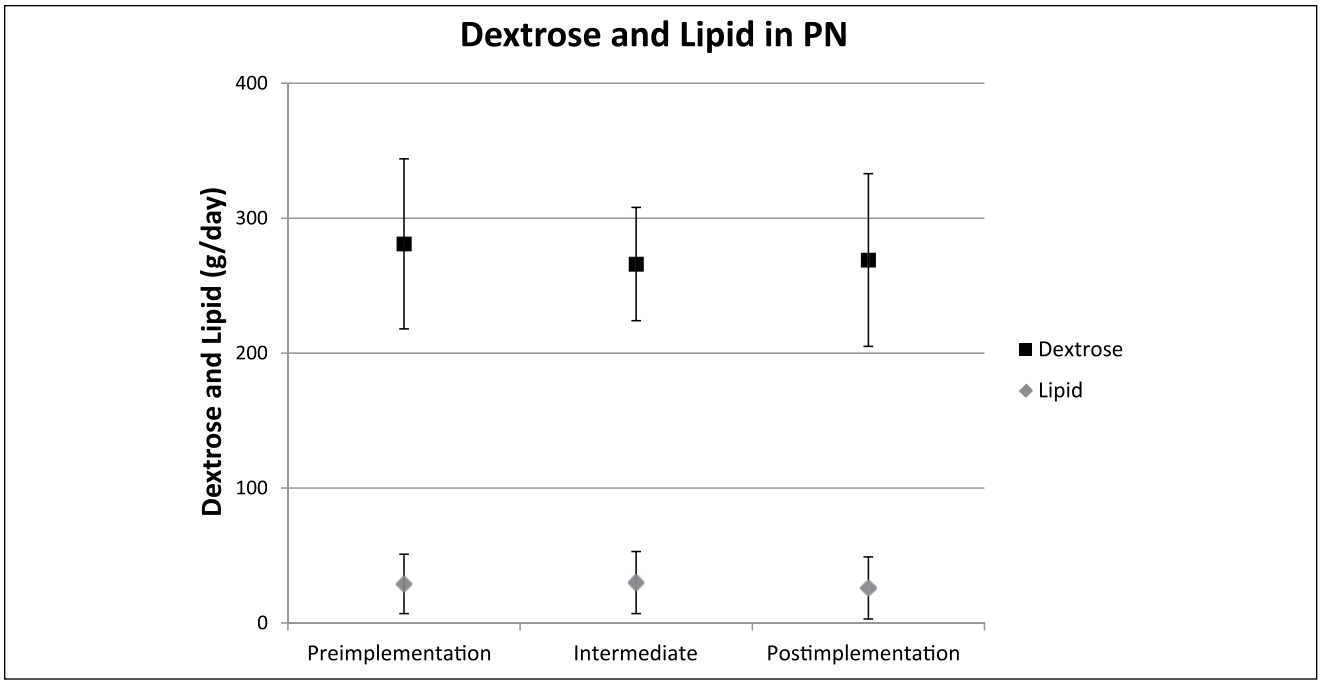

Figure 2. Quantity of dextrose and intravenous lipid administered in PN per patient per day. Values are presented ± standard error of the mean. PN, parenteral nutrition.

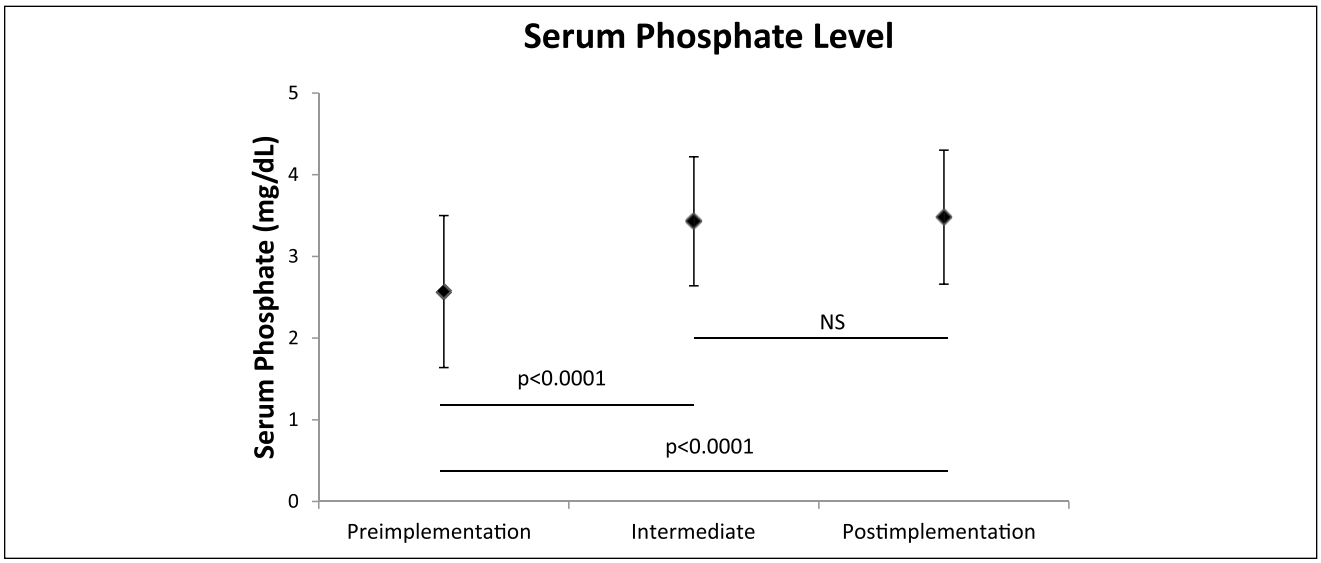

Figure 3. Daily serum phosphate level. Values are presented ± standard error of the mean. NS, not significant ($P > .05$).

Patients in the intermediate and postimplementation periods were less likely to develop hypophosphatemia than patients in the preimplementation period (odds ratio [OR], 0.07; 95% confidence interval [CI], 0.03–0.18), $P < .0001$ and OR, 0.09; 95% CI, 0.03–0.27, $P < .0001$, respectively). There was no difference in likelihood to develop hypophosphatemia between intermediate and postimplementation periods (OR, 0.76; 95% CI, 0.25–2.36, $P = .63$).

Discussion

Critically ill patients requiring PN and CRRT are complex, with fluid and electrolyte imbalances, acid-base disturbances, and hypercatabolism demanding diligence in their care.[1,9,10] A change to prescribing premixed renal replacement fluids in conjunction with insufficient communication resulted in an increased incidence of hypophosphatemia among patients

receiving both PN and CRRT. While no severe clinical complications occurred from these episodes, this experience highlights the impact of national drug shortages on patient care and the importance of communication and education on a systems level when multiple providers are caring for complex patients.

The first and most crucial step in this process was identification of the problem. Electrolytes are easily filtered during CRRT.[3] An individualized system of providing renal replacement fluids containing electrolytes sufficient to maintain homeostasis was converted to use of premixed fluids without phosphate due to drug shortages in accordance with published recommendations.[5,11,12] However, this change precipitated an increase in hypophosphatemia in this patient population, raising concern for patient safety while attempting to cope with national drug shortages.[13,14] Fortunately, the NST recognized an increase in severe electrolyte disturbances that was occurring in CRRT patients, and only then were the premixed replacement fluids identified as the precipitating factor. Unfortunately, no safeguards had been instituted to prompt system-wide education to all services affected by this change. Almost certainly, other services were affected.

In total, 3 formal changes were implemented by the NST and nephrology. First, the NST prescribed maximum quantities of phosphate in the PN of patients receiving PN and CRRT as it was the patients' consistent source of phosphate delivery. Since maximum concentration of phosphate in PN is 30 mmol/L at our institution,[8] additional scheduled supplemental phosphate was prescribed per a change in the CRRT order set. Nephrology modified the CRRT order set to include scheduled supplemental phosphate as a default order even for patients not receiving PN. The final intervention involved development and deployment of a lecture and examination-based educational competency for NST members providing PN to CRRT patients to fill knowledge gaps that were previously unrecognized.

Since not all NST members had the same understanding of CRRT, an educational program was developed and successful completion was required prior to writing PN orders independently for patients on CRRT. The components of the educational program included (1) dialysis principles for both diffusion and convection along with molecule size clearance for diffusion vs convection; (2) indications for CRRT and goals and types of CRRT; (3) dosing of CRRT to deliver optimal clearance of solute; (4) types of anticoagulation and alterations in CRRT composition with use of citrate anticoagulation; (5) machine, fluid, and blood circuits; (6) nutrition assessment in AKI with calorie, protein, and micronutrient needs with continuous dialysis; (7) the function of all solutions employed in CRRT and how they may affect serum electrolytes or serum glucose; (8) coordination with nephrology of electrolyte supplementation by PN vs boluses and scheduled doses; (9) transitioning from PN to EN; and (10) how and when to transition from CRRT to hemodialysis with subsequent PN solution modifications. An NST dietitian (C.E.K.) developed the curriculum in conjunction with nephrology and taught the didactic portion of the course. Subsequently, the trained NST members (C.E.K. and C.S.C.) mentored newly trained NST members in writing PN orders during CRRT. Once the learners demonstrated understanding, they completed a written competency examination that incorporated questions addressing PN calculations for different CRRT scenarios. After demonstrating competence in PN ordering and successfully completing the examination, NST members were approved to independently write PN orders for CRRT patients. Previously, no such educational tool was in place.

This study aims to evaluate the effect of these 3 changes in preventing hypophosphatemia in patients receiving PN and CRRT. The preimplementation period was significantly different from the intermediate and postimplementation periods such that patients in the intermediate and postimplementation periods had significantly higher average phosphate levels and were significantly less likely to develop hypophosphatemia than patients in the preimplementation period. However, results from the intermediate and postimplementation periods were not significantly different. Together, these results suggest that the implemented changes had an immediate effect on the incidence of hypophosphatemia. Again, definition and understanding of the problem were essential to its correction.

There are several limitations to our study. First, this retrospective study cannot determine whether other responses beyond these NST changes affected the incidence of hypophosphatemia among these patients. However, once the NST recognized the problem and implemented the first response to the problem, there was an immediate impact, so it seems likely that the NST changes had a direct effect. Second, there was a time period when NST members were inconsistent in altering the phosphate in PN during our preimplementation period. If anything, this practice would decrease the number of episodes of hypophosphatemia during our preimplementation period. In addition, we did not assess how our change in practice affected the incidence of hyperphosphatemia or if calcium levels were affected. Episodes of hyperphosphatemia (serum phosphate >4.5 mg/dL) were present in all groups, but the most common cause of hyperphosphatemia in this patient population was CRRT pump malfunction, which was not evaluated or correlated with the incidence of hyperphosphatemia. Finally, hypophosphatemia was not evaluated in enterally fed patients on CRRT; no conclusions about overall phosphate requirements in this population can be made from this study.

Conclusions

At our institution, a change to commercial renal replacement fluids for patients on CRRT led to an increase in hypophosphatemia. Once this change was recognized as the source of hypophosphatemia, measures implemented by the nutrition and

nephrology services almost immediately corrected this systems-based problem. These measures included maximizing phosphate in PN, adding supplemental phosphate to the standard CRRT order set, and development and deployment of a competency for administering PN to CRRT patients. This study highlights how drug shortages and resultant minor systems changes can affect multiple services and patient care. Widespread communication and education are necessary when dealing with complex patients.

Authors' Note

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Statement of Authorship

R. A. Busch, C. E. Kight, K. A. Kudsk, L. Maursetter, and C. S. Curtis contributed to the acquisition, analysis, and interpretation of the data; C. S. Curtis contributed to the conception and design of the research; and G. E. Leverson and Y. Ma contributed to the analysis and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Hypophosphatemia in Enterally Fed Patients in the Surgical Intensive Care Unit: Common but Unrelated to Timing of Initiation or Aggressiveness of Nutrition Delivery

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Abstract

Introduction: Hypophosphatemia has been associated with refeeding malnourished patients, but its clinical significance is unclear. We investigated the incidence of refeeding hypophosphatemia (RH) in the surgical intensive care unit (SICU) and its association with early enteral nutrition (EN) administration and clinical outcomes. *Methods*: We performed a retrospective review of a 2-year database of patients receiving EN in the SICU. RH was defined as a post-EN phosphorus (PHOS) level decrement of >0.5 mg/dL to a nadir <2.0 mg/dL within 8 days from EN initiation. We investigated the risk factors for RH and examined its association with clinical outcomes using multivariable regression analyses. *Results*: In total, 213 patients comprised our analytic cohort. Eighty-three of 213 (39%) individuals experienced RH and 43 of 130 (33%) of the remaining patients experienced non-RH hypophosphatemia (nadir PHOS level <2.0 mg/dL). Overall, there was a total 59% incidence of hypophosphatemia of any cause (N = 126). Nutrition parameters did not differ between groups; most patients were initiated on EN within 48 hours of SICU admission, and timing of EN initiation was not a significant predictor for the development of RH. The median hospital length of stay (LOS) was 21 and 24 days for those with and without RH, respectively ($P = .79$); RH remained a nonsignificant predictor for hospital LOS in the multivariable analysis. *Conclusions*: RH is common in the SICU but is not related to timing or amount of EN. Hypophosphatemia is also common in the critically ill, but regardless of etiology, it was not found to be a predictor of worse clinical outcomes. (*Nutr Clin Pract*. 2017;32:252-257)

Keywords

refeeding syndrome; enteral nutrition; hypophosphatemia

Phosphorus is an essential constituent of human physiology and plays an important role in intracellular messaging, mitochondrial function, pH buffering, glycolysis, and 2,3-diphosphoglycerate (2,3-DPG) synthesis. In addition, phosphorus is the source of high-energy phosphate bonds (adenosine triphosphate [ATP]) required for muscular contraction and neurologic function.[1,2] The impaired cellular energy stores and tissue hypoxia (from decreased erythrocyte 2,3-DPG) are believed to underlie the diverse clinical manifestations of hypophosphatemia,[1] including myocardial dysfunction, diaphragmatic weakness, seizures, coma, rhabdomyolysis, and red blood cell dysfunction.[2]

Hypophosphatemia occurs in 2% of hospitalized patients but in up to 30% of surgical intensive care unit (ICU) patients.[3,4] "Classic" risk factors for hypophosphatemia include alcoholism, massive blood transfusion, insulin infusion, parenteral nutrition (PN), and diuretic therapy, but the association of hypophosphatemia with the timing of enteral nutrition (EN) initiation and EN amount in the surgical intensive care unit (ICU) is unknown. It is important to explore if a relationship exists, since the onset of hypophosphatemia in a patient initiating nutrition will often raise suspicion for the refeeding syndrome. As initially described, the refeeding syndrome includes severe electrolyte derangements such as hypophosphatemia, hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia, hyperglycemia, and vitamin deficiency, as well as life-threatening clinical findings such as fluid overload, rhabdomyolysis, cardiopulmonary failure, seizures, encephalopathy, and coma.[5–7] Unfortunately, a universally

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accepted definition of refeeding syndrome with unambiguous criteria is lacking.[6] However, a systematic review of all reported cases of refeeding syndrome since 2000 demonstrated that hypophosphatemia is present in >95% of documented cases,[5,6] and this electrolyte imbalance is commonly used in clinical practice as a surrogate marker or the refeeding syndrome. Some have even referred to hypophosphatemia as the "hallmark of refeeding syndrome."[7] This may not be appropriate, though, as hypophosphatemia may be unrelated to nutrition intake or may be asymptomatic even if it is related to nutrition intake. Yet, most authors recommend discontinuing nutrition or advancing very slowly and cautiously in the setting of confirmed or suspected refeeding syndrome.[5,7,8] This may result in well-intentioned, although inappropriate, iatrogenic underfeeding.

Critically ill surgical patients are often malnourished at baseline, and most are underfed during the first few days of critical care.[9] Previous studies have demonstrated that increasing caloric and protein deficits in the ICU are associated with worse clinical outcomes.[10–12] The aims of this study were to estimate the incidence of refeeding hypophosphatemia in the surgical ICU receiving EN, characterize its association with the timing and aggressiveness of EN delivery, and determine whether nadir phosphate level during critical illness is correlated with clinical outcomes. We also sought to characterize the significance of hypophosphatemia not related to refeeding.

Materials and Methods

Patient Selection

This retrospective, case-control study was approved by our local institutional review board, and the requirement for informed consent was waived. We reviewed an existing database (spanning March 2012 to May 2014) of adult patients (aged >18 years) admitted to the surgical ICUs of the general hospital who received EN for at least 72 hours in the ICU. Exclusion criteria were as follows: patients with a previous ICU stay within the same hospitalization, had received EN prior to ICU admission, or had an absolute contraindication to EN (eg, mechanical intestinal obstruction, paralytic ileus, or high-output enterocutaneous fistula).

Data Collection and Definitions

Data collected included demographic information such as ICU admission diagnosis, age, sex, body mass index (BMI), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Deyo-Charlson Comorbidity Index (CCI).[13] Nutrition data collected included initial nutrition status, hours from ICU admission to EN initiation, kcal and grams of protein prescribed and received, and total caloric and protein deficit. Nutrition data collection was continued for 14 days after ICU admission until ICU discharge, death, or permanent progression to oral intake. Clinical outcomes included incidence of complications (infectious, cardiovascular, or gastrointestinal), ICU length of stay (LOS), hospital LOS, 28-day ventilator-free days (VFDs), and in-hospital mortality. Complications were treated as a continuous variable with each episode counted separately even when occurring in the same patient.

Clinical Management

EN was administered via nasogastric, postpyloric, or gastrostomy tube. Our surgical ICU standard practice is to routinely begin with gastric feeding and reserve postpyloric (small intestinal) feeding only for patients with repeated emesis or high (>500 mL) gastric residual volume. A registered dietitian (RD) was routinely consulted at initiation of EN. If no contraindication was present, EN was started, based on the American Society for Parenteral and Enteral Nutrition (ASPEN) Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient.[14] The nutrition status was determined by the RD at initial assessment. Patients were categorized as adequately nourished, moderately malnourished, or severely malnourished based on percentage of body weight lost, dietary habits preceding ICU admission, and physical examination. Because of the difficulty in obtaining an accurate dietary history in the majority of critically ill patients and the inability to obtain accurate anthropometric measurements (secondary to edema), not all patients were able to be assessed by standard malnutrition criteria. Ultimately, the designation was decided upon by the licensed RD according to clinical discretion. Adequately nourished patients had experienced neither weight loss nor inadequate intake prior to ICU admission. Moderate malnutrition was classified as weight loss prior to admission according to the following parameters: 1%–2% over the preceding 1 week, >5% over the preceding 1 month, >7.5% over the preceding 3 months, >10% over the preceding 6 months, or >20% over the preceding 1 year. Severe malnutrition was classified as weight loss equivalent to moderate malnutrition criteria combined with overt signs of muscle wasting (eg, hollowing, scooping, or depression of the temple region; visible or protruding bone in the clavicle region; square-appearing shoulder to arm joint; prominent bones; and depressed area between thumb and forefinger).

Serum phosphorus levels were measured at ICU admission and daily serum phosphorus levels were obtained as per standard ICU practice and more frequently as clinically indicated. The following replacement protocol was used: for phosphorus levels between 2.2 and 3.2 mg/dL, a total dose of 30 mmol sodium phosphate was administered intravenously over a 4-hour period. For phosphorus levels of 1.5–2.1 mg/dL, a repletion intravenous (IV) dose of 45 mmol over 6 hours was prescribed. If phosphorus levels were measured below 1.5 mg/dL, 60 mmol of IV sodium phosphate was administered over 8 hours.[15]

Nadir phosphate serum level during ICU admission was collected and the number of days from EN initiation to nadir phosphate was calculated (the day of EN initiation was considered

Table 1. Patient Demographics.

Characteristics	All (N = 213)	No Refeeding Hypophosphatemia (n = 130)	Refeeding Hypophosphatemia (n = 83)	*P* Value
Age, median (IQR), y	63 (51–76)	64 (51–77)	62 (51–73)	.77
Male sex, No. (%)	152 (71)	98 (75)	54 (65)	.10
BMI, median (IQR), kg/m^2	26.5 (22.8–30.1)	27.0 (23.0–31.0)	25.4 (22.5–28.4)	.021
Age-adjusted CCI, median (IQR)	2 (0–4)	2 (0–4)	2 (0–4)	.94
APACHE II, median (IQR)	14 (10–20)	14 (10–19)	14 (12–22)	.096
Reason for admission, No. (%)				.72
Elective surgery	59 (28)	38 (29)	21 (25)	
Emergency surgery	36 (17)	21 (16)	15 (18)	
Medical	54 (25)	30 (23)	24 (29)	
Trauma	64 (30)	41 (31.5)	23 (28)	
Nadir serum phosphate level, median (IQR), mg/dL	1.8 (1.4–2.0)	2.1 (1.9–2.4)	1.6 (1.4–2.2)	<.001

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCI, Deyo-Charlson Comorbidity Index; IQR, interquartile range.

day 0). Patients experiencing a post-EN initiation nadir phosphate within 8 days after EN initiation were identified, and the difference between pre-EN phosphate and post-EN nadir phosphate was calculated. Refeeding hypophosphatemia was defined as a decrement of >0.5 mg/dL to a nadir <2.0 mg/dL within 8 days of EN initiation.[16,17] Non–refeeding hypophosphatemia was defined as an absolute nadir serum phosphorus level <2.0 mg/dL occurring prior to EN initiation or >8 days after EN initiation. Patients were divided into 2 groups according to whether they experienced refeeding hypophosphatemia. Caloric and protein deficits were defined as the difference between prescribed and received calories and proteins.

Outcomes

Our primary outcome was the incidence of refeeding hypophosphatemia in critically ill patients receiving EN in the surgical ICU. Secondary outcomes were the association of refeeding hypophosphatemia with timing of EN initiation and initial nutrition status, the association of refeeding hypophosphatemia with clinical outcomes, and clinical outcomes in all patients who experienced hypophosphatemia.

Statistical Analysis

Since most of the continuous variables were not normally distributed, they were summarized using medians with interquartiles and compared using Wilcoxon rank sum tests. Categorical variables were summarized using frequency with percentage and compared using χ^2 tests. A multivariable logistic regression model was used to identify risk factors for refeeding hypophosphatemia. To determine the association between refeeding hypophosphatemia or hypophosphatemia (serum phosphorus level <2.0 mg/dL regardless of the etiology) and hospital LOS, quantile regression analysis was used to account for the non-normally distributed outcome variable while controlling for potential confounding factors such as sex, BMI, and APACHE II. Data analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC), and a 2-sided $P < .05$ was considered statistically significant.

Results

A total of 213 patients were included. Most of the patients were male (71%) and the median age was 63 years. Eighty-three (39%) patients experienced refeeding hypophosphatemia. The incidence of refeeding hypophosphatemia was not significantly affected by the repletion protocol changes secondary to the temporary shortage of sodium phosphate; refeeding hypophosphatemia incidence was 40% (61/152) in the early period (2012–2013) when a more aggressive protocol was being implemented and 36% (22/61) during the last year of the study when a less aggressive protocol was used ($P = .58$). When comparing the refeeding hypophosphatemia and no–refeeding hypophosphatemia groups, age, sex, reason for admission, APACHE II scores, and age-adjusted CCI were not significantly different. Group demographics are summarized in Table 1 with statistical comparisons between refeeding hypophosphatemia and no–refeeding hypophosphatemia groups. Overall, the refeeding hypophosphatemia group had a lower median BMI (25.4 vs 27 kg/m^2, $P = .010$), and the nadir serum phosphate level was significantly lower (1.5 vs 2.1 mg/dL, $P < .001$). Nutrition parameters are summarized in Table 2. Caloric and protein prescription and delivery did not differ between groups, and initial nutrition status was similar. Most patients were initiated on EN within 48 hours of surgical ICU admission. A multivariable logistic regression analysis was performed, including age, sex, BMI, APACHE II score, and timing of EN initiation, and only BMI was identified as an independent predictor for the development of refeeding hypophosphatemia after the initiation of EN (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.90–0.99). Clinical outcomes

Table 2. Nutrition Characteristics.

Nutrition Parameters	All (N = 213)	No Refeeding Hypophosphatemia (n = 130)	Refeeding Hypophosphatemia (n = 83)	*P* Value
Initial nutrition status, No. (%)				.64
Nourished	178 (84)	110 (85)	68 (82)	
Moderately malnourished	19 (9)	10 (8)	9 (11)	
Severely malnourished	8 (4)	6 (5)	2 (2)	
Unknown	8 (4)	4 (3)	4 (5)	
EN initiation <48 hours	144 (68)	85 (65)	59 (71)	.39
Hours until EN initiation, median (IQR)	35 (17–56)	33 (16–61)	36 (18–49)	.73
Calories prescribed, median (IQR), kcal/kg/d	24.1 (21.5–26.6)	23.6 (21.0–26.5)	24.7 (22.2–26.9)	.18
Grams of protein prescribed, median (IQR), g/kg/d	1.3 (1.1–1.5)	1.2 (1.1–1.5)	1.3 (1.1–1.5)	.26
Calories received, median (IQR), kcal/kg/d	17.8 (14.2–21.4)	17.4 (13.8–21.5)	17.9 (14.8–21.1)	.5
Grams of protein received, median (IQR), g/kg/d	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.0 (0.8–1.2)	.8
Total caloric deficit, median (IQR), kcal	3220 (1675–5962.5)	3190 (1476–6063.2)	3750 (1915–5960)	.61
Total protein deficit, median (IQR), g	153.8 (41.9–322)	137.3 (29.3–322)	190.7 (52.8–325.5)	.47

EN, enteral nutrition; IQR, interquartile range.

Table 3. Clinical Outcomes.

Outcomes	All (N = 213)	No Refeeding Hypophosphatemia (n = 130)	Refeeding Hypophosphatemia (n = 83)	*P* Value
ICU LOS, median (IQR), d	12 (7–21)	12 (7–22)	12 (8–20)	1.0
Hospital LOS, median (IQR), d	22 (15–35)	24 (14–36)	21 (15–35)	.79
28-day VFD, median (IQR)	20 (14–24)	20 (13–24)	20 (16–25)	.43
Total complications, median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	.89
Cardiovascular complications, No. (%)	62 (29)	41 (31.5)	21 (25)	.41
In-hospital mortality, No. (%)	39 (18)	26 (20)	13 (16)	.42

ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; VFD, ventilation-free day.

are summarized in Table 3. There were no significant differences between the 2 groups (refeeding hypophosphatemia and no refeeding hypophosphatemia) in any of the clinical outcomes examined.

Hypophosphatemia unrelated to EN occurred in an additional 43 patients (20% of the entire cohort). Thus, there was a 59% incidence of hypophosphatemia of *any* cause (n = 126/213) in the entire cohort. There were only 9 patients in the entire cohort who experienced severe hypophosphatemia (serum phosphorus level <1.0 mg/dL): 6 in the refeeding hypophosphatemia group and 3 in the non-EN-associated hypophosphatemia group. All 6 patients in the refeeding hypophosphatemia group experienced their nadir phosphorus level within the first 2 days of EN initiation and the 3 patients in the non-EN-associated hypophosphatemia group experienced phosphorus <1.0 mg/dL 1 day prior to the initiation of EN. When controlling for age, sex, BMI, APACHE II, surgical ICU-related complications, and timing of EN initiation, we found that hypophosphatemia during ICU admission, regardless of the etiology, was not associated with an increased risk of prolonged hospital LOS.

Discussion

In this study, we report that the incidence of refeeding hypophosphatemia in critically ill surgical patients receiving EN is high (39%) but within the range previously reported by others.[16,18] In addition, hypophosphatemia unrelated to EN was also prevalent (20%), and thus more than half of all patients receiving EN in the surgical ICU developed hypophosphatemia at some point. Contrary to conventional teaching, we did not find an association between refeeding hypophosphatemia and admission nutrition status, timing of EN initiation, or aggressiveness of caloric/protein delivery. Furthermore, when controlling for age, sex, BMI, APACHE II, surgical ICU-related complications, and timing of EN initiation, developing refeeding hypophosphatemia did not seem to increase mechanical ventilation days or hospital

length of stay. Thus, while there might be a theoretical link between refeeding hypophosphatemia and diaphragmatic dysfunction, we were unable to detect differences in clinical outcomes between groups. Similarly, in a large retrospective study of over 10,000 phosphate measurements in critically ill patients, Suzuki et al[19] reported that hypophosphatemia is not an independent predictor of ICU or in-hospital mortality. Rather, those authors concluded that hypophosphatemia should be considered a general marker of illness severity.

Marik et al[17] performed a prospective observational study of 62 medical and surgical ICU patients who were refed after at least 48 hours of starvation. Similar to our findings, they reported a 34% incidence of refeeding hypophosphatemia, and there was no difference in energy (J/d) received when comparing the refeeding hypophosphatemia vs the non–refeeding hypophosphatemia group. However, they reported that those patients who did develop refeeding hypophosphatemia had a significantly longer duration of mechanical ventilation and hospital stay. Another series of exclusively surgical ICU patients reported a 28.8% incidence of hypophosphatemia[3] and reported a much higher mortality rate in those who developed hypophosphatemia compared with those that did not (30% vs 15.2%, $P < .05$). In that French study, serum phosphorus values were checked only at admission and twice a week. In contrast, it is the standard of care in our ICU to measure serum phosphorus daily or more frequently in severely critically ill patients. It is possible that vigilant monitoring for and treatment of hypophosphatemia in our ICU, as well as overall improvements in critical care over the past 20 years, have mitigated the adverse effects, and therefore we did not find any differences in any of the clinically meaningful outcomes examined.

We consider our results to be of interest and relevance. Nonetheless, we acknowledge the limitations, which are worth discussing. This was a single-center study performed at an urban, academic hospital, and our cohort mainly comprised general surgery and trauma patients. Thus, our outcomes may not necessarily be generalized to a more diverse population. Furthermore, this was a retrospective study, and we can only demonstrate correlation but not causality. We have attempted to mitigate bias by controlling for age, sex, BMI, APACHE II, surgical ICU-related complications, and timing of EN initiation. However, our results must be interpreted with caution, as there may be unadjusted confounders. Given the relatively small sample size, we might have been underpowered to detect significant differences. The relatively low APACHE II score, while typical for a surgical ICU, limits our ability to draw conclusions about more critically ill patients. Only 15% of our patients were malnourished at ICU admission, and the number of malnourished patients with hypophosphatemia (both refeeding and non-EN-associated) is too small to draw meaningful conclusions. Additional study in malnourished patients with hypophosphatemia being treated with appropriate calorie/protein prescription and modern phosphate repletion strategies is required. Despite these limitations, we feel that our results contribute to the existing literature by confirming the high incidence of hypophosphatemia in the surgical ICU and demonstrating an absence of association between EN initiation and adequacy with refeeding hypophosphatemia. As such, we believe that with appropriate caloric targets (~25 kcal/kg/d) and close electrolyte monitoring with aggressive phosphorus repletion, clinicians may overcome their reluctance to provide early and adequate EN to critically ill patients. Well-intentioned precautionary recommendations of slow caloric advancement in patients with suspected refeeding syndrome diagnosed by hypophosphatemia may be detrimental to the critically ill patient due to the resultant energy deficits.

Conclusions

In conclusion, hypophosphatemia occurs frequently in enterally fed surgical ICU patients. However, we found no correlation of refeeding hypophosphatemia with timing of EN initiation or aggressiveness of EN (caloric) delivery. Further research is needed to determine whether aggressively optimizing serum phosphorus levels with aggressive repletion during surgical ICU admission improves clinical outcomes.

Statement of Authorship

E. Fuentes, D. D. Yeh, S. A. Quraishi, H. Kaafarani, and G. Velmahos contributed to the conception and design of the research; D. D. Yeh, S. A. Quraishi, E. A. Johnson, and Y. Chang contributed to the acquisition and analysis of the data; H. Kaafarani, J. Lee, D. R. King, M. DeMoya, P. Fagenholz, and K. Butler contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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High Prevalence of Suboptimal Vitamin D Status and Bone Loss in Adult Short Bowel Syndrome Even After Weaning Off Parenteral Nutrition

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Abstract

Background: Previous studies have noticed the high incidence of suboptimal vitamin D (VtD) status and bone loss in short bowel syndrome (SBS) with parenteral nutrition (PN) dependence. However, limited data have focused on adult SBS without PN dependence. Therefore, our objective was to investigate the incidence and risk factors of suboptimal VtD status and bone loss in adult SBS even after weaning off PN. *Materials and Methods:* We performed a prospective study of 60 adult patients with SBS. Serum 25-hydroxyvitamin D (25-OHD) was measured by radioimmunoassay. Bone mineral density (BMD) was measured using dual-energy x-ray absorptiometry (DEXA). Medical records and various laboratory parameters were collected in all participants. *Results:* Suboptimal VtD status was identified in all individuals, including 3 (5.0%) with VtD insufficiency and 57 (95.0%) with VtD deficiency. Residual small bowel length (B, 0.072, P = .001) and duration of SBS (B, –0.066, P = .020) were both significantly correlated with suboptimal VtD levels. Overall, only 2 patients presented a normal BMD; osteopenia and osteoporosis were noted in 41 (68.3%) and 17 (28.3%) individuals, respectively. Low 25-OHD concentration was associated with a decreased BMD (B, 0.065, P = .029). There were no other demographic characteristics or clinical examinations associated with suboptimal VtD levels and bone loss. *Conclusion:* Suboptimal VtD status and bone loss were common in adult SBS even after weaning off PN. Despite routine oral VtD supplementation, most patients did not achieve satisfactory status. This emphasizes the critical importance of routine surveillance of 25-OHD and BMD, as well as consideration of alternative methods of supplementation after weaning off PN. (*Nutr Clin Pract*. 2017;32:258-265)

Keywords

vitamin D deficiency; metabolic bone diseases; osteoporosis; parenteral nutrition; short bowel syndrome; vitamin D

Short bowel syndrome (SBS), which is characterized as a state of malabsorption, intractable diarrhea, and weight loss, is a highly disabling condition that typically arises after extensive intestinal resection.[1] Many individuals with SBS develop intestinal failure (IF), which ensues when the remaining functioning intestinal mass is insufficient to digest and absorb adequate amounts of nutrients, and the nutrition needs of the individual cannot be maintained without dietary and pharmacologic support.[2] Previous studies have shown that patients with SBS are at significantly increased risk of developing vitamin D (VtD) deficiency and metabolic bone disease because they may lack adequate ultraviolet B (UVB) exposure due to chronic illness, have poor intestinal absorption that affects VtD metabolism, and because standard PN only provides 400 IU of VtD in the multivitamin preparation.[3,4] To meet daily nutrient requirements, parenteral nutrition (PN) is currently recommended as the primary therapeutic strategy for SBS when enteral nutrition (EN) becomes insufficient.[5] Although PN has revolutionized SBS treatment, it reduces quality of life and carries significant risks, mainly hepatic failure, risk of infection, and metabolic bone disease.[6] Furthermore, VtD deficiency results in an elevation of parathyroid hormone (PTH), which in turn results in significant bone reabsorption over time.[7]

Ultimately, VtD sufficiency is necessary for homeostasis of calcium and phosphate, as well as bone health.[8,9] Recent evidence suggested that VtD exerts autocrine and/or paracrine activities, which have been best characterized in infections and all-cause mortality.[10] In addition, data from Hadjittofi et al[11] showed that VtD is strongly associated with intestinal

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growth and postresection intestinal adaptation, where VtD regulates cell differentiation and maturation. Several studies have established the high incidence of VtD deficiency and low bone mineral density (BMD) in patients with SBS who have PN dependence.[12,13] However, limited data have shown VtD status and BMD in adult SBS after weaning off PN or even after transitioning to 100% oral feeding. Therefore, the present study is dedicated to investigate the status of VtD and BMD in adult SBS after weaning off PN and identify the risk factors associated with suboptimal VtD levels and bone loss.

Materials and Methods

Ethical Consideration

This study was designed according to the ethical principles outlined by the Declaration of Helsinki and approved by the local ethics committee of Jinling Hospital. All the participants provided written informed consent.

Participants

From January 2014 to June 2015, a total of 112 patients diagnosed with SBS had been admitted into our center and followed up. Based on inclusion and exclusion criteria, 60 adult patients with SBS were prospectively followed. Inclusion criteria for patients with SBS were age between 20 and 65 years who had weaned off PN. The exclusion criteria primarily consisted of the following aspects: (1) PN dependence, (2) primary hyperparathyroidism, and (3) age ≤20 years or ≥65 years. The diagnosis of SBS was defined by a small bowel remnant 150 cm or less without an ileocecal valve or a small bowel remnant 100 cm or less with an ileocecal valve. Patients with PN dependence, significant renal disease (<50% function for age as measured by creatinine), congenital bony abnormalities (eg, Paget disease, renal osteodystrophy, and primary hyperparathyroidism), receipt of an intestinal transplant, and malignancy that could confound effect or measurement were excluded. Following our center's clinical practice, treatment with oral VtD (cholecalciferol [D3]; Double Whale Pharmaceutical, Qingdao, China) at a dose of 1200 IU daily if their serum 25-hydroxyvitamin D (25-OHD) levels were <30 ng/mL was started and followed up for at least 2 months.

Data Collection

All patients underwent collection of medical history, physical examination, anthropometric measurement, and biochemical screening. The body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. The nutrition risk score was evaluated by the Nutrition Risk Screening 2002 (NRS 2002), which was determined by 2 components: nutrition status and severity of disease. Any patient with a total score ≥3 is considered at nutrition risk.[14] Small bowel length was defined per the operative note from the surgical procedure at which the diagnosis of SBS was made. Remaining small bowel was routinely subdivided into ileum and jejunum length. Data, including age, sex, etiology of SBS, presence of the ileocecal valve, colon in continuity, duration of PN use, and medications (including enteral VtD supplementation), were also collected.

Fasting blood samples were obtained in the morning following admission. Blood was rapidly centrifuged and serum was frozen at −20°C. The samples from all individuals for each parameter were analyzed in a single batch. Serum concentration of 25-OHD was measured via radioimmunoassay using a direct competitive chemiluminescence immunoassay (DiaSorin Liaison, Stillwater, MN), and intra-assay and inter-assay coefficients of variation were below 4% and 9%, respectively. Serum 25-OHD <10 ng/mL was considered as VtD severe deficiency, between 10 and 19 ng/mL as VtD moderate deficiency, between 20 and 29 ng/mL as VtD insufficiency, between 30 and 70 ng/mL as normal, and >100 ng/mL as VtD toxicity. Customarily, patients underwent measurement of serum 25-OHD measurements every 2–4 weeks. Serum levels of calcium and phosphate were measured and analyzed by routine hospital laboratory methods. Intact PTH was measured by an immunoradiometric assay (Diasorin Liaison). BMD was measured via dual-energy x-ray absorptiometry (DEXA), using a Hologic Discovery A scanner, and results were analyzed with auto low-density software version 12.6.1 (Hologic, Bedford, MA). Concurrent DEXA BMD and T score were defined as measures done within 1 week of serum 25-OHD measurements. BMD measurements were expressed as T score, derived from comparisons to age- and sex-matched, equipment- and protocol-specific reference values. Osteoporosis was defined as a T score of lumber spine or femoral neck of −2.5 or less based on the criteria proposed by the International Society for Clinical Densitometry, and osteopenia was defined as a bone density T score between −1.0 and −2.5. BMD T score ≥–1.0 was considered normal.[15]

Statistical Analysis

Continuous variables were presented as mean ± SEM, and descriptive statistics were calculated as frequencies. Standard statistical analyses were performed, including Student *t* test, Fisher exact test, and logistic regression. The statistical analysis was performed using the SPSS statistical software (version 20; SPSS, Inc, an IBM Company, Chicago, IL). Statistical significance was accepted at the $P < .05$ level.

Results

Demographics and Clinical Variables

A total of 60 (of 112) adult patients with SBS (42 men and 18 women) were enrolled in this study, with a mean of 3 (range, 1–6) serum 25-OHD levels and 1.4 (range, 1–3) BMD checked

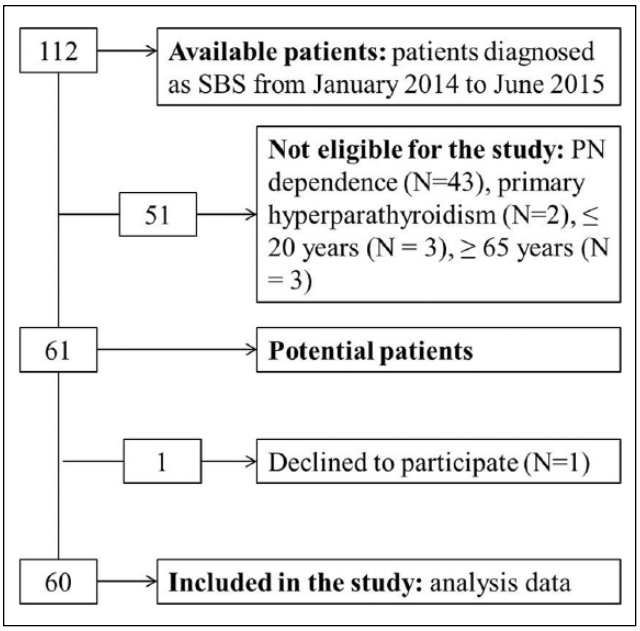

Figure 1. Flowchart: Screening of patients for data analysis. PN, parenteral nutrition; SBS, short bowel syndrome.

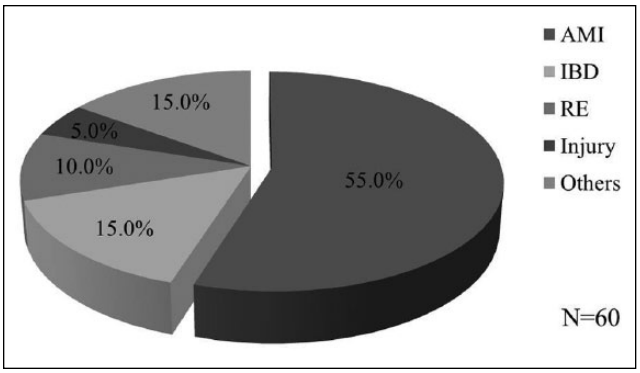

Figure 2. Etiologies of short bowel syndrome. AMI, acute mesenteric ischemia; IBD, inflammatory bowel disease; RE, radiation enteritis.

per patient during the 1.5-year study period. See Figure 1 (flowchart) for detailed descriptions of excluded patients (n = 52). Mean age (interquartile range [IQR]) of the cohort was 46.3 (20–64) years, and 70.0% were male. The most common etiology of SBS was acute mesenteric ischemia (AMI) (55.0%, 33/60), followed by inflammatory bowel disease (IBD) (15.0%, 9/60), radiation enteritis (RE) (10.0%, 6/60), injury (5.0%, 3/60), and others (15.0%, 9/60). See Figure 2 for detailed descriptions of the etiologies of SBS. Residual small bowel length in this cohort was 89.6 ± 35.6 cm, with 56.7% (34/60) of patients lacking an ileocecal valve and 38.3% (23/60) having a history of cholestasis. Mean follow-up was 10.0 ± 5.4 months (range, 4–16 months). Prior to study enrollment, duration of PN dependence in this cohort was 14.1 ± 8.4

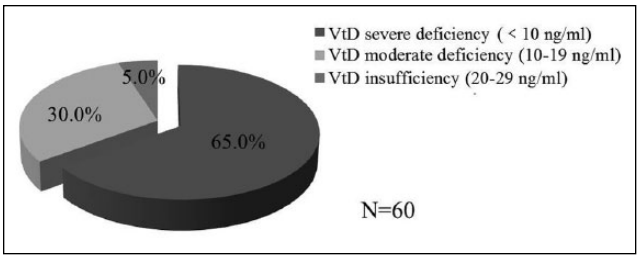

Figure 3. Serum 25-hydroxyvitamin D levels of short bowel syndrome. VtD, vitamin D.

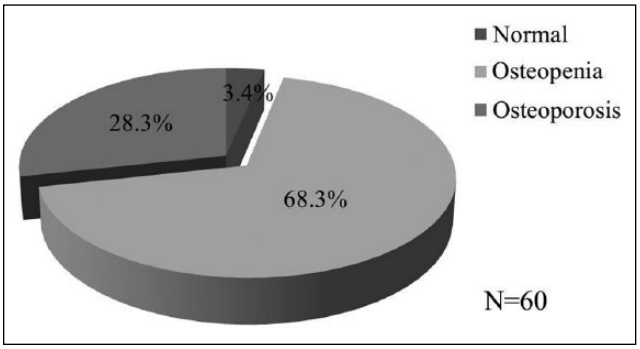

Figure 4. The bone condition of short bowel syndrome.

months, and all patients had weaned off PN by the time of the study's outset. Overall, 20% (12/60) were receiving EN, and 80% (48/60) were on diets according to food instruction made by us, which was based on the literature by Thompson et al.[1] Serum levels of calcium (9.23 ± 0.58 mg/dL), phosphorus (4.28 ± 0.39 mg/dL), magnesium (1.97 ± 0.18 mg/dL), and PTH (38.01 ± 7.75 pg/mL) were within the normal range.

Frequency of Suboptimal VtD Status and Bone Loss

While no one had secondary hyperparathyroidism, suboptimal VtD levels were identified in all individuals, including 5.0% (3/60) with VtD insufficiency and 95.0% (57/60) with VtD deficiency. Overall, 65% (39/60) of the patients were severely deficient, with serum 25-OHD levels <10 ng/mL; 30% (18/60) were moderately deficient; and no one had optimal VtD status (≥30 ng/mL) (Figure 3).

Mean lumbar spine BMD T score was −2.07 ± 1.07. In total, 96.6% (58/60) of patients satisfied criteria for bone loss with a BMD T score <–1.0. Only 2 patients presented a normal BMD; osteopenia was noted in 68.3% (41/60) of patients and osteoporosis in 28.3% (17/60) of the entire cohort based on review of radiographic images (Figure 4). Seven patients had a history of bone pain, of whom 4 reported lower extremity pain, 2 had upper extremity pain, and 1 had back pain. No patient was diagnosed with skeletal fractures during the study period.

Table 1. Clinical Characteristics of Patients With Short Bowel Syndrome and Suboptimal VtD Levels.

Characteristic	Adults With VtD Deficiency (n = 57)	Adults With VtD Insufficiency (n = 3)	*P* Value
Age, mean ± SD, y	46.5 ± 13.6	42.7 ± 6.5	.32
Male sex, No. (%)	40 (70.2)	2 (66.7)	.90
BMI, mean ± SD, kg/m^2	18.7 ± 4.0	20.8 ± 0.7	.19
NRS 2002, No. (%)			.13
NRS 2002 ≥3	42 (73.7)	1 (33.3)	
NRS 2002 <3	15 (26.3)	2 (66.7)	
Etiology of SBS, No. (%)			.15
AMI	32 (56.1)	1 (33.3)	
IBD	9 (15.8)	0 (0.0)	
RE	6 (10.5)	0 (0.0)	
Injury	2 (3.5)	1 (33.3)	
Others	8 (14.0)	1 (33.3)	
Residual small bowel length, mean ± SD, cm	87.5 ± 35.3	128.3 ± 7.6	.03[a]
Jejunum	81.5 ± 41.5	106.7 ± 11.5	.15
Ileum	6.1 ± 11.3	21.7 ± 7.6	.01[a]
Ileocecal valve presence, No. (%)	24 (42.1)	2 (66.7)	.40
Colon in continuity, No. (%)	45 (78.9)	2 (66.7)	.62
Delay since last surgery, mean ± SD, mo	35.8 ± 25.2	4.3 ± 1.5	.02[a]
Serum parameters, mean ± SD			
25-OHD, ng/mL	8.24 ± 4.09	21.54 ± 0.96	.00[a]
PTH, pg/mL	37.84 ± 7.73	41.20 ± 9.17	.23
Calcium, mg/dL	9.24 ± 0.58	9.06 ± 0.52	.30
Phosphate, mg/dL	4.28 ± 0.39	4.36 ± 0.22	.36
Magnesium, mg/dL	1.98 ± 0.18	1.85 ± 0.06	.11

25-OHD, 25-hydroxyvitamin D; AMI, acute mesenteric ischemia; BMI, body mass index; IBD, inflammatory bowel disease; NRS 2002, Nutrition Risk Screening 2002; PTH, parathyroid hormone; RE, radiation enteritis; SBS, short bowel syndrome; VtD, vitamin D.
[a]Statistically significant ($P < .05$).

Risk Factors Associated With Suboptimal VtD Levels

The clinical characteristics of patients with insufficient and deficient 25-OHD levels are shown in Table 1. Age, sex distribution, BMI, NRS 2002, etiology of SBS, presence of an ileocecal valve, and serum concentrations of PTH, calcium, phosphate, and magnesium were similar between VtD-insufficient and VtD-deficient patients ($P > .05$). In contrast, residual small bowel length (128.3 ± 7.6 cm vs 87.5 ± 35.3 cm, $P = .03$) and residual ileum length (21.7 ± 7.6 cm vs 6.1 ± 11.3 cm, $P = .01$) were significantly longer in the VtD-insufficient group compared with those in VtD-deficient group. Meanwhile, duration of SBS (4.3 ± 1.5 months vs 35.8 ± 25.2 months, $P = .02$) was statistically shorter in VtD-insufficient patients. Notably, residual jejunum length (106.7 ± 11.5 cm vs 81.5 ± 41.5 cm, $P = .15$) showed no significant difference between these 2 groups.

We further investigated the correlation between the existence of suboptimal VtD levels and the various clinical variables, including age, sex, BMI, NRS 2002, etiology of SBS, residual small bowel length, residual jejunum length, residual ileum length, presence of the ileocecal valve, colon in continuity, and duration of SBS. According to the result of linear logistic regression analysis, residual small bowel length (B, 0.072; $P = .001$; 95% confidence interval [CI], 0.034–0.110) and duration of SBS (B, –0.066; $P = .020$; 95% CI, –0.121 to 0.011) emerged as potential risk factors (Figure 5A and B). Other variables were found unrelated to the presence of suboptimal VtD status in SBS.

Risk Factors Associated With Bone Loss

Table 2 shows the clinical characteristics of patients with low (osteoporosis or osteopenia) and normal BMD. There was a significant difference in risk of bone loss based on serum 25-OHD concentrations; patients with low 25-OHD concentrations were more likely to have bone loss (8.68 ± 4.87 vs 15.32 ± 2.74, $P = .03$). Otherwise, there were no significant differences in age, sex, BMI, NRS 2002, etiology of SBS, residual small bowel length, presence of an ileocecal valve, duration of SBS, and baseline laboratory values.

On linear logistic regression analysis, age, sex, BMI, NRS 2002, etiology of SBS, residual small bowel length, presence of the ileocecal valve, colon in continuity, duration of SBS, and serum concentrations of 25-OHD, calcium, and phosphate were screened for correlation with osteopenia or osteoporosis. The only statistically significant variable associated with bone

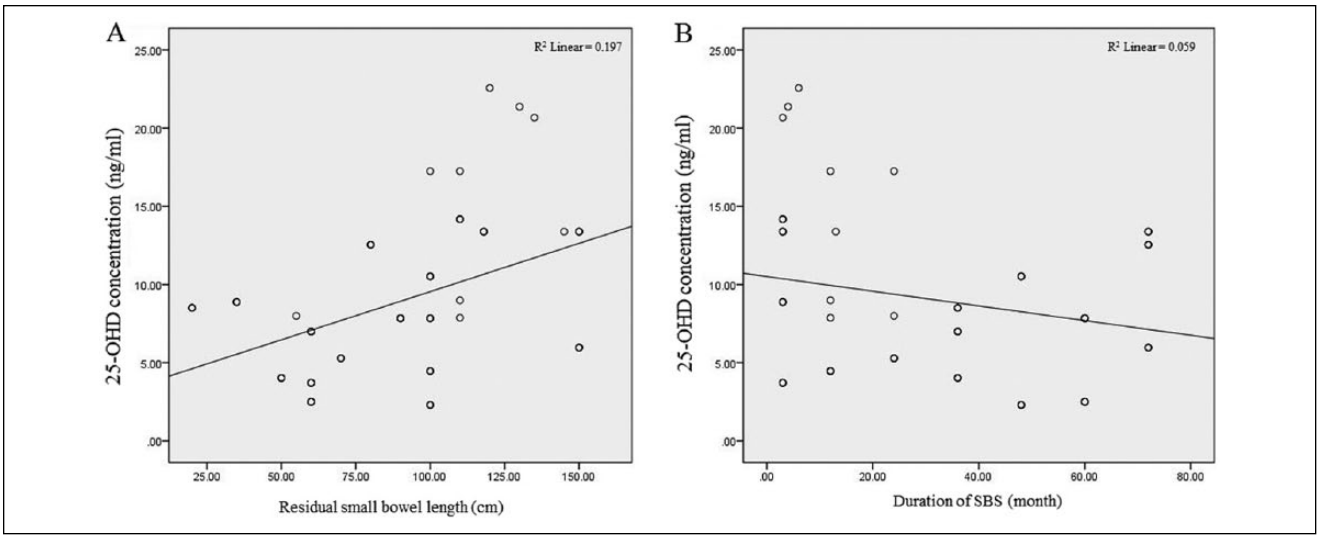

Figure 5. Correlation between (A) residual small bowel length and (B) duration of SBS with serum 25-OHD concentration. 25-OHD, 25-hydroxyvitamin D; SBS, short bowel syndrome.

Table 2. Clinical Characteristics of Patients With Short Bowel Syndrome and Low vs Normal BMD.

Characteristic	Adults With Low BMD (n = 58)	Adults With Normal BMD (n = 2)	*P* Value
Age, mean ± SD, y	46.5 ± 13.5	40.0 ± 2.8	.25
Male sex, No. (%)	40 (69.0)	2 (100.0)	.35
BMI, mean ± SD, kg/m^2	18.8 ± 4.0	20.9 ± 0.5	.23
NRS 2002, No. (%)			.49
NRS 2002 ≥3	42 (72.4)	1 (50.0)	
NRS 2002 <3	16 (27.6)	1 (50.0)	
Etiology of SBS, No. (%)			.06
AMI	32 (55.2)	1 (50.0)	
IBD	9 (15.5)	0 (0.0)	
RE	6 (10.5)	0 (0.0)	
Injury	2 (3.3)	1 (50.0)	
Others	9 (15.5)	0 (0.0)	
Residual small bowel length, mean ± SD, cm	88.4 ± 35.4	122.5 ± 31.8	.09
Jejunum	82.0 ± 41.3	105.0 ± 21.2	.22
Ileum	6.5 ± 11.5	17.5 ± 10.6	.09
Ileocecal valve presence, No. (%)	25 (43.1)	1 (50.0)	.85
Colon in continuity, No. (%)	46 (79.3)	1 (50.0)	.32
Delay since last surgery, mean ± SD, mo	34.8 ± 25.7	18.5 ± 7.8	.19
Serum parameters, mean ± SD			
25-OHD, ng/mL	8.68 ± 4.87	15.32 ± 2.74	.03[a]
PTH, pg/mL	38.45 ± 7.50	37.20 ± 5.69	.41
Calcium, mg/dL	9.24 ± 0.59	9.08 ± 0.20	.35
Phosphate, mg/dL	4.30 ± 0.27	4.12 ± 0.15	.18
Magnesium, mg/dL	1.97 ± 0.18	2.04 ± 0.17	.30

25-OHD, 25-hydroxyvitamin D; AMI, acute mesenteric ischemia; BMD, bone mineral density; BMI, body mass index; IBD, inflammatory bowel disease; NRS 2002, Nutrition Risk Screening 2002; PTH, parathyroid hormone; RE, radiation enteritis; SBS, short bowel syndrome.
[a]Statistically significant ($P < .05$).

loss was low serum VtD concentrations. Low serum VtD concentration was associated with a decreased BMD (B, 0.057; $P = .011$; 95% CI, 0.014–0.101) (Figure 6). However, no other demographic characteristics or clinical examinations were associated with bone loss.

Changes in Serum 25-OHD Concentration After Routine VtD Supplementation

All 60 patients with suboptimal 25-OHD levels were started on enteral VtD supplementation with 1200 IU/d as per our

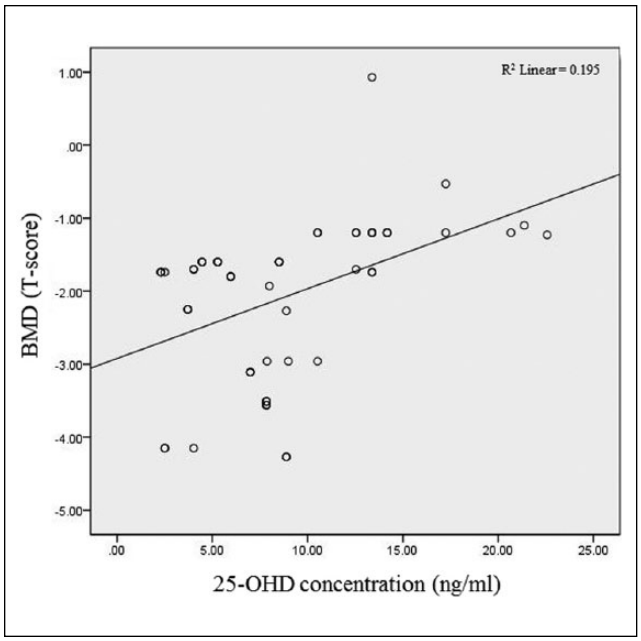

Figure 6. Correlation between serum 25-OHD concentration and BMD T score in patients with short bowel syndrome. 25-OHD, 25-hydroxyvitamin D; BMD, bone mineral density.

center's standard of care. Eight of the 60 patients (13.3%) had repeat serum 25-OHD levels drawn during the study period that showed improvement and increased their serum 25-OHD into the sufficient range. However, the remainder of the individuals (n = 52) did not achieve satisfactory serum 25-OHD response. Twenty-three patients had intermittent or persistent deficiency even after therapeutic doses of VtD had been started.

Discussion

VtD is synthesized in the skin under the influence of UVB exposure from sunlight, or it is derived from food, specifically from a combination of natural sources and fortified foods.[16] Patients with SBS are therefore at high risk for VtD insufficiency or deficiency due to inadequate oral intake, poor absorption, and lack of UVB exposure. As such, they require higher supplemented doses of VtD or greater exposure to sunlight to achieve adequate VtD levels.[17] Several studies of SBS receiving PN have shown that most patients have either deficient or insufficient serum VtD levels.[3,18,19] Similarly, a recent study found that 5 of 19 children (26.3%) had suboptimal VtD levels during or after weaning off PN.[13] A second report of 65 pediatric patients with SBS found that 41.5% had a documented VtD deficiency during the 9-year study period. A third study of pediatric and young adult patients with IF found that only 49 of 123 individuals (39.8%) had VtD deficiency.[12] Of note, these studies documented VtD status in patients with SBS receiving PN therapy. Data regarding the incidence and risk factors of suboptimal VtD levels in adult SBS, especially after weaning off PN, remain sparse.

In our patient cohort, 100% (n = 60) of adult patients with SBS had suboptimal VtD levels, even though they had weaned off PN. Compared with previous publications, our study recognized a more serious situation in VtD insufficiency or deficiency. Of the 95% (n = 57) of patients with VtD deficiency, 65% (n = 39) had severe deficiency. Furthermore, most patients did not achieve satisfactory status despite routine oral VtD supplementation with 1200 IU. This emphasizes the critical importance of routine surveillance of serum VtD levels and consideration of much higher daily oral doses or alternative methods of supplementation (such as intravenous [IV] or intramuscular administration) even after weaning off PN. Meanwhile, we found that patients with a greater small bowel length or shorter SBS course were less likely to have VtD deficiency. This may occur from VtD storage making up for short-term consumption and shorter small bowel length resulting in limited absorptive capacity. Patients with greater small bowel length therefore may be more likely to absorb VtD from enteral sources. This is supported by the finding by Mutanen et al[20] that greater remnant small bowel length was associated with higher VtD levels.

The frequency of bone loss observed in this population of patients was also greater than those documented in previous investigations, with 96.7% (n = 58) of patients having a BMD T score <–1.0 even with normal serum concentrations of calcium and phosphorus. Only 2 patients presented a normal BMD; osteopenia was noted in 68.3% (n = 41) of patients and osteoporosis in 28.3% (n = 17) of the entire cohort. This rate was somewhat higher than that of prior studies where bone loss has been reported in 10%–60% of patients with SBS receiving PN.[7,12,13] The clinical consequences of bone loss in our series were not particularly notable, with only 11.7% (n = 7) of patients reporting bone pain, while no one had pathologic fracture. Some researchers have speculated that ileal resection may play a role in bone loss, as this region plays a key role in VtD absorption and in the production of glucagon-like peptide 2 (GLP-2), which has been shown to improve BMD in some patients.[21] However, our data did not show any significant association between residual ileum length and bone loss. Among the variables investigated, the only factor that significantly predicted low BMD was suboptimal VtD concentration. There was a trend toward increased prevalence of bone loss in patients with decreased 25-OHD concentration. Interestingly, in our study cohort, there was no significant difference in serum concentrations of calcium and phosphate between patients with normal and low BMD. A previous study confirmed that there was no statistically significantly difference between low BMD and decreased VtD concentration, while BMI and serum levels of calcium and PTH were significantly different,[7,22] which was different from our observations. In addition, no other demographic characteristics or clinical examinations were associated with bone loss.

A previous study recognized that standard adult multivitamin formulations meet the current daily nutrition recommendations, providing 400 IU of VtD.[23] However, without adequate UVB exposure, some researchers recommend the required enteral dose should be about 800–1000 IU/d.[24] Higher doses of VtD were also recommended for patients with SBS.[13] Optimal VtD dosing is a significantly important issue given that suboptimal VtD may result in infections and metabolic bone disease. Severe VtD deficiency is associated with osteopenia or osteoporosis in adults. In fact, several studies have described decreased BMD based on DEXA in patients with SBS and PN dependence. Our study showed that bone loss could be found not only in patients with PN dependence but also in patients who had weaned off PN.

Compared with previous studies, our patient cohort encompassed a more diverse population, including adult patients weaning off PN or even transitioning to 100% oral feeding. Another advantage was that we evaluated almost all the variables that may predict suboptimal VtD levels and bone loss. Furthermore, oral VtD supplementation was routinely conducted according to our center's standard of care. Although it showed no satisfactory response, our study suggested that much higher oral dosing of VtD may be needed in patients with SBS, and alternative methods should be explored, such as IV or intramuscular administration. There were several limitations to our study. First, as a single-center study, a potential selection bias may be produced. Second, since only 60 patients with SBS were enrolled in our study, the sample size might be too small to detect the real risk factors of suboptimal VtD status and bone loss. However, considering the prevalence of SBS was low, we could consider our sample size appropriate. Third, the doses of oral VtD supplementation we provided were relatively low. Although higher doses of VtD were also recommended for patients with SBS with PN dependence, there has been no general consensus until now.[3,25] In addition, all patients enrolled in our study were weaning off PN and transitioning to 100% oral feeding, which meant some compensation of the intestine has been acquired and the intestine has a certain ability to absorb some nutrients. That is why we did not increase the doses of VtD to a high level. Finally, the duration of time the patients were off PN at the time of enrollment was not analyzed in this study. The reason was that some patients weaned off it directly, while others weaned off it with the help of EN and then gradually transited to oral diets. The process of weaning off PN varied with different patients and was difficult to be unified. With this in mind, we thought it was not a good parameter to evaluate the status of VtD and BMD in our patients. Despite the limitations, our study adds to the growing body of research on suboptimal VtD status and bone loss in adult SBS, especially among patients who had weaned off PN. Actually, based on this study, prospective research of exploring much higher oral doses, as well as alternative therapies treated with oral VtD supplementation in patients with SBS, is ongoing in our center. We will report the results in the future.

Conclusions

The present findings indicate that suboptimal VtD status and bone loss are common and serious in adult SBS even after weaning off PN. Although routinely treated with oral VtD supplementation, most patients cannot achieve satisfactory VtD and BMD. This emphasizes the critical importance of routine surveillance of serum 25-OHD and BMD and consideration of much higher oral doses, as well as alternative methods of supplementation such as IV or intramuscular administration. In addition, we suggest that it is necessary to treat patients with SBS with prophylactic high doses of VtD supplementation. However, due to the limitations of this study, further studies are needed to determine the best method and doses for VtD supplementation.

Statement of Authorship

S. Fan, Y. Li, and J. Li contributed to the conception and design of the research; S. Fan, X. Ni, J. Wang, Y. Zhang, S. Tao, and W. Kong contributed to the acquisition, analysis, and interpretation of the data; S. Fan, X. Ni, J. Wang, Y. Zhang, S. Tao, and W. Kong drafted the manuscript; and S. Fan, Y. Li, and J. Li critically revised the manuscript. All authors agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Aluminum Content of Neonatal Parenteral Nutrition Solutions: Options for Reducing Aluminum Exposure

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Abstract

Introduction: Calcium chloride ($CaCl_2$) has been the only calcium additive available in the United States that has a low aluminum (Al) content. Calcium gluconate in glass vials (CaGluc-Gl) has a high Al content while calcium gluconate in plastic vials (CaGluc-Pl) has a low Al content. The purpose of this study was to measure Al concentrations in neonatal parenteral nutrition (PN) solutions prepared using various calcium additives. *Methods:* Samples of solutions compounded with $CaCl_2$ or CaGluc-Gl and sodium phosphate (NaPhos) as well as CaGluc-Pl and sodium glycerophosphate (NaGP) with and without cysteine were analyzed for Al content. Samples of the cysteine and calcium gluconate additives were also sent for analysis. *Results:* Solutions containing $CaCl_2$ and CaGlu-Pl had mean Al concentrations of 1.2–2.3 mcg/dL, while those with CaGlu-Gl had mean concentrations of 14.6–15.1 mcg/dL. Solutions made with NaGP were low in Al content. The measured Al content of 2 lots of the cysteine additive were 168 ± 23 mcg/L and 126 ± 5 mcg/L. The Al concentration equalled 2730 ± 20 mcg/L for the CaGlu-Gl additive and 310 ± 80 mcg/L for the CaGlu-Pl additive. *Conclusion:* The study indicates that solutions containing $CaCl_2$ or CaGluc-Pl and NaPhos or NaGP are low in Al content. Using these options for calcium and phosphate additives can limit aluminum intake from neonatal PN to levels within the Food and Drug Administration guideline of ≤5 mcg/kg/d. (*Nutr Clin Pract*. 2017;32:266-270)

Keywords

calcium gluconate; calcium chloride; plastic vials; sodium glycerophosphate; cysteine

A recent article has reviewed the issue of aluminum (Al) toxicity associated with parenteral nutrition (PN).[1] Particularly concerning for neonatal patients has been the association of PN solutions containing high Al concentrations with neurodevelopmental impairment.[2] That randomized controlled study found that solutions made with calcium chloride ($CaCl_2$) contained significantly less Al than solutions made with calcium gluconate in glass vials (CaGluc-Gl). A follow-up study associated the high Al exposure from PN solutions containing CaGlu-Gl with reduced bone mass in adolescence.[3] The American Society for Parenteral and Enteral Nutrition (ASPEN) acknowledges that Al contamination of PN solutions is a risk factor for metabolic bone disease of preterm infants and recommends that "efforts be made to reduce the aluminum content of PN."[4] The current recommendation from the Food and Drug Administration (FDA) for premature infants is to limit the intake of Al from all sources in PN to ≤5 mcg/kg/d whenever possible.[5] Aluminum is a contaminant introduced into many small- and large-volume parenteral products during the manufacturing process, as well as due to leaching of Al during sterilization of glass containers.[6] Poole et al[7] have found that the FDA recommendation to limit the intake of Al due to PN contamination could not be met when using CaGluc-Gl as the preferred source of calcium in neonatal PN as is often done in the United States. Other additives to neonatal PN may also have high levels of Al contamination. Potassium phosphate contains high Al levels compared with sodium phosphate (NaPhos).[8] Cysteine additives may also have relatively high levels of Al.[9] These 2 additives are also commonly used in neonatal PN solutions in the United States.

Other options that have been available in Europe, but not in the United States, such as using calcium gluconate in plastic

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Conflicts of interest: None declared.

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Table 1. Aluminum Content Listed by the Manufacturer for Parenteral Nutrition Additives Used for All Study Solutions.

Additive	Manufacturer	Al, mcg/L	Dose/dL	Al (mcg/dL of PN)
Dextrose 70%[a]	Baxter Healthcare, Deerfield, IL	25	10 g	0.357
Sodium acetate (2 mEq/mL)[b]	Hospira, Lake Forest, IL	360	2 mEq	0.36
Potassium chloride (2 mEq/mL)[b]	Hospira, Lake Forest, IL	100	1 mEq	0.05
Magnesium sulfate 50%[b]	APP Pharmaceuticals, Schaumburg, IL	300	0.5 mEq	0.039
Infuvite pediatric (multivitamins)[b]	Baxter Healthcare, Deerfield, IL	30	1.5 mL	0.045
Heparin (100 units/mL)[a]	BD Pharmaceuticals, Schaumburg, IL	NR	50 units	—
Zinc chloride (1 mg/mL)[a]	Hospira, Lake Forest, IL	150	400 mcg	0.06
Copper (40 mcg/mL)[a]	Hospira, Lake Forest, IL	340	20 mcg	0.17
Selenium (8 mcg/mL)[b]	American Reagent, Shirley, NY	500	2 mcg	0.125
L-Carnitine (20 mg/mL)[b]	Sigma-Tau, Gaithersburg, MD	NR	5 mg	—
Water[a]	Baxter Healthcare, Deerfield, IL	25	QS	0.4–1.2

Al, aluminum; NR, not reported; PN, parenteral nutrition; QS, quantity sufficient.
[a]Plastic container.
[b]Glass container.

vials (CaGluc-Pl) as the calcium additive or using sodium glycerophosphate (NaGP) in combination with $CaCl_2$, also appear to have the potential to limit Al exposure to acceptable levels in neonatal patients.[10,11] Calcium gluconate in plastic vials has just become available in the United States, but recent studies confirming the low Al content of this additive could not be found in a literature search. Using an organic phosphate would appear to provide the best option since organic phosphates have been shown to significantly increase the solubility of calcium with phosphate in solutions containing either $CaCl_2$ or CaGluc.[12–14] Sodium glycerophosphate is low in Al content but has only been approved for use in patients in the United States when no sodium or potassium phosphate is available due to additive shortages.

The purpose of this study was to measure aluminum levels in neonatal PN solutions containing $CaCl_2$ or CaGluc-Gl and NaPhos as well as solutions containing CaGluc-Pl and NaGP. A second objective was to evaluate the contribution of a cysteine additive to the Al content of PN solutions.

Methods

Study solutions were compounded by a neonatal pharmacist in the neonatal intensive care unit (NICU) pharmacy at Randall Children's Hospital in clear plastic Exacta Mix 250 mL EVA containers (Baxa Corporation, Englewood, CO) using a Baxa Exactamix 2400 Compounder (Baxa Corporation). All solutions contained standard neonatal dosages of dextrose, electrolytes, magnesium, copper, zinc, selenium, multivitamins, heparin, and levocarnitine. Table 1 lists these additives with the Al content of each additive as reported by the manufacturer. The final volume of each solution was 100 mL. Two studies were performed.

In study 1, solutions containing 3% amino acids (Trophamine; B. Braun Medical, Irvine, CA) were compounded with 1 mmol/dL (40 mg/dL) elemental calcium as $CaCl_2$ or CaGlu-Gl and 0.75 mmol/dL NaPhos. These concentrations of calcium and phosphate were based on recent compatibility studies for $CaCl_2$ and phosphates.[15,16] Seven solutions containing each calcium additive were compounded with and without cysteine, 50 mg/dL. Five samples of the cysteine additive were also sent for analysis.

In study 2, solutions containing 3% amino acid (AA) (Trophamine; B. Braun Medical) were compounded with 2 mmol/dL (80 mg/dL) elemental calcium as CaGlu-Pl and 2 mmol/dL NaGP. These concentrations of calcium and phosphate were based on maximum recommendations for calcium and phosphorus intake in neonatal PN.[17] Seven solutions containing CaGlu-Pl and NaGP were compounded with and without cysteine, 90 mg/dL. Five samples of the CaGlu-Pl and cysteine additives were also sent for analysis.

All samples were placed in acid-washed plastic tubes and refrigerated. Samples were sent to NMS Labs (Willow Grove, PA) for analysis of Al content using inductively coupled plasma/mass spectrometry. Samples were analyzed within 1 week of compounding. The Al content of the AA, calcium, phosphate, and cysteine additives included in the studies, as determined by the manufacturer, is listed in Table 2.

Results of the analysis of the Al content of the CaGlu-Pl additive were not felt to be reliable by the referral laboratory. The issue was due to matrix interference producing a high internal standard response due to an unidentified component of the additive. This was not a problem with the cysteine additive or the PN solutions. Some additional samples of calcium gluconate were, therefore, transported to the Oregon State University Radiation Center (Corvallis, OR) for analysis of Al content using neutron activation.[18,19] Three samples of the CaGlu-Gl additive and 7 samples of the CaGlu-Pl additive were analyzed.

The predicted Al content of study solutions was calculated using the manufacturer's maximum labeled Al concentration of additives. Means of the Al concentration of each study group were compared using Student *t* tests after entering data into an Excel spreadsheet (Microsoft Corp, Redmond, WA). An n of 7

Table 2. Aluminum Content Listed by the Manufacturer for Parenteral Nutrition Additives That Varied Among Study Solutions.

Additive	Manufacturer	Al, mcg/L	Dose/dL	Al (mcg/dL of PN)
Sodium phosphate (3 mmol/mL)[a,b]	APP Pharmaceuticals, Schaumburg, IL	16,300	0.75 mmol	4.075
Calcium chloride (1.36 mEq/mL)[a,b]	IMS Ltd, So. El Monte, CA	NR	1 mmol	—
CaGluc-Gl 10%[a,b]	APP Pharmaceuticals, Schaumburg, IL	9400	1 mmol	41.736
L-Cysteine (50 mg/mL)[a,b]	Sandoz, Princeton, NJ	5000	50 mg	5
Trophamine 10%[b,c]	B. Braun Medical, Irvine, CA	25	3 g	0.75
Glycophos (1 mmol/mL)[d,e]	Fresenius Kabi Norge AS, Halden, Norway	550	2 mmol	1.1
CaGluc-Pl 10%[d,e]	Fresenius Kabi USA, Lake Zurich, IL	9400	2 mmol	80.4
L-Cysteine (50 mg/mL)[b,d]	Sandoz, Princeton, NJ	5000	90 mg	9

Al, aluminum; CaGluc-Gl, calcium gluconate in glass vials; CaGluc-Pl, calcium gluconate in plastic vials; NR, not reported; PN, parenteral nutrition.
[a]Included in study 1.
[b]Glass container.
[c]Included in studies 1 and 2.
[d]Included in study 2.
[e]Plastic container.

Table 3. Planned Comparisons.

	Group 1		Group 2	
Study	Additive	n	Additive	n
1	$CaCl_2$	7	CaGlu-Gl	7
1	$CaCl_2$-Cys	7	CaGlu-Gl-Cys	7
1	$CaCl_2$	7	$CaCl_2$-Cys	7
1	CaGlu-Gl	7	CaGlu-Gl-Cys	7
2	CaGlu-Pl	7	CaGlu-Pl-Cys	7

$CaCl_2$, calcium chloride; $CaCl_2$-Cys, calcium chloride with added cysteine; CaGlu-Gl, calcium gluconate in glass vials; CaGlu-Gl-Cys, calcium gluconate in glass vials with added cysteine; CaGlu-Pl; calcium gluconate in plastic vials; CaGlu-Pl-Cys, calcium gluconate in plastic vials with added cysteine.

for each group was selected based on review of previous studies of Al content in PN.[2,8,10,11,20] Table 3 lists the planned comparisons for both studies.

The studies were approved by the institutional review board for the Legacy Health System (Portland, Oregon). No formal review was required since no human participants were involved.

Results

Results of study 1 are shown in Table 4. Although there was a significant difference between solutions containing $CaCl_2$ and CaGlu-Gl in Al content, there was no significant difference between solutions containing the same calcium additive related to cysteine content. Measured Al was about 30% of predicted for solutions without cysteine. For solutions containing cysteine, measured Al content was about 19% of predicted for $CaCl_2$ and 28% for CaGlu-Gl. The measured Al content of the cysteine additive was 168 ± 23 mcg/L (n = 5).

Results of study 2 are shown in Table 5. There was no significant difference in the measured Al content between solutions containing cysteine vs those without cysteine. The measured Al content was 1.5% and 1.6% of predicted for solutions without cysteine and with cysteine, respectively. The measured Al content of the cysteine additive was 126 ± 5 mcg/L (n = 5).

The measured Al content of the calcium gluconate additives using neutron activation was 2730 ± 20 mcg/L (n = 3) for the CaGlu-Gl additive and 310 ± 80 mcg/L (n = 7) for the CaGlu-Pl additive.

Discussion

This study found that PN solutions containing $CaCl_2$ or CaGluc-Pl can limit the Al content from contamination of additives to levels that are within the FDA recommendation. This finding is consistent with the earlier studies from Europe.[2,10] The high Al content of solutions containing CaGluc-Gl is consistent with multiple earlier studies.[2,8,20] The solutions containing CaGlu-Pl and NaGP were low in Al content, which is consistent with previous studies.[10,11] The Al content of solutions made with sodium phosphate is also lower than those made with potassium phosphate.[2,8,21]

The 2 methods most often used to measure Al content of PN solutions are inductively coupled plasma/mass spectrometry (ICP-MS) and atomic absorption spectroscopy (AAS). Previous studies have shown that results are comparable between the 2 methods.[22,23] Both methods have been used in the studies referenced above, and a recent review of methods used by 10 clinical laboratories that do Al testing found that both procedures are used equally.[24] Results using neutron activation are also comparable.[22] While matrix interference when determining Al concentration can be a potential issue with all methods, including ICP-MS,[25] current procedures can usually correct for these interferences. Phosphorus can interfere with Al measurements by neutron activation, however.[26]

As noted in the Methods, the amount of calcium and phosphate used in study 1 and study 2 differed due to calcium/

Table 4. Aluminum Content of Neonatal Parenteral Nutrition Solutions Containing Calcium Chloride or Calcium Gluconate in Glass Vials (1 mmol/dL)[a] and Sodium Phosphate (0.75 mmol/dL) With and Without Added Cysteine (50 mg/dL).

	$CaCl_2$		CaGlu-Gl	
Group	No Cysteine	Cysteine	No Cysteine	Cysteine
n	7	7	7	7
Al-M, mean ± SD, mcg/dL	2.2 ± 0.4	2.3 ± 0.1	14.6 ± 0.5[b]	15.1 ± 1.8[b]
Al-P,[c] mcg/dL	7.3	12.3	48.2	53.2

Al-M, measured aluminum concentration; Al-P, predicted aluminum concentration; $CaCl_2$, calcium chloride; CaGlu-Gl, calcium gluconate in glass vials.
[a]One mmol of calcium equals 40 mg or 2 mEq.
[b]$P < .001$ compared with $CaCl_2$.
[c]Predicted aluminum content is based on concentrations listed in column 5 of Tables 1 and 2.

Table 5. Aluminum Content of Neonatal Parenteral Nutrition Solutions Containing Calcium Gluconate in Plastic Vials (2 mmol/dL)[a] and Sodium Glycerophosphate (2 mmol/dL) With and Without Added Cysteine (90 mg/dL).

Group	No Cysteine	Cysteine
n	7	7
Al-M, mean ± SD, mcg/dL	1.3 ± 0.2	1.5 ± 0.2
Al-P,[b] mcg/dL	84.8	93.8

Al-M, measured aluminum concentration; Al-P, predicted aluminum concentration.
[a]One mmol of calcium equals 40 mg or 2 mEq.
[b]Predicted aluminum content is based on concentrations listed in column 5 of Tables 1 and 2.

phosphate compatibility differences for the solutions used in each study. The same amount of calcium and phosphate was used for solutions containing $CaCl_2$ and CaGlu-Gl in study 1, which would allow the reader to estimate the impact of using CaGlu-Gl as the calcium additive in doses that differ from the concentration of 1 mmol/dL (40 mg/dL) used in this study. Since there were not solubility limits when using NaGP as the phosphate additive, a maximum recommended amount of calcium and phosphate was used in study 2 to assess a worst-case scenario with regard to Al contamination in solutions containing CaGlu-Pl.

The measured Al content of solutions in the current study ranged from 1.5%–30% of the predicted Al content compared with the ranges reported in previous studies of 6%–53%.[8,20,27] The difference between measured and predicted Al content in the current study appears to be primarily related to differences in the actual vs predicted amounts of Al contamination of the calcium and cysteine additives. This appears to be especially true for the very low measured vs predicted Al content of the solutions containing CaGluc-Pl and NaGP, where the manufacturer's estimated Al content of CaGluc-Pl was the same as for CaGluc-Gl (9400 mcg/L). The only previous study identified that measured Al content of solutions containing CaGluc-Gl compared with solutions containing CaGluc-Pl reported a content of 3000–6000 vs 105–195 mcg/L, respectively.[10] The NaGP additive used in the current study was packaged in a plastic vial. The only previous study that we have seen that compares the Al content of NaGP in glass vs plastic vials found concentrations of 460 vs <10 mcg/L, respectively.[10]

The measured Al content of the cysteine additive was also much lower than predicted, averaging 126 and 168 mcg/L for 2 different lots from the same manufacturer compared with 5000 mcg/L. This resulted in the finding that there was no significant increase in Al content of solutions compounded with added cysteine compared with those compounded without added cysteine, even though the dose of cysteine was 50 mg/dL in study 1 and 90 mg/dL in study 2. A study from Mexico, however, reported a much higher Al content for a cysteine additive from a different manufacturer of 2560 mcg/L.[21]

The lower dose of cysteine, used in study 1, approximates a dose that has been found to increase glutathione synthesis in preterm infants.[28] Higher doses do not appear to further enhance glutathione production. The last Cochrane review found no significant effect of cysteine supplementation on growth or clinical outcomes and insufficient evidence with which to evaluate the risks due to metabolic acidosis associated with cysteine supplementation.[29] Acidification of PN solutions associated with cysteine supplementation does decrease the risk of calcium and phosphate precipitation, however, and higher doses, ranging from 20–40 mg/g of amino AA in PN are often used in neonatal PN in the United States.[17] The higher dose of cysteine of 90 mg/dL, used in study 2, is based on an average of this dosage range.

A limitation of this study is that each additive was produced by only 1 manufacturer. The Al content of additives may vary from manufacturer to manufacturer, and additives made by the same manufacturer may also vary from lot to lot. Only 1 lot of the $CaCl_2$, CaGluc-Gl, and NaPhos additives was tested, but 2 lots of the CaGluc-Pl, NaGP, and cysteine additives were tested. Three lots were tested for all the other additives. The Al content of the solutions containing $CaCl_2$ and NaPhos is consistent with previous studies that evaluated PN solutions containing $CaCl_2$ and NaPhos additives supplied by other manufacturers.[2,8] The same can be said for solutions containing CaGluc-Gl and NaPhos[2,8] and CaGluc-Pl and NaGP.[10]

Conclusions

In conclusion, the recent introduction of CaGluc-Pl into the United States provides another option, in addition to $CaCl_2$, for limiting the Al exposure from PN of neonatal patients to levels within the FDA guideline. Calcium gluconate in glass vials has consistently been shown to contain high amounts of Al, resulting in the exposure of preterm infants to levels associated with adverse outcomes. The best option, still not available for routine use but recently imported into the United States due to the shortage of mineral phosphates in the United States, would be to use sodium glycerophosphate as the phosphate additive in neonatal PN due to its high degree of solubility with either calcium gluconate or calcium chloride.[13,14] The combination of NaGP with either $CaCl_2$ or CaGluc-Pl would allow clinicians to increase calcium and phosphorus intakes above amounts possible when compounding calcium additives with mineral phosphates while limiting Al exposure. This practice would not only decrease the possibility of adverse outcomes due to Al exposure but also may improve bone mineralization.

Statement of Authorship

R. K. Huston, C. F. Heisel, J. M. Christensen, and L. Minc equally contributed to the conception and design of the research; C. F. Heisel, B. R. Vermillion, and L. Minc contributed to the acquisition, analysis, and interpretation of the data; and R. K. Huston and J. M. Christensen contributed to the analysis and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Thiamin, Pyridoxine, Vitamin D, and Carotene Deficiency in a Malnourished Patient Following Billroth II Gastrectomy

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Abstract

We describe the case of a malnourished 48-year-old man who had previously undergone a Billroth II procedure for severe peptic ulcer disease. He was found to have a severely stenotic gastrojejunal anastomosis with inflamed mucosa that prevented him from tolerating solid food. Laboratory assessment revealed deficiencies in thiamin, pyridoxine, vitamin D, and carotene. This case demonstrates potential vital micronutrient complications following a partial gastrectomy. (*Nutr Clin Pract*. 2017;32:271-274)

Keywords

Billroth II; gastroenterostomy; gastrectomy; vitamin deficiencies; vitamin B-6 deficiency; thiamin deficiency; vitamin D deficiency; beta carotene

Case Report

A 48-year-old white male was admitted to the gastroenterology service at UF Health Shands Hospital with constant intractable epigastric pain, nausea, and frequent emesis. The patient's medical history included hypertension, peptic ulcer disease (PUD), migraine headaches, anxiety, tobacco use, chronic obstructive pulmonary disease (COPD), nonischemic cardiomyopathy, and New York Heart Association (NYHA) class 3A heart failure with placement of an implantable cardioverter defibrillator (ICD). Pertinent surgical history included the aforementioned ICD placement, laproscopic cholecystectomy, and a partial gastrectomy with Billroth II (BII) reconstruction performed 5 years prior to admission for severe PUD. He initially presented to an outside institution, where an esophagogastroduodenoscopy (EGD) was concerning for a gastric outlet obstruction. He was ultimately referred to our institution for further workup.

The patient's epigastric symptoms reportedly began 1.5 years prior to admission but had acutely worsened over the most recent 6 months, during which time he had experienced a 14-kg weight loss (from 66 to 52 kg). In the month preceding presentation, the patient was able to tolerate only a liquid diet due to the immediate regurgitation of all solid foods. He was malnourished on physical examination, as evidenced by his cachectic appearance resulting from a 21% body weight loss in the preceding 6 months. A nutrition-focused physical assessment revealed severe bilateral muscle wasting and severe fat losses. Laboratory data demonstrated severe hypokalemia (2.1 mmol/L [normal, 3.3–5.1 mmol/L]), a chronic problem for which the patient frequently required emergent potassium replacement. Due to the patient's recent state of malnourishment, multiple serum micronutrient laboratory tests were ordered on the day of admission (Table 1). No overt symptoms of micronutrient deficiency were apparent. Our patient was anemic, displaying a red blood cell count of 3.25 million/mm^3 (normal, 4.5–5.9 million/mm^3), serum iron of 45 mcg/dL (normal, 45–160 mcg/dL), total iron binding capacity of 530 mcg/dL (normal, 225–430 mcg/dL), and iron saturation of 8% (normal, 20%–55%).

Our patient adamantly refused enteral feeding tube placement. Thus, a parenteral nutrition (PN) consult was placed to the nutrition support services team on the day of admission in light of the patient's prolonged intolerance of solid food, recent severe weight loss, and the concern for obstruction based on outside imaging. Subsequently, an upper gastrointestinal (GI) endoscopy revealed a severely stenotic gastrojejunal anastomosis with highly ulcerated, edematous, and friable mucosa. Due to the high risk of perforation secondary to severe swelling and inflammation at the site of the anastomosis, our patient did not undergo a dilation procedure during his admission. Instead, maximization of pharmacologic therapy with cholestyramine, sucralfate, and esomeprazole was initiated, and he was sent home on PN.

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Table 1. Micronutrient Concentrations and Corresponding Reference Ranges in Our Malnourished Patient.

Nutrient	Serum Concentration	Normal Range	Interpretation	Repeat Concentration (at 8 Months)
Thiamin (vitamin B_1), nmol/L	5	8–30	Low	36
Pyridoxine (vitamin B_6), nmol/L	4.6	20–125	Low	24.9
25-OH vitamin D, ng/mL	19.6	>20	Low	17.5
Carotene, mcg/dL	20	60–200	Low	47
Zinc, mcg/dL	61	60–120	Normal	62
Ceruloplasmin, mg/dL	28	20–60	Normal	28

OH, hydroxide.

Upon 8-week follow-up, the patient was able to eat some soft foods and had gained 3.2 kg; PN was discontinued at this time due to nutrition improvement and concomitant central access complications (peripherally inserted central catheter [PICC] line thrombosis). A repeat EGD revealed a lack of improvement at the anastomotic stricture, and a 15-mm dilation was performed that briefly alleviated symptoms.

The patient ultimately underwent an open revision of his BII to a Roux-en-Y gastrojejunostomy 8 months after his initial admission due to the recurrence of intolerable GI pain and emesis. His weight was unchanged from the prior visit (55 kg) at the time of this encounter. Micronutrient serum concentrations were repeated at that time and are depicted in Table 1. Aside from total iron binding capacity (354 mcg/dL), iron studies were largely unchanged at this visit; serum iron was identical to the patient's initial presentation (45 mcg/dL), and iron saturation had risen modestly (13%). The patient was counseled extensively during this admission with regard to postsurgery dietary considerations and advancement. He was discharged with instructions to take daily multivitamin, calcium, and vitamin D supplements according to guideline recommendations.[1]

Background

A BII procedure is a partial gastric resection (gastrectomy) in which the gastrin-secreting antrum, the distal portion of the stomach, is removed and the remaining gastric remnant is anastomosed to the side of the jejunum. This type of procedure is indicated for gastric malignancies that are restricted to the antrum and for the treatment of ulcers that are recurrent, resistant to typical therapy, and/or produce significant complications.[2] Indeed, the patient in our case had severe peptic ulcer disease prior to his procedure, stating that he could recall painful symptoms from early childhood. Individuals who undergo gastric resections for ulcers are typically not fully relieved of discomfort, and it is likely that ongoing pain contributed to this patient's poor oral intake and, thus, his malnourishment.

Micronutrient deficiencies are potential complications following both partial (ie, BII) and total (ie, Roux-en-Y gastric bypass) gastrectomy procedures. The removal of any part of the stomach and/or small bowel results in a reduction of the available GI surface area needed for the absorption of nutrients.[3] Unfortunately, the available literature describing specific micronutrient deficiencies following a partial gastrectomy, such as a BII procedure, is sparse compared with the amount of information published on this topic in the setting of major bariatric procedures performed for morbid obesity. However, it is known that anemia resulting from vitamin B_{12}, folate, and/or iron deficiency can occur following a partial gastrectomy, as can osteopenia.[4] The exact mechanism of bone disease following gastrectomy remains unclear but may be due to the reduced dietary intake or absorption of vitamin D and calcium.

A 30-year evaluation of postgastrectomy patients (including 186 who had undergone a BII) described the most common nutrition deficiencies seen in this setting.[5] Iron deficiency was noted in 32% of males and 61% of females by the end of the first decade after surgery. The prevalence increased over time, with 68% of males and 92% of females experiencing this deficiency by year 30. Vitamin B_{12} deficiency increased over time starting in the second decade, eventually affecting 70% of males and 83% of females. Vitamin D deficiency was noted primarily in women.[5]

Thiamin deficiency following total and partial gastrectomy has been reported in a group of patients with polyneuropathy.[6] All 17 patients in this series demonstrated symmetric polyneuropathy with primarily lower limb involvement due to definite thiamin deficiency and not an underlying neurological disorder such as chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, mitochondrial encephalopathy, or the like. Of the 17 total patients, 4 had undergone a BII procedure. The remarkable symptomatic improvement of the patients in this study following thiamin supplementation supported the hypothesis that postgastrectomy thiamin deficiency was the primary etiologic factor contributing to neuropathy.[6]

Gregg et al[7] reported the case of a severely anemic and neutropenic 44-year-old woman who had undergone a BII procedure 5 years prior to presentation. She had a history of chronic anemia refractory to iron, folate, and vitamin B_{12} repletion and required red blood cell transfusions every 2 months. Based on morphologic findings on a bone marrow assessment during workup, the patient was presumed to have myelodysplastic syndrome and was referred for a bone marrow transplant for treatment. However, a nutrition assessment

completed as part of the pretransplant evaluation revealed an undetectable copper level, which was promptly treated with intravenous and oral copper. Upon copper repletion, the myelodysplastic-like cellular morphologies resolved, as did all other hematological abnormalities, including the hemoglobin concentration, the ceruloplasmin concentration, and the mean corpuscular volume.[7]

Discussion

We report the case of a malnourished patient who demonstrated several uncommon micronutrient deficiencies in the setting of a previous BII procedure and recent intolerance of oral nutrition. Our patient exhibited both reduced oral intake due to GI symptoms and reduced nutrient absorption due to BII-related stenotic complications. It is unclear how much each factor contributed to the micronutrient deficiencies seen. However, it is likely that the BII procedure at least exacerbated any ongoing micronutrient deficiencies and malnutrition. There are several complicating factors in using laboratory values alone to assess malnutrition—serum levels must often be interpreted in concert with other laboratory values (eg, zinc and its binding protein, serum albumin) and are not always indicative of total body stores, and many micronutrient concentrations may be altered by the acute phase response.[8]

It must be noted that this patient was thinly built at baseline, with a maximum recorded weight of 66 kg. The possibility exists that the patient was chronically malnourished secondary to his history of painful PUD beginning during childhood. Indeed, his nonspecific histories of nonischemic cardiomyopathy and heart failure (HF) raise further questions regarding his nutrition status, since various micronutrient deficiencies (eg, thiamin, vitamin B_6, selenium) have been linked to the development of HF.[9] In turn, the patient's use of the loop diuretic furosemide (40 mg twice daily) may have further contributed to thiamin deficiency via enhancement of urinary excretion.[10,11] Serum levels of multiple micronutrients, including selenium, vitamin B_{12}, and folic acid, were not measured as a part of this patient's nutrition workup, but it is not unreasonable to expect that these may have also been low given the coexisting micronutrient deficiencies.

Micronutrients were supplemented according to our institutional standard of practice, with 10 mL of intravenous multivitamin (INFUVITE; Baxter Healthcare Corporation, Deerfield, IL) added to PN daily and 1 mL of trace minerals (MULTITRACE; American Regent, Inc, Shirley, NY) added every other day due to a product shortage. More tailored micronutrient supplementation was not implemented as laboratory results had not returned prior to the patient's discharge. Regardless, improvements in thiamin, pyridoxine, and carotene levels were evident 8 months after initial presentation to our institution. This likely reflects the initial repletion of body stores following 2 months of PN and the temporarily improved oral intake as a result of dilation of the anastomotic stricture.

Evidence surrounding repletion of specific micronutrient deficiencies is sparse in the asymptomatic setting. For instance, the recommended dietary allowance (RDA) of thiamin for an adult man is 1.2 mg/d,[12] while the recommended beriberi treatment dose ranges from 5–100 mg/d based on severity of illness.[13] Our patient received 12 mg/d within his PN. The RDA of pyridoxine for a male of our patient's age is 1.3 mg/d.[12] Recommended dosing of pyridoxine in the setting of deficiency is reported as 2–20 mg/d for at least 3 weeks[14]; our patient received 12 mg/d. The RDA for vitamin D, which is primarily synthesized following exposure to sunlight, is 600 international units per day.[12] In the setting of deficiency, the recommended dose increases to 1000–2000 international units/d and may be as high as 6000–10,000 international units/d in patients with malabsorption syndromes or prior gastric bypass.[15] Our patient received 400 international units daily within his PN, seemingly without additional oral supplementation, which may explain why his serum concentration did not improve over time.

The micronutrient deficiencies described herein add to the small body of evidence available pertaining to such anomalies in the partial gastrectomy population. Thiamin deficiency has been observed following total and partial gastrectomy for malignancy or gastric ulcers.[5] Unlike the patients described by Koike et al,[6] our patient did not experience concurrent polyneuropathy. Carotene deficiency following partial gastrectomy has been reported rarely in the literature[16,17] and appears to be an uncommon affliction. Likewise, we are not aware of any other reports of pyridoxine deficiency following a BII. It is unclear whether the lack of literature regarding carotene and pyridoxine deficiency is reflective of a true paucity of similar reactions in this patient population or simply the product of underreporting or underassessing.

If presented with a similar case in the future, early assessment of vitamin B_{12} and folate would be a priority. Although these micronutrients were not checked at baseline in this case, they were assessed at the patient's 8-month follow-up visit prior to Roux-en-Y revision and were within normal limits (folate, 9.7 ng/mL [normal, 4.4–19.9 ng/mL]; vitamin B_{12}, 465 pg/mL [normal, 243–894 pg/mL]). The effect of nutrition improvement on these laboratory parameters cannot be assessed in this case due to the lack of initial monitoring, which is a limitation of this report.

Conclusion

Several clinically relevant micronutrient deficiencies have been described following partial gastrectomy. Herein, we describe the case of a malnourished 48-year-old man who had undergone a BII gastrectomy for severe peptic ulcer disease 5 years prior to presentation. A laboratory assessment revealed deficiencies in thiamin, pyridoxine, vitamin D, and carotene. This case and the similar cases before it stress that clinicians should be cognizant of the various nutrition

deficiencies that may be present in patients following partial gastrectomy procedures.

Statement of Authorship

M. D. Lahey and A. Y. Kamel equally contributed to the conception and design of the research, as well as the acquisition, analysis, and interpretation of the data; and M. D. Lahey drafted the manuscript. Both authors critically revised the manuscript, gave final approval, and agree to be fully accountable for ensuring the integrity and accuracy of all aspects of the work.

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Reversible Facial Hyperpigmentation Associated With Vitamin B12 Deficiency

Leeda Tayem, MD[1]; Noureddine Litaiem, MD[1]; Mariem Jones, MD[1]; and Faten Zeglaoui, MD, PhD[1]

Abstract

Vitamin B12 (cobalamin) deficiency is common in developing countries. Its dermatologic manifestations include hair and nail changes and glossitis. Cases of generalized hyperpigmentation associated with vitamin B12 deficiency have rarely been reported. Localized hyperpigmentation is less frequently described, affecting palms, soles, and flexural areas. We report a rare case of reversible melasma-like cutaneous hyperpigmentation associated with pernicious anemia and discuss the possible mechanisms of this association. (*Nutr Clin Pract*. 2017;32:275-276)

Keywords

vitamin B12; vitamin B12 deficiency; cobalamin; pernicious anemia; hyperpigmentation

Pernicious anemia (PA) is caused by lack of intrinsic factor. A common cause is autoimmune disease in which antibodies are produced against intrinsic factor and gastric parietal cells. PA is associated with atrophy of the fundus and body of the stomach, as well as vitamin B12 (cobalamin) malabsorption and deficiency. The most common manifestations of vitamin B12 deficiency are neurological, but there are some physical signs, including hair and nail changes and glossitis. Skin changes such as hyperpigmentation are rarely reported.

Observation

We report a case of a 46-year-old female patient with a history of primary ovarian failure who presented with paraplegia evolving over 1 year in association with weakness, sphincter incontinence, and facial hyperpigmentaion. Physical examination revealed pallor and melasma-like, symmetrical hyperpigmentation along the mandible (Figure 1) associated with pigmentation of the vermilion zone (Figure 2) and atrophy of the lingual papillae. Neurologic examination revealed generalized brisk deep tendon reflexes and impaired joint position sensation. Physical examination was otherwise unremarkable. Laboratory investigations showed megalocytic aregenerative anemia (hemoglobin, 8.1 g/dL; mean corpuscular volume, 117.3 fL) associated with thrombocytopenia. Renal function tests, thyroid function tests, and cortisol levels were normal. Gastroesophageal endoscopy showed an atrophic fundal mucosa. Cerebrospinal magnetic resonance imaging (MRI) was unremarkable. Histologic examination of the mandibular skin specimen revealed hyperpigmentation of the basal layer of the epidermis and dermal melanophages. The diagnosis of PA was achieved in the department of gastroenterology, where daily 1000-mg intramuscular vitamin B12 injections were started for 1 week, followed by monthly 1000-mg intramuscular cobalamin injections, leading to rapid improvement in the hematologic tests and neurologic status. The hyperpigmentation slowly but remarkably ameliorated without any further treatments.

Discussion

The association between vitamin B12 deficiency and hyperpigmentation, although unusual, has been previously described. In most of the reported cases, the hyperpigmentation was generalized, involving sun-exposed areas, flexural areas, oral mucosa, and nails. Cases of localized hyperpigmentation were less frequently described, affecting commonly the palms, soles, and the interphalangeal joints.[1–6] In our case, the hyperpigmentation affected the face and mucosa. The main differential diagnoses are melasma and postinflammatory hyperpigmentation. In the absence of family history, significant sun exposure, and particularly hormonal factors in this patient with primary ovarian failure, the diagnosis of melasma is deemed improbable.

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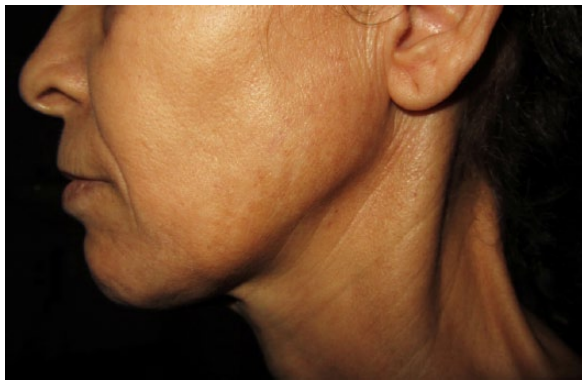

Figure 1. Brown pigmentation mimicking mandibular melasma.

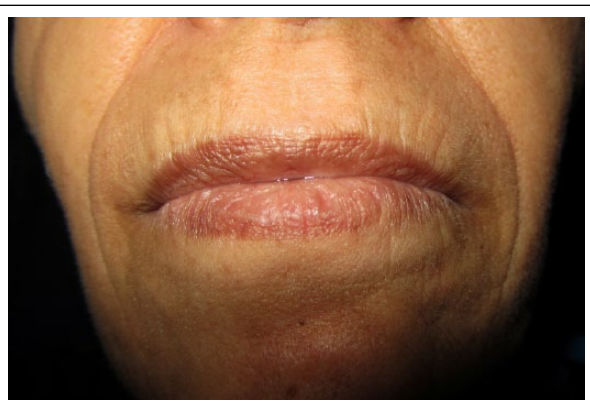

Figure 2. Pigmented brown macules of the upper lip.

Vitamin B12 deficiency is probably an underrecognized etiology of localized hyperpigmentation. The presence of neuropathy, atrophy of gastric mucosa, and glossitis are classical findings in PA.[7] The exact mechanism of hyperpigmentation is unknown, but there are many hypotheses. It has been suggested that vitamin B12 deficiency causes a decrease in the amount of intracellular reduced glutathione, which inhibits tyrosinase. This results in an increase in melanogenesis manifesting clinically as hyperpigmentation.[7] A second hypothesis is through biopterin. Biopterin is necessary for the hydroxylation of phenylalanine (a major substrate in melanin biosynthesis), and elevated levels are found in folate deficiency.[7] This could explain the hyperpigmentation also found in vitamin B12 deficiency.[7] Another mechanism could be related to a defect in melanin transport and incorporation into keratinocytes.[8] Finally, as vitamin B12 is essential for purine and pyrimidine metabolism, its deficiency may lead to a decrease in the ability to synthesize DNA and consequently epidermal changes.[8]

This unusual presentation of melasma-like hyperpigmentation in association with PA should alert the physician to the possibility of nutrition deficiencies in case of pigmentary changes.

Statement of Authorship

L. Tayem, M. Jones, N. Litaiem, and F. Zeglaoui all contributed to the acquisition, analysis, and interpretation of the data; L. Tayem and M. Jones contributed to the first draft of the manuscript; N. Litaiem critically revised the manuscript; and F. Zeglaoui critically revised the manuscript and gave final approval. All authors read and approved the final manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work.

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Transition to a Tube Feeding Formula With Real Food Ingredients in Pediatric Patients With Intestinal Failure

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Abstract

Due to concerns related primarily to allergic response and malabsorption, enteral nutrition therapy has traditionally relied on the use of elemental formulas in children with intestinal failure (IF). Blended food diets via a gastrostomy tube have been reported to improve feeding tolerance in pediatric populations receiving long-term enteral nutrition therapy. Complex macronutrients have been shown to stimulate intestinal adaptation in animal models. We report on our experience in children with IF who had an overall improvement in stool output when transitioned from an elemental formula to a tube feeding formula with real food ingredients (TFRF). Data were collected in a retrospective chart review of children with IF, >1 year of age, who were receiving enteral nutrition via continuous infusion, bolus feeding, or both. Indications for the TFRF trial were diarrhea or inconsistent stooling patterns. Ten children with a mean small bowel length of 48.3 cm were trialed on TFRF. Nine of 10 (90%) children tolerated the transition to 100% TFRF, of which 7 of 9 (78%) had their entire colon in continuity. The average age at successful transition was 29.2 months, and the average length of time to transition to 100% TFRF was 67.3 days. TFRF is well tolerated in children >1 year of age with IF; it also improves their stooling patterns. A commercially available TFRF is a cost-effective and nutritionally adequate means of providing nutrition to this patient population. (*Nutr Clin Pract*. 2017;32:277-281)

Keywords

intestinal failure; short bowel syndrome; enteral nutrition; pediatrics; blended food diet; gastrostomy; tube feeding formula

The metabolic and nutrition needs of patients with intestinal failure (IF) are complex, and they pose a dietary challenge as children age.[1] Breast milk and amino acid–based formulas have been shown to be effective in decreasing the duration of parenteral nutrition in infants with IF; therefore, they seem to be the recommended choice when enteral feeding is initiated.[2-4] Multiple choices of nutritionally complete, age-appropriate formulas are available for children who require enteral nutrition support after 1 year of age; however, no consensus exists to date on which formula is best, and formula choice appears to be based on clinical experience.[5] Each available formula has potential limitations for the IF patient population >1 year of age. Elemental formulas are expensive, have high osmolality and poor taste, and lack complex nutrients, including fiber. Other formulas considered after age 1 for this patient population typically include peptide-based formulas or intact protein formulas, of which the latter can contain excess sugars leading to malabsorption and diarrhea. Interest is growing in the use of blended foods or pureed foods for management of feeding difficulties, reflux, and improved bowel function in the pediatric population.[6,7] Petunick et al[6] recently reported on the high parental satisfaction they observed with feeding a pureed-by-gastrostomy-tube diet in place of commercially available formula to a group of pediatric patients following Nissen fundoplication. Similar to our experience, families inquired about the use of blended real foods because of the perceived health benefits. Parents seem to want to avoid feeding their children processed ingredients, such as refined sugars, which they may feel contribute to feeding intolerance.[7] Blended food diets appeal to the health-conscious consumer in both pediatric and adult populations. Hurt et al conducted a cross-sectional study to determine the use of blenderized tube feeding (BTF) prevalence in an adult home enteral nutrition population. They found that the most common reasons for using BTF were as follows: better tolerance, perception as "more natural," and preference for eating the same nutrition as

Update: After publication of this article OnlineFirst, the authors learned that Nestlé Health Sciences has changed the product formulation of Compleat Pediatric 1.0 by adding ingredients such as FOS, pea protein, and inulin that were not part of the product during our review.

While the authors stand by their results with the original Compleat Pediatric 1.0, these results may not be reproducible with the new product formulation.

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Table 1. Individual Outcomes, Diagnoses, and Surgical History of 10 Patients With Intestinal Failure Who Transitioned to Tube Feeding Formula With Real Food Ingredients.

Patient	Days[a]	Age,[b] mo	Sex	GA, wk	Diagnosis	Length of Bowel, cm	Ileocecal Valve	Colon	Formula[c]	Dairy[d]	Weight Gain, kg[e]
1	17	12	F	36	Gastroschisis	All	Y	All	Elemental	Y	1.86
2	18	16	F	37	Gastroschisis/malrotation	38	N	Partial	Elemental	Y	4.8
3	322	32	F	25	Necrotizing enterocolitis	47	Y	Partial	Elemental	N	2.6
4	17	30	M	24	Necrotizing enterocolitis	63	Y	All	Elemental	N	2.5
5	Failed	18	F	24	Necrotizing enterocolitis	All	N	Partial	Elemental	N	N/A
6	98	23	F	38	Atresia/malrotation	All	Y	All	Elemental	N	1.3
7	2	30	M	28	Necrotizing enterocolitis	34	Y	All	Hydrolysate	Y	2.6
8	16	18	F	26	Necrotizing enterocolitis	52	Y	All	Elemental	N	3.66
9	26	30	F	24	Necrotizing enterocolitis	46	Y	All	Elemental	Y	3
10	90	72	F	33	Atresia/malrotation	45	Y	All	Hydrolysate	Y	1

F, female; GA, gestational age; M, male; N, no; N/A, not applicable; Y, yes.
[a]Total days to transition to tube feeding formula with real food ingredients.
[b]Age at transition.
[c]What the patient transitioned to from tube feeding formula with real food ingredients.
[d]Previous exposure to dairy.
[e]Weight gain 1 year following transition to tube feeding formula with real food ingredients.

other family members at meal time. Patients receiving the BTF also self-reported less diarrhea, constipation, nausea, bloating, and vomiting as compared with commercial enteral nutrition.[8]

Barriers to providing a blended food diet exist in the clinical setting. Teaching families how to prepare a blended food diet with jarred baby foods or from table foods reconstituted to puree consistency with a high-performance blender is time-consuming and requires in-depth planning and close monitoring by a registered dietitian.[7] There are additional safety concerns regarding the use of blended foods. The inability to assess crude nutrient intake from day to day in a patient population that inherently experiences malabsorption potentially puts patients at high nutrition risk for macronutrient and micronutrient deficiencies.[8] Noncompliance with daily vitamin and mineral supplementation could be worrisome for the clinician prescribing the diet, as pediatric patients with IF are at risk for micronutrient deficiency.[9] Additionally, there is a risk for food particles obstructing the gastrostomy tube, as well as microbial contamination.[10]

We report on the tolerability and improved stooling pattern in patients with IF who were transitioned to a commercially prepared, milk-based tube feeding formula with real food ingredients (TFRF).

Methods

Patients

Twenty-one patient records of children >1 year of age, who were followed by the intestinal rehabilitation team at Connecticut Children's Medical Center for IF from January 2012 to October 2014, were retrospectively reviewed with approval from the Connecticut Children's Medical Center Institutional Review Board. Children were included if they had congenital or acquired severe gastrointestinal disease and required parenteral nutrition for >60 days. We identified 10 patients who, after 1 year of age, presented with symptoms of diarrhea or inconsistent stooling patterns and were started on TFRF (Compleat Pediatric 1.0; Nestlé Health Science, Florham Park, NJ), All children were receiving continuous enteral nutrition infusion or a combination of continuous and bolus feedings. All children were weaned from parenteral nutrition. Mean age to wean from parenteral nutrition was 11.4 months (median, 9 months). Stool variables reported by parents included stool consistency, frequency, and volume. Consistency was defined as liquid, loose, semiformed, or formed; frequency was defined as the total number of stools in a 24-hour period; and volume was defined as small or large.

Diet Transition

The decision to trial a TFRF was determined by the dietitian, physician, and family on the basis of the child's symptoms. Prior to the transition, all patients were maintained on elemental or semielemental formula prepared to 20–24 calories per ounce. The volume was replaced 1:1 with TFRF, which is a 30-calorie/ounce formula containing a mixture of whole food–pureed ingredients, including chicken, green bean, pea, peach, and cranberry juice. Previous exposure to dairy, from either a whey-based protein hydrolysate formula or table food, was reviewed with the family in detail by the dietitian. Patients were started on TFRF at 25% of total enteral volume, with the remaining volume provided as the prescribed elemental or semielemental formula they were receiving. For example, if the patient was receiving 600 mL of enteral feeds per day, 150 mL was provided by TFRF, and 450 mL was given as elemental. The ratio of TFRF was advanced to 50%, 75%, and then transitioned to 100% TFRF over a range of time, depending on each individual's level of tolerance (measured in total days to transition to TFRF; see Table 1). Storage

safety of the TFRF and appropriate hang times for nocturnal infusions were reviewed. All opened Tetra Pak packages of TFRF were to be tightly covered, refrigerated, and used within 24 hours. Formula hang time is defined as the length of time that the formula is safe to be delivered to the patient once it is decanted. Compleat Pediatric meets the American Society for Parenteral and Enteral Nutrition's enteral nutrition practice recommendations for a commercially sterile liquid formula decanted from a carton; therefore, the recommended hang time was 8 hours.[11] Tolerance and details of stooling patterns were recorded at each return visit to the intestinal rehabilitation clinic or via weekly telephone consultation with the primary caregiver. Descriptions of feeding intolerance included a report of the following variables: stool consistency and volume (number of stools in a 24-hour period), abdominal distension, gas, vomiting, and overall comfort level of the patient. The ratio of TFRF was advanced per individual patient tolerance.

Results

Ten children with a mean small bowel length of 48.3 cm (range: 34.0–64.0 cm, median: 46.5 cm) were transitioned to TFRF via continuous and/or bolus infusion. Six of 10 children had history of necrotizing enterocolitis (60%); 2 of 10, gastroschisis (20%); and 2 of 10, intestinal atresias (20%). Nine children had a gastrostomy tube in place, and 1 had a surgical jejunostomy tube in place. Nine of 10 (90%) children tolerated the transition to 100% TFRF, of which 7 of 9 (78%) had their entire colons in continuity and the remainder had part of their colons in continuity. The child who failed transition received TFRF via a gastrostomy tube and subsequently had worsening diarrhea and extensive perianal skin breakdown during the trial. This patient had only one-third of her colon remaining and no ileocecal valve (Table 1). The average age at successful transition was 29.2 months (range: 12–72, median: 30 months). Average length of time to transition to 100% TFRF was 67.3 days (range: 2–322, median: 18). Parents of children with diarrhea (n = 7) as a primary symptom reported the stool changing from "loose, liquid, large" to "semiformed" or "formed," as well as a decrease in the total number of stools, changing from >3 per day (range: 3–8, mean/median: 5) to <3 per day (range: every other day to 2 per day). Parents of children with difficulty stooling (n = 2) as a primary symptom reported an overall improvement in stool frequency, changing from 1–3 times weekly with straining to once daily or every other day. Improvement in stool consistency was reported as changing from "large" and/or "hard" to "soft" and/or "formed."

Supplemental fibers (Nutrisource, Nestlé Health Sciences; Sure-Jell Certo) that had been prescribed prior to the transition to TFRF and used in conjunction with elemental formulas were successfully discontinued in all 9 children. Daily doses of stool softener were successfully eliminated for children experiencing difficulty with stooling; however, periodic dosing was occasionally required. All children transitioned to TFRF maintained age-appropriate weight gain at 6 months and 1 year following the transition to TFRF (Table 1). Of the 10 children, 5 had previous exposure to dairy from either complementary foods (eg, yogurt or cheese) or whey-based partially hydrolyzed formula (Peptamen Jr 1.0; Nestlé Health Science). The patient who failed transition to TFRF was also unable to include any dairy into her diet due to excessive stool output and perianal skin breakdown.

Discussion

Long-term dietary management of patients with IF can be challenging and complicated for families and clinicians alike. Malabsorption and diarrhea can lead to excessive electrolyte losses, poor weight gain, and painful perianal skin breakdown and impede progression toward toilet training, an important milestone for families. In our review, we found that diarrhea and inconsistent stooling improved in 90% of the children who transitioned to TFRF. Self-reported parental satisfaction with TFRF was excellent. Remarkably, parents mostly reported that stool consistency and frequency improved within 2–3 days of changing to 100% TFRF. The effect appeared to be sustained, as families continued to report satisfaction with stooling patterns at follow-up clinic visits throughout the first year following the transition to TFRF.

Interest in the use of real food via a gastrostomy tube to improve the overall health of children is increasing among the general public as well as clinicians. As discussed earlier, Pentiuk et al[6] showed marked improvement in gagging and retching among a population of pediatric patients who underwent fundoplication when fed a pureed-by-gastrostomy-tube diet. In their study, feeds were composed of strained baby foods, including meat, fruits, and vegetables. Yogurt and oil was used in addition to 2 oz of milk or commercial formula; 52% of children were reported to have a reduction in gagging and retching by 76%–100%. There was also high parental satisfaction with the use of blended foods.

Elemental formulas can be continued past 1 year of age to provide nutrition via gastrostomy tube, to minimize potential risks associated with malabsorption. Furthermore, toddlers with IF who are receiving enteral nutrition support may not be eating a variety of complementary foods due to the oral aversions observed in this patient population.[3] Last, in our experience, many parents of patients with IF have expressed concerns with introducing new foods, particularly fruits, as they often are fearful of increasing episodes of diarrhea. This theoretical combination of prolonged elemental feedings and minimal oral food intake puts this patient population at high risk for a diet lacking complex nutrients, potentially hindering optimal intestinal adaptation.

The use of TFRF may have improved the stooling patterns in this patient population for several reasons, including incorporating complex whole food nutrients, varying the fiber type and amount, and altering the type of fat (Table 2). Increased nutrient complexity is reported to be associated with superior adaptation in animal models, likely due to the increased digestive activity

Table 2. Nutrient Composition of Tube Feeding Formula With Real Food Ingredients: Compleat Pediatric.[a]

Nutrition Information	Amount per 250 mL
Calories	250 kcal
Total fat (34%)	9.7 g
MCT:LCT ratio: 20:80	
n6:n3 ratio: 3.7:1	
Sodium	190 mg
Potassium	410 mg
Total carbohydrate (51%)	33 g
Dietary fiber	1.7 g
Fiber content (source): 6.8 g/L (Nutrisource Fiber, fruits, and vegetables)	
Protein (15%)	9.5 g
Protein source: chicken, sodium caseinate, pea puree	
NPC:N ratio: 142:1	

LCT, long-chain triglycerides; MCT, medium-chain triglycerides; N, nitrogen; n3, ω-3; n6, ω-6; NPC, nonprotein calorie.
[a]Nestlé Health Sciences (Florham Park, NJ). Reprinted with permission from Nestlé Health Sciences.

required for nutrient absorption.[12] Additionally, whole plant foods, fiber, and polyphenols have been shown to potentially modify the microbiota of the human gut.[13] The TFRF includes several plant-based carbohydrates that could help modify the gut microbiome, potentially leading to an overall improvement in carbohydrate and protein utilization and stool output.

The source of fiber in commercially available TFRF (Compleat Pediatric 1.0; Nestlé Health Sciences) is a combination of partially hydrolyzed guar gum plus natural fibers from fruits and vegetables (Table 2). Hydrolyzed guar gum is a fiber powder commonly used to supplement elemental feeds in this patient population. It is possible that patients benefited from not only a net increase in total dietary fiber consumption but also the variety of carbohydrate polymers naturally occurring in the foods contained in the formula. The 10 patients under review were inconsistently receiving the prescribed dose of fiber supplementation or none at all, which contributed <6.8 g/L of total fiber per day as provided by TFRF. That patients with a larger portion of their colons intact were more likely to transition to TFRF may have been due to a net increase in the production of short-chain fatty acids in the colon by bacterial fermentation of carbohydrates, possibly leading to increased fluid absorption and therefore improved stooling patterns.[1] Animal studies have suggested that long-chain fats can stimulate intestinal adaptation.[14] The primary source of fat in TFRF is long-chain triglycerides (80%), whereas elemental formulas contain only 66% of fat as long-chain fat.

An additional benefit to the use of TFRF is the cost when compared with the cost of amino acid–based formulas. The cost of elemental formula can be burdensome for families, especially if insurance denies coverage. Total cost savings with the transition to TFRF is $11 per 1000 calories. The average cost for elemental formula per month plus supplemental fiber amounts to approximately $710 per month versus $375 per month with TFRF. To supply families with TFRF during the transition, prescriptions for TFRF were given as a 2-week trial and refilled as tolerance was established. Families no longer needed to prepare powdered formula daily with additives such as fiber. The hermetically sealed aseptic tetra pack of TFRF was reported to make travel easier in regard to "feeding on the go" and storage safety. All parents reported that they spent less time changing clothing and bedding, as stool consistency and volume improved on TFRF. Elimination of these added tasks and the ability to work on toilet training resulted in high parental satisfaction.

One of the potential limitations to using TFRF is palatability. TFRF is marketed as a tube feeding formula and is generally not consumed orally. For our patients, we used lactose-free milk (4% fat) offered by mouth in place of commercially available oral supplements to reduce total sugar intake, avoid excessive osmotic load, and lower the incidence of dental caries. By using lactose-free milk, we also eliminated the need for >1 enteral formula (1 for tube feeds and 1 to drink), which added to cost savings for families. Limitations to these results include the retrospective design of the study and the reliance on parental report of stooling patterns, as all children initiated the TFRF in the outpatient setting. However, demonstration of age-appropriate weight gain and the improvement in the consistency of stool, as visible at clinic appointments for some patients, supported the reports by most parents. The age at which TFRF was introduced to each patient was not standardized among this group, which resulted in the age at successful transition to TFRF to vary widely (12–72 months). This was due in part to the heterogeneity of this patient population. Some children were not deemed clinically ready to be advanced to TFRF based on symptoms at the time of each outpatient clinic visit (high stool outputs, intercurrent illnesses, social reasons, and hospitalizations). We are now screening every patient with IF at 1 year of age who is receiving enteral feeds for the potential to initiate TFRF.

Benefits of a commercially available TFRF exist as compared with a homemade blended food diet for the IF population. Many pediatric patients with IF are on continuous infusions of gastrostomy tube feeds, and homemade blended formula is not recommended for feedings that will last >2 hours due to potential for bacterial contamination.[15] TFRF is a sterilized product that is aseptically packaged and hermetically sealed for safety. This is especially significant in a patient population with compromised bowel integrity, and it complies with the American Society for Parenteral and Enteral Nutrition's enteral nutrition practice recommendations, which state that, when nutritionally appropriate, sterile liquid formulas should replace powdered products due to sterility issues.[11]

Conclusion

In our group of patients with IF, we observed an improvement in stooling patterns in 90% of patients transitioned to TFRF. Based on our experience, transition at 1 year of age from elemental formula to TFRF is well tolerated in pediatric patients with IF who are experiencing diarrhea or inconsistent stooling patterns and who have 30–40 cm of small bowel, an intact ileocecal valve, and at least two-thirds of their colons in continuity.

Statement of Authorship

K. Samela, K. Emerick, and Z. H. Davidovics contributed to the conception and design of the research and drafted the manuscript. All authors contributed to acquisition, analysis, or interpretation of the data; revised the manuscript; agree to be fully accountable for ensuring the integrity and accuracy of the work; and read and approved the final manuscript.

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Detecting Enteral Nutrition Residues and Microorganism Proliferation in Feeding Tubes via Real-Time Imaging

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Abstract

Background: Enteral nutrition (EN) residues that persist in feeding tubes provide substrates for microorganisms to proliferate and occlude the tubes. Visible EN residues in tubes are easily identified, but smaller residues can persist. We developed a new imaging technique to visualize EN residues and proliferation of microorganisms in feeding tubes. *Materials and Methods:* (1) Feeding tubes containing EN labeled with fluorescent dye and either with or without various types or amounts of thickeners were flushed once with water and then seeded with *Pseudomonas aeruginosa* Xen05 with recombinant luciferase DNA. (2) Because EN fluoresces intrinsically, EN in the feeding tubes without fluorescent dye was repeatedly flushed until the intrinsic fluorescence levels reached background levels. Fluorescent images of EN residues and bioluminescent images of microorganisms were acquired via an optical imaging system. *Results:* (1) Fluorescence images showed that the amount of EN residues increased at various sites in tubes depending on EN viscosity and the thickening agent, and bioluminescence images showed that microorganism proliferation was associated with a commensurate increase in EN residues. (2) The intrinsic fluorescence of EN also enabled the detection of EN residues in tubes even in the absence of fluorescence dye. Higher EN viscosity required more flushes to reach undetectable levels. *Conclusion:* EN residues and microorganism proliferation in enteral feeding tubes were detected on fluorescence and bioluminescence images, respectively. This simplified approach allowed the real-time visualization of EN residues and microorganisms in feeding tubes. (*Nutr Clin Pract*. 2017;32:282-287)

Keywords

enteral nutrition; biofilms; feeding tubes; bacteria; fluorescence; bioluminescence

Enteral nutrition (EN) residues persisting in enteral feeding systems not only facilitate bacterial contamination but also obstruct the systems. As EN is supplied prepackaged in sealed bags, the risk of bacterial contamination originating from containers is relatively lower than the risk of contamination from EN feeding tubes.[1,2] Such tubes are repeatedly reused in medical practice, and they are flushed and/or sterilized as required.[3] The interiors of indwelling tubes that are used for the long-term management of enteral feeding are difficult to dry and thus become susceptible to bacterial contamination.[4,5] In contrast, the flow of even highly viscous EN can be increased through the use of wider-bore tubes. The administration of high-viscosity EN to prevent gastroesophageal reflux seems paradoxical,[6,7] because it could produce an environment that is conductive to bacterial contamination due to an increase in EN residues remaining inside EN tubes.[8] Once EN is exposed to contamination, bacteria rapidly proliferate, and infusion with contaminated EN can cause sepsis, fever, and gastrointestinal dysfunction.[9,10] For instance, patients given contaminated EN developed gastrointestinal symptoms within 24 hours 10.5 times more frequently than those given noncontaminated EN.[9] The infusion of EN contaminated with $>10^3$ colony-forming units per milliliter of gram-negative bacteria causes severe infection.[11] Furthermore, the growth of bacteria lowers the pH inside EN tubes, leading to the denaturation of compounded protein in EN that leads to curd production and tube occlusion.[12]

Flushing the tube with 20–100 mL of water before and after feeding will reduce the possibility of tube occulusion.[13,14] However, 100-mL water flushing is thought to be too much and may lead to fullness and thus intolerance of feeding. Instead, flushing the tube with 20–30 mL of water before and each feeding and visually monitoring EN residues responsible for bacterial contamination and tube occlusion have gained wide acceptance in the routine clinical setting. However, these practices cannot detect microscopic amounts of residues and those diluted with the water used for flushing. This might

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Conflicts of interest: All authors are employees of Otsuka Pharmaceutical Factory, Inc, and have no other conflicts to declare. Hine Jelly and Hine, as used in the text, are the products of Otsuka Pharmaceutical Factory, Inc.

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explain why infectious complications arising from handling EN tubes do not significantly decline. Due to these issues, the development of EN products that do not remain attached to enteral tubes and that help to suppress bacterial proliferation remains clinically important.

The balance of EN remaining after flushing must be weighed to quantify EN residues inside EN tubes. However, the amount of water remaining in flushed tubes cannot be ignored. The dry weight of EN inside tubes comprises residues from administered EN. Additionally, the assessment of bacterial contamination requires the incubation of tube contents and bacterial counts. These approaches are complex, time-consuming, and not suitable for routine medical practice.

Fluorescence and bioluminescence imaging technology has become more widespread because it enables real-time and spatial imaging of target substances in a nondestructive and noncontact manner.[15,16] We speculated that this technology could visualize relatively small amounts of EN residues inside tubes, as well as bacterial proliferation and biofilm formation on the inside attributed to the residues. We initially hypothesized that fluorescence imaging of EN labeled with fluorescent dye would reveal EN residues invisible to the naked eye and that bioluminescence imaging would show that the residues affect the proliferation of the model bacterium, *Pseudomonas aeruginosa*. In addition, we hypothesized that the intrinsic fluorescence of EN enables the detection of EN residues inside tubes even in the absence of a dye that emits fluorescence. We suspect that these imaging techniques could demonstrate the effects of repeated flushing upon EN residues with different degrees of viscosity as well as amounts and types of thickening agents.

Materials and Methods

EN With Thickening Agents

The viscosity of the Hine formulation (Otsuka Pharmaceutical Factory, Inc, Naruto, Japan) was increased with different concentrations of a xanthan gum–based thickener: EN-XG (L), (M), and (H) at 3.5, 4.5, and 6 g/dL, respectively. Hine jelly (EN-A) is representative of viscous EN, with an agar-based thickener. Hine (the default EN in this experiment) is a standard EN formula (1 kcal/mL) that does not contain these fibers and was therefore used as a negative control without additives. Each EN was mixed beforehand with the fluorescent dye 0.01% indocyanine green (Wako Pure Chemical Industries, Ltd., Osaka, Japan) to detect EN in feeding tubes. The viscosity levels of EN, EN-A, EN-XG (L), EN-XG (M), and EN-XG (H) measured at 12 rpm, 25°C, with a Brookfield viscometer were as follows: 10, 6000, 1350, 4530, and 9300 mPA·s, respectively.

Fluorescence and Bioluminescence Imaging of EN Residues and Bacterial Proliferation

The silicon catheters of gas barrier gastrostomy tubes (length, 255 mm; inside diameter, 8 mm) were filled with an EN and left for 5 min. The EN then passed through the tubes in free fall, and the tubes were washed once for 10 seconds with 30 mL of distilled sterile water, which is within the recommended range for flushing in medical practice.[17] The distribution of fluorescence inside flushed tubes was monitored with the IVIS Spectrum live imaging system (Perkin Elmer Inc, Waltham, MA) with excitation and emission at 745 and 840 nm, respectively. The flushed tubes were loaded with 1×10^6 colony-forming units per milliliter of the bioluminescent bacterium[18] *P aeruginosa* Xen05 (Caliper Life Sciences, Hopkinton, MA) that had been incubated at 35°C in Mueller-Hinton Broth medium overnight and resuspended in sterile distilled water. The tubes were sealed and cultured at 35°C for 4, 8, and 24 hours after being spiked with *P aeruginosa*; then, the distribution of bioluminescence inside the tubes was photographed in real time with the IVIS. All tubes that were incubated for 24 hours were washed twice with 30 mL of distilled sterilized water for 10 seconds to remove floating bacteria and allow bioluminescence imaging of adherent bacteria. Regions of interest were placed over the catheter at locations excluding the funnel and balloon to determine fluorescent and bioluminescent signals. Photon emission in regions of interest was standardized in terms of exposure duration, binning, and f/stop.

Imaging Intrinsic Fluorescence of EN Residues

By changing excitation and emission wavelengths, we similarly detected EN, EN-A, EN-XG (L), EN-XG (M), and EN-XG (H) residues after several washes with water in the absence of the fluorescent dye. Briefly, all types of EN were allowed to free-fall through 20F silicon tubes (length, 30 cm) for 5 minutes. The tubes were flushed with 30 mL of water for 10 seconds, and the intrinsic fluorescence of EN was visualized at excitation and emission wavelengths of 430 and 500 nm, respectively. The tubes were then repeatedly flushed until the emitted fluorescence reached <10 % of the loaded amount. Regions of interest were placed around the catheters to determine photon signals from the tubes. Interactions between EN (variate) and the number of washes (covariate) were tested by covariance analysis.

Results

Fluorescence and Bioluminescence Imaging of EN Residues and Bacterial Proliferation

Figure 1 shows the distribution of (1) fluorescence inside tubes containing EN with various viscosities and thickening agents after a single wash and (2) bioluminescence emitted at 4, 8, and 24 hours after the tubes were spiked with *P aeruginosa* Xen05. Figure 1D–F shows that a single wash resulted in more residual fluorescence intensity of EN-XG, with a xanthan gum–based thickener. The bioluminescence intensity of the bacteria inside tubes containing EN-XG also increased in parallel with the residual fluorescence (Figure 2). The amounts of fluorescence residues

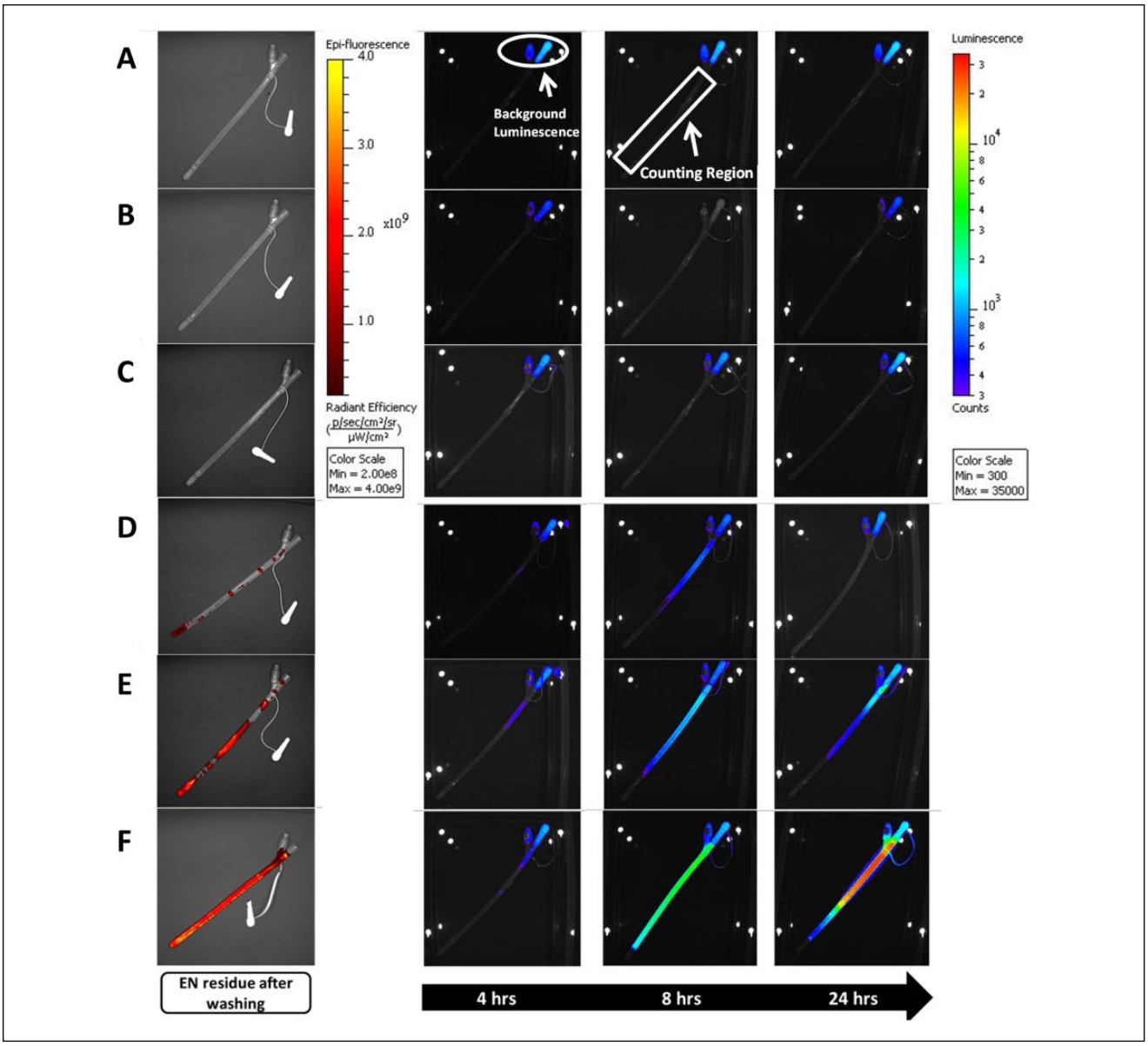

Figure 1. Representative images of enteral nutrition (EN) residues and proliferation of bioluminescent bacteria in percutaneous endoscopic gastrostomy tubes: (A) tubes without treatment; (B) tubes containing Hine formulation enteral nutrition; (C) Hine jelly; (D–F) Hine formulation enteral nutrition with xanthan gum–based thickener at 3.5, 4.5, and 6 g/dL, respectively.

left by EN-A, with an agar-based thickener, and EN without a thickener were similar, even though the viscosity of EN-A was between that of EN-XG (M) and EN-XG (H). Furthermore, biofilm formed inside tubes containing EN-XG (M) and EN-XG (H) at 24 hours after spiking with bacteria (Figure 3).

Intrinsic Fluorescence Imaging of EN Residues

Excitation of ENs at a wavelength of 430 nm results in the emission of various amounts of fluorescence (Figure 4). In addition, EN residues in tubes were detected per their intrinsic fluorescence (Figure 5). Residues of EN and EN-A fell below the detectable limit after a single wash. In contrast, significantly more washes were required to remove EN-XG due to increased viscosity (Figure 6).

Discussion

Accumulating EN residues inside feeding tubes create an environment suitable for bacterial growth and tube occlusion. Fluorescence and bioluminescence imaging allowed the detection of invisible EN residues as well as the growth of a bioluminescent bacterium and biofilm formation inside tubes.

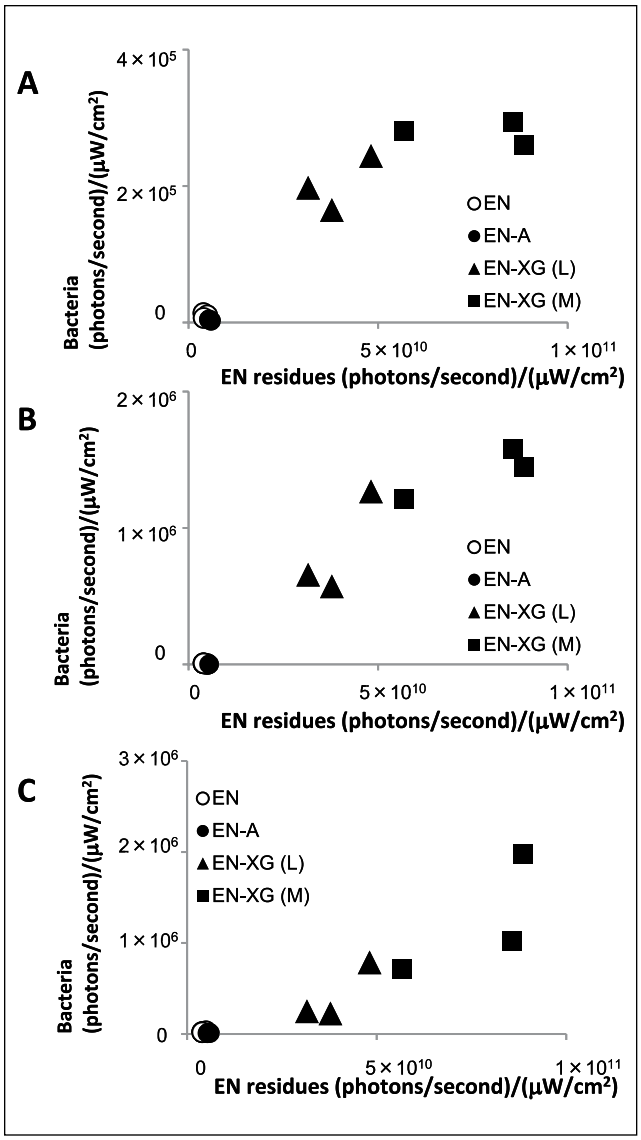

Figure 2. Regression analysis of enteral nutrition residue vs proliferating bioluminescent bacteria in tubes: (A–C) correlation coefficients of 0.93, 0.97, and 0.92 at 4, 8, and 24 hours, respectively. EN, Hine formulation enteral nutrition; EN-A, Hine jelly; EN-XG (L) and (M), Hine formulation enteral nutrition with xanthan gum–based thickener at 3.5 and 4.5 g/dL, respectively.

Fluorescence imaging can identify and locate a target of interest in a nondestructive and noncontact manner. This is the first study to visualize EN residues remaining inside feeding tubes via fluorescence imaging rather than visual assessment or weighing tubes. Concentrated EN residues can easily be visualized during free fall through the tubes, but EN residues diluted by several washes with water are too small to see with the naked eye. We found that the amount of EN residues remaining inside tubes increases with higher viscosity, which is in line with the findings of a previous study showing that viscous EN frequently occludes tubes.[19,20] As bacteria proliferate in EN systems immediately after contamination, open-system EN should be administered within 8 hours.[21] The number of bacteria challenged was similar to the number found in EN prepared and administered in hospital or in the home.[21,22] Our methodology can be used for infection control where EN is administered. For example, formulations could be designed to suppress the adhesion of residues, or a new method of washing tubes could be considered.

The fluorescence reagent used in this study is not immediately available for clinical application, because it is not permitted as a food additive nor approved for this medical purpose. However, EN has intrinsic fluorescence that allows the detection of residues without the need for a fluorescent reagent. Foodstuffs comprise vitamins, amino acids, and natural trace components, each of which has a fluorescence peak wavelength and intensity. Therefore, using the same wavelengths for excitation and for emission revealed differences in the intensity of intrinsic fluorescence generated by each EN. In EN with similar compositions, the intrinsic fluorescence is also similar. As a result, it is easy to compare EN formulations with the same default levels. The amount of residues inside EN tubes increases as viscosity increases. Even though the viscosity did not significantly differ when compared with EN with xanthan gum–based thickener, the amount of residues remaining after washing viscous EN with agar-based thickener was similar to that of EN without a thickening agent. This finding suggests that thickening agents significantly alter the effect of washing EN tubes. Thickening agents are categorized into either agar, which promotes gelation, or gum, which increases viscosity by promoting sol synthesis. A gelled matrix resembles a solid more than a sol and maintains its shape against natural aeration or flushing water, implying that it can pass through an EN tube with minimal distortion due to air and water pressure. In contrast, a sol is highly elastic and easily distorted by these pressures. Water and air therefore pass through EN tubes leaving more solid residues inside.

Powdered EN is difficult to dissolve at relatively higher concentrations. For example, in terms of density (1.5 kcal/mL), the viscosity of the EN formulas based on raw materials identical to the EN used herein (1.0 kcal/mL) was 356 mPA·s. Furthermore, commercially available EN (1.0, 1.5, 2.0 kcal/mL) was more viscous at 1.0 kcal/mL when compared with others in which the viscosity was increased with various concentrations of thickeners.[23] Flushing tubes containing condensed EN and thickened EN at various energy densities might be very practical on a daily basis. Further investigation is warranted.

Flushing EN tubes is an effective measure to prevent tube occlusion. However, the type of EN affects the outcomes of simple flushing with water. Fluorescence imaging can be used

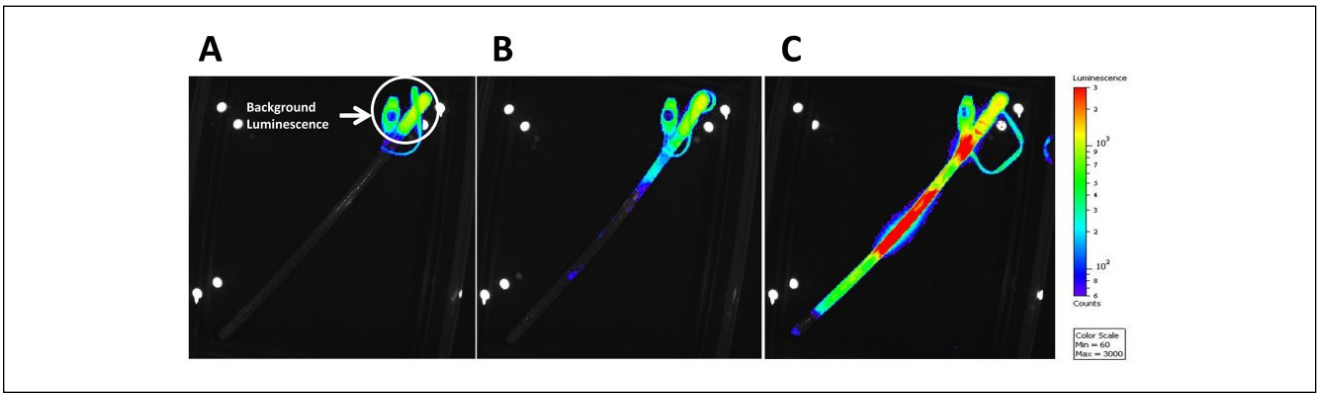

Figure 3. Representative images of biofilm-forming bioluminescence bacteria: (A–C) tubes containing Hine formulation enteral nutrition with xanthan gum–based thickener at 3.5, 4.5, and 6 g/dL, respectively.

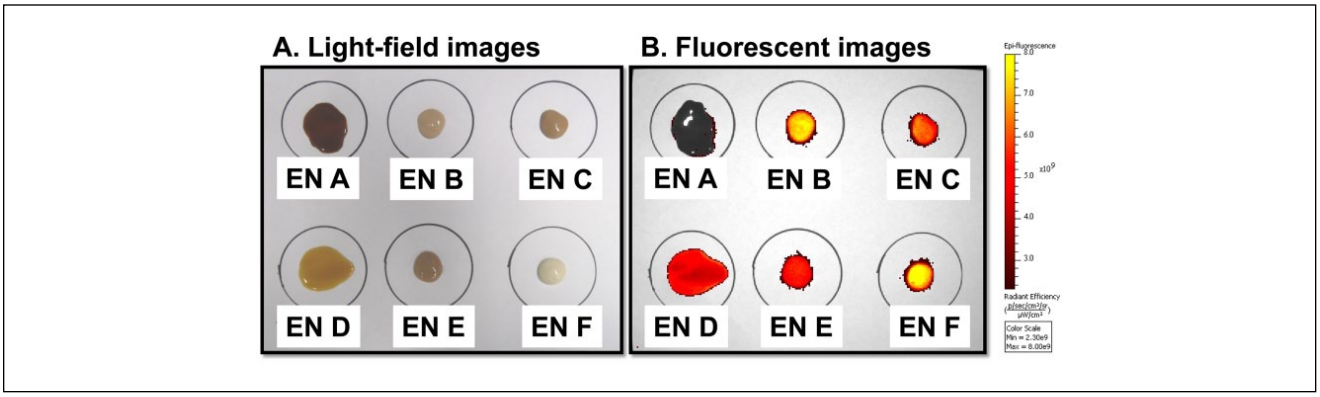

Figure 4. Intrinsic fluorescence emitted by enteral nutrition (EN). Commercially available EN (A–F) emits intrinsic fluorescence, and almost all EN samples emitted varying amounts of fluorescence when visualized at excitation and emission wavelengths of 430 and 500 nm, respectively.

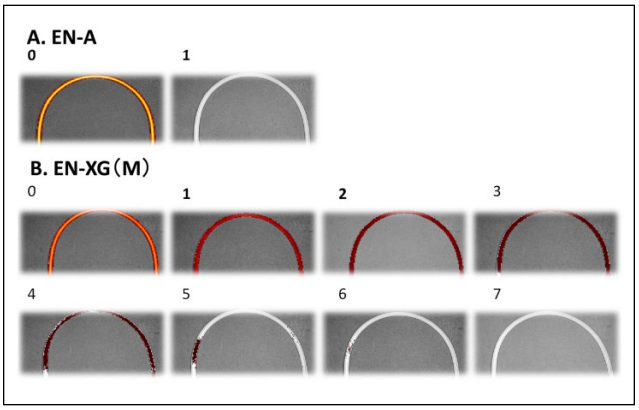

Figure 5. Representative images of enteral nutrition (EN) residues in tubes: (A) agar- and (B) xanthan gum–based semisolid EN formulations with similar viscosity were poured into percutaneous endoscopic gastrostomy tubes (0) that were subsequently washed with water. Intrinsic fluorescence was assessed by imaging (1–7). EN-A, Hine jelly; EN-XG (M), Hine formulation enteral nutrition with xanthan gum–based thickener at 4.5 g/dL.

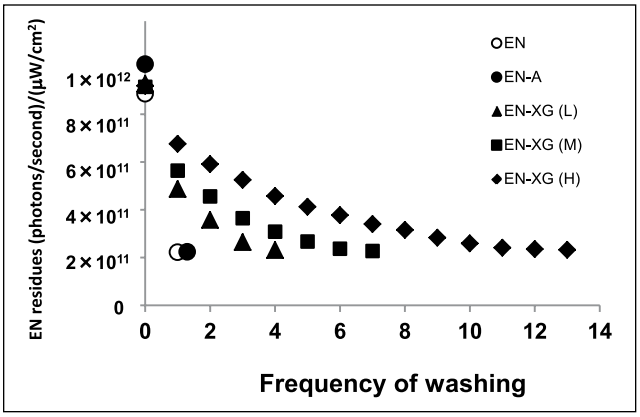

Figure 6. Effect of washing frequency on photon count inside tube. Same amounts of enteral nutrition (EN) were poured into tubes and then repeatedly washed until EN-associated photon counts reached background level. Slopes of photon-count curves significantly differed among EN ($P < .001$). EN, Hine formulation enteral nutrition; EN-A, Hine jelly; EN-XG (L), (M), and (H), Hine formulation enteral nutrition with xanthan gum–based thickener at 3.5, 4.5, and 6 g/dL, respectively.

as a high-throughput method of monitoring the efficiency of flushing tubes.

Statement of Authorship

I. Yamaoka and G. Ebisu contributed to the conception/design of the research; I. Yamaoka, T. Kagawa, and K. Mizugai contributed to the acquisition, analysis, and interpretation of the data; all authors drafted the manuscript; and I. Yamaoka critically revised manuscript. All authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Calorie and Protein Content of Parenteral Amino Acid Solutions

Parenteral nutrition (PN) therapy relies on an accurate calculation of the amounts of energy and protein in PN solutions. Yet current clinical nutrition textbooks, websites, and clinical reviews, including a comprehensive review of PN recently published in this journal,[1] err by asserting that the amino acids in PN solutions are equivalent to formed protein and hence provide 4.0 kcal/g. But aqueous free amino acids are not the same as formed protein, just as aqueous dextrose is not the same as starch. The hydrated status of aqueous dextrose reduces its calorie density from 4.0 to 3.4 kcal/g. Similarly, the hydrated status of the free amino acids in PN admixtures reduces their calorie density from 4.0 to 3.4 kcal/g and reduces the amount of protein substrate they provide by 17%. For example, 100 g of hydrated mixed amino acids in a PN solution provides 83 g of high-quality protein substrate.[2]

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Notice of Changes to Compleat Pediatric 1.0

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Samela K, Mokha J, Emerick K, Davidovics ZH. Transition to a tube feeding formula with real food ingredients in pediatric patients with intestinal failure [published online August 4, 2016]. *Nutr Clin Pract*. (Original DOI: 10.1177/0884533616661011)

After publication of this article OnlineFirst, the authors learned that Nestlé Health Sciences has changed the product formulation of Compleat Pediatric 1.0 by adding ingredients such as FOS, pea protein, and inulin that were not part of the product during our review.

While the authors stand by their results with the original Compleat Pediatric 1.0, these results may not be reproducible with the new product formulation. The article has been updated to include this acknowledgment.