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Enteral Feeding and Vasoactive Agents: Suggested Guidelines for Clinicians

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Many patients, including those hypotensive and vasopressor-dependent, may benefit from enteral nutrition. Much controversy exists in the area of enteral nutrition in the hemodynamically supported patient. Although enteral nutrition increases GI tract blood flow, it also increases intestinal metabolic demand, and perhaps, contributes to bowel necrosis in cases of impaired mesenteric perfusion. However, enteral nutrition may be undertaken with relative safety using a thorough, four-phase process to select appropriate patients with subsequent monitoring once enteral nutrition has begun. Experience-guided recommendations are provided for initiating enteral feeding in this patient population.

INTRODUCTION

Enteral nutrition (EN) is preferable to parenteral nutrition (PN) in critically ill patients due to a reduction in infectious complications, a decreased stress response with EN compared to PN, maintenance of enterocyte viability and growth, and the promotion of a strong gut mucosal barrier (1). However, considerable controversy exists regarding the role of EN in hypotensive, critically ill patients requiring vasopressor support. Although limited data suggest that initiation of enteral nutrients within 24–48 hours of critical illness may offer outcome benefits (2), there is a concern that beginning EN while a patient is hemodynamically tenuous may compromise splanchnic perfusion (1). Splanchnic perfusion can be reduced during sepsis and shock and restoration of volume status does not immediately resolve the alterations in perfusion (3). The actions of vasopressor medications are complex. In some, resolution of hypotension and increased cardiac output contributes to improved splanchnic perfu-

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Table 1
Phases for progressing with enteral nutrition in vasoactive agent-dependent patients

Phase I: Evaluate patient's pre-morbid medical and nutritional history
A. Patient risk factors predisposing to ischemic gut
   – Diabetes, cardiovascular disease
   – Medications
B. Potential benefit for individual
   – Poor pre-operative nutritional status
   – Higher metabolic demand in any post-surgical state

Phase II: Evaluate current physiologic status
A. Hemodynamic state with respect to vasoactive medication
   – Stable pressor requirement without transfusion requirement
   – Epinephrine ≤5 mcg/min, norepinephrine ≤5 mcg/min, dopamine ≤10 mcg/kg/min, vasopressin ≤0.04 units/min
   – MAP greater than 60 mm Hg
B. Other measures of physiologic stability
   – Close monitoring of vital signs every hour
   – Hourly urine output
   – Laboratory values: lactate, base deficit

Phase III: Logistics of initiating enteral nutrition
A. Route to be used to initiate enteral nutrition
   – PEG tube
   – Jejunostomy tube
   – Dobhoff-type oro- or nasogastric tube or other oro- or nasogastric sump-type tube
B. Type of nutritional supplement—standard-polymeric without fiber (<700 mOsm)

Phase IV: Post-initiation clinical monitoring
A. Serial abdominal exams every 8–12 hours
B. Gastric residual checks every 6 hours
C. Laboratory studies
   – Lactate, hemoglobin and hematocrit every 6–12 hours, WBC
D. Radiographic monitoring per clinician discretion
   – Serial abdominal x-ray
   – CT scan

sion; while in others, the pharmacology of some agents causes a decrease in perfusion (4,5). The effect of enteral nutrients on the mesentery is likewise twofold in that nutrients increase splanchnic blood flow, but the absorption of these nutrients also increases mucosal oxygen requirements (6,7).

One review has documented that the occurrence of mesenteric ischemia during EN is infrequent, from 0.3%–3.8% (8). However, case reports of patients receiving EN who subsequently developed non-occlusive mesenteric ischemia (NOMI) are sobering, and raise important questions:

- Are enteral feedings a cause, contributor, or innocent bystander in patients that have developed NOMI?
- Are there situations where concern for adequate mesenteric perfusion outweighs the potential benefits of providing EN?
- When does a wariness of EN contribute to a delay in providing nutrition that can result in malnutrition or inappropriate use of PN?

Unfortunately, there are no large randomized studies that answer these questions authoritatively. The limited data available oblige us to develop guidelines for providing EN to the critically ill patient based on information gleaned from case series, reviews, small short-term randomized studies, and bedside experience. This article aims to delineate practical recommendations for providing EN in critically ill patients to potentially avoid the accrual of large nutrition deficits or the complications from unnecessary PN.

FOUR-PHASED APPROACH

First, the practitioner considers a patient's relative risk for EN-related bowel complications. This evaluation includes a review of chronic conditions and pre-hospital health and medications, as certain conditions and medications may predispose the patient to NOMI. Second, a thoughtful analysis is performed of the patient's physiologic state while on vasopressors; stable low-dose pressor requirements in the face of hemodynamic stability without the need for transfusion, suggest a lower likelihood of NOMI. Third, once the benefits are determined to outweigh the risks of beginning EN, the type of nutrition formula should be carefully chosen. Enteral formulas with modest osmolality and minimal fiber may help minimize complications related to the feeding formula (6). Fourth, after the initiation of EN, monitoring must be done for clinical signs of distress. Serial abdominal exams, gastric residual checks and periodic

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radiographic imaging help ensure that early signs of gastrointestinal distress are detected and can be prevented from progressing to a critical stage.

Following are three case reports that illustrate the above four phased approach (Table 1). Each patient was deemed a reasonable candidate for EN in spite of their vasopressor requirements. Subsequent and vigilant monitoring were utilized to ensure that signs of significant gut dysfunction were identified early and intervened upon as necessary.

CASE REPORTS

Case #1

A 28-year-old male was diagnosed with a gastric tumor invading the duodenum and transverse colon. He had no history of cardiovascular disease, diabetes, or hypertension. He took no medications prior to admission. Based solely on his history, the patient was considered to be a relatively low risk for NOMI. Surgical intervention for the tumor included partial resection of his stomach, duodenum, and colon. A jejunostomy tube was placed, and EN was begun on post-operative day number one (POD1). His vasopressor requirement was minimal, consisting of epinephrine less than 5 mcg/min for two days. A one calorie per mL, fiber free polymeric formula was selected to avoid contributing to gas or distension. Serial abdominal exams were performed every eight hours and gastric residual checks every six hours. Findings of these two clinical parameters were unremarkable until post-operative day POD8. The patient at that point developed acidosis, abdominal pain, and distension and the EN was discontinued. He underwent reoperation for concern of an anastomotic breakdown, but was found instead to have 75 cm of necrotic bowel. A long segment of small bowel beginning just distal to the jejunostomy was resected. Upon examination, the resected bowel was found to have inspissated, or thickened and dried, EN.

Case #2

An 83-year-old male suffered worsening shortness of breath, fatigue, syncope, and weight loss consistent with cardiac cachexia. He was diagnosed with significant left main coronary artery disease with a low ejection fraction, severe aortic stenosis, mitral and tricuspid valve regurgitation. He underwent aortic and mitral valve replacement, tricuspid valve repair, and coronary artery bypass grafting. His past medical history was significant for: diabetes mellitus, hyperlipidemia, hypertension, peripheral vascular disease, and chronic obstructive pulmonary disease. Given the known vascular disease, the patient was considered a relatively high risk for NOMI. On post-operative day POD7, a percutaneous endoscopic gastrostomy (PEG) tube was placed as the patient was exhibiting severe dysphagia. The patient proved difficult to wean off epinephrine less than 5 mcg/min, and therefore remained on a low dose for several days after PEG placement. A 1.5 calorie/mL non-fiber formula was selected for him in order to minimize his overall fluid intake. The patient's serial abdominal exams and gastric residual checks were all within normal limits without concerning findings. He ultimately recovered from his surgery and was discharged to a skilled nursing facility.

Case #3

A 73-year-old male was diagnosed with severe mitral regurgitation and a left ventricular aneurysm with coronary artery disease. He initially underwent a mitral valve repair and left ventricular aneurysm repair. He represented to the emergency department on POD13 with complaints of dyspnea, tachypnea, and malaise, and was found to have mediastinitis and a large left pleural effusion. He underwent mediastinal washout with primary closure. His postoperative course was significant for severe methicillin resistant Staphylococcus aureus sepsis requiring multiple vasopressors including epinephrine less than 5 mcg/min, norepinephrine less than 5 mcg/min, milrinone at 0.375 mcg/kg/min and vasopressin 0.04 units/min. Past medical history was significant for hypertension, congestive heart failure, and chronic obstructive pulmonary disease. Based on this, he was classified as moderate to high risk for NOMI. Nonetheless, the patient was deemed a candidate for a trial of EN because of his high metabolic demand and preoperative malnutrition. A one calorie/mL, nonfiber, high protein formula was chosen via a 12Fr nasogastric

feeding tube. Serial abdominal exams and gastric residual checks were unremarkable throughout his hospital course, and he was discharged two weeks after his readmission.

DISCUSSION

These cases highlight several key points concerning EN in patients with the potential for gastrointestinal hypoperfusion. First, determining who is at risk for complications upon initiating EN is a complex task. Case #1 illustrates that even when there are no predisposing health conditions preoperatively, all patients, regardless of age, are at risk. The higher risk, older patients in cases #2 and #3, interestingly did not suffer the same complication as the patient in case #1. Nonetheless, NOMI has been shown to occur more frequently in elderly patients with cardiovascular disease, arrhythmias, and aortic insufficiency (8). Patients with DM and smokers are at particular risk, as are those who have previously suffered sepsis and major infections (8). Drugs promoting vasoconstriction, notably digoxin or alpha-adrenergic agonists (ie. phenylephrine), have been associated with NOMI (8). Physiologically, it appears that both hemodynamically stable and unstable patients on vasopressors are at risk for NOMI. The degree of risk may be difficult to determine based solely on the absolute dose of vasoactive agents. However, patients on increasing doses of pressors, or those with a high transfusion requirement, are generally deemed a higher risk. Patients receiving a stable pressor dose without transfusion requirement, although still at risk, appear to be in a state of relative hemodynamic equilibrium, such that, theoretically, their gut is adequately perfused.

Undoubtedly, some evidence suggests that EN could carry a greater risk of gut injury in hypotensive patients on vasopressors compared to normotensive patients (9). Indeed, mortality has been shown to be higher in NOMI related to EN than for other causes of mesenteric ischemia. Park, et al in 2002 reported that NOMI was associated with 80% mortality, whereas mesenteric embolism and thrombosis were associated with a mortality rate of 31% and 32% respectively (9).

Also important to consider is the degree to which EN itself increases the metabolic demand on the intestine and whether this predisposes the gut to ischemia. Nonocclusive bowel necrosis (NOBN) is the final common outcome for both severe gut microvascular ischemia and mucosal injury and inflammation (Figure 1). Metabolic stress increases the enterocyte energy demand in patients on vasopressor medications. The vasoconstrictive properties of pressors may cause a form of visceral hypoperfusion via sympathetic stimulation and other mechanisms, and the gut mucosa preferentially receives flow in this setting, leaving the submucosa, muscularis externa and serosa comparatively underperfused. Hypoperfusion is a precursor to intestinal necrosis and, either primarily or secondarily, may be linked to mucosal inflammation and injury, which may be worsened by subsequent reperfusion.

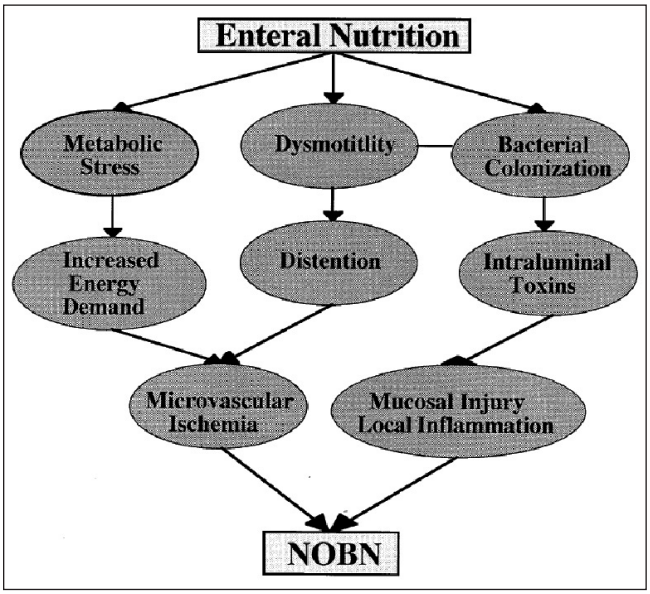

Figure 1. Non-occlusive bowel necrosis may result when enteral feeding leads to microvascular ischemia, mucosal injury, or local inflammation. Feeding the gut may cause some metabolic stress, dysmotility, and/or bacterial colonization that drive the aforementioned processes (13). Reproduced with permission from Elsevier Publishing.

Experimentally, some evidence supports the notion that EN has the potential to exacerbate gut ischemia. For example, a rat model of total occlusion of the superior mesenteric artery (SMA) demonstrated that the degree of gastrointestinal tract injury is significantly worse when metabolizable nutrients (fructose or glucose) are infused, as demonstrated by increases in tissue hypoxemia and mucosal permeability (7).

However, note that in this model of total SMA occlusion, there was no possibility for intestinal nutrients to stimulate increased mucosal blood flow (hyperemia), which would normally occur in the setting of EN. Clinical experience lends support to the pathophysiologic loss of intestinal function in hypotensive patients. Scaife, et al presented a case series of four burn patients who received continuous EN and presented with signs of an ileus or obstruction including abdominal distension and high nasogastric tube output (10). All four underwent surgery and two were found to have evidence of ischemia, albeit limited to a very small surface area (10). Even though this series of hypotensive patients did not appear to have transmural ischemia, other studies of non-normotensive patients found that ischemic complications are not infrequent (11).

Other animal studies suggest that EN may actually protect against bowel ischemia. Experimentally, some animal models indicate that the body's stress response is decreased after the initiation of EN. Kazamias, et al demonstrated an increased intestinal microcirculation and blood flow through the portal vein after dogs were begun on EN following a period of induced hypotension (6). The additional blood flow throughout the bowel was hypothesized to have had a protective effect for the dogs. The gut may also protect itself from an ischemic insult with its ability to enhance oxygen extraction by increasing the density of perfused capillaries (4).

Experimental data from the clinical setting has furthermore suggested that EN might lead to increased perfusion of the gastrointestinal tract. In a small study Revelly, et al measured changes in various physiologic parameters following the initiation of EN in patients with stable pressor requirements post-cardiovascular surgery (12). In nine postoperative patients on dobutamine alone or dobutamine and norepinephrine, cardiac index and stroke volume increased once EN was begun, mean arterial blood pressure and systemic vascular resistance decreased; none of these patients had clinical evidence of bowel ischemia (12).

FORMULA SELECTION—CONSIDERATIONS

With respect to the composition of the EN, most formulas are isotonic or only mildly hypertonic, and some contain fiber. Very hypertonic enteral solutions (>700 mOsm) or those containing fiber have been theorized to cause fluid to be drawn into the gut, predisposing the patient to decreased gastrointestinal tract perfusion as well as dysmotility that may ultimately set the stage for small bowel bacterial overgrowth (13). In a normotensive patient without signs of ileus, peristaltic movements could compensate for the fluid shift and promote gut emptying. Concomitantly, decreased capillary flow and ultimately, malperfusion would occur.

Furthermore, gut dysmotility promotes bacterial overgrowth. Toxins and metabolic derivatives such as D-lactate are released as byproducts of nutrient consumption by bacteria potentially leading to mucosal injury and local inflammation. D-lactate is not normally produced by human enzymatic pathways in significant amounts. In the clinical setting, unless otherwise specified, L-lactate is generally measured, and references to "lactate" without the stereoisomer preface refer to L-lactate. However, increased serum D-lactate, presumably produced via gastrointestinal flora, has been reported in intra-abdominal hypertension, and rapid decreases in D-lactate were correlated with improved survival in critically ill patients (14,15). Of note, formulas with high fiber may promote D-lactate production, as it has been hypothesized that bacteria preferentially use this substrate in their fermentation process (10). The use of fiber-containing

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Table 2
Clinical and radiographic signs and symptoms of nonocclusive bowel ischemia (NOMI) that should be continuously monitored for in patients begun on enteral feedings while on vasopressors

NOMI Signs and Symptoms
- Abdominal distension
- Ileus/Failure to have a bowel movement
- High oro- or nasogastric tube output
- Bloating/Cramps

NOMI Radiographic Signs
- Normal (25%–30%)
- Dilated, thickened loops
- Pneumatosis intestinalis
- Portal venous gas

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Table 3
Suggested Experience-Driven Guidelines for Clinicians

Appropriate candidates for EN
- Patients should be considered for EN with monitoring of GI tolerance if hemodynamically stable on:
  - Epinephrine 5 mcg/min or less, and/or,
  - Norepinephrine 5 mcg/min or less, and/or,
  - Dopamine 10 mcg/kg/min or less, and/or,
  - Vasopressin 0.04 units/min or less, and/or,
  - Milrinone 0.375 mcg/kg/min
- Thorough assessment completed of pre-morbid medical conditions and nutritional history

Inappropriate candidates for EN
- Any hemodynamically unstable patient
- Those with active bleeding requiring ongoing transfusions
- A mean arterial blood pressure consistently <60 mmHg
- An increasing requirement for vasoactive agents
- Those requiring massive fluid resuscitation
- A low flow state as a result of cardiac pump failure
- Known critical stenosis in the mesenteric vasculature
- Patients on:
  - Epinephrine >5 mcg/min
  - Norepinephrine >5 mcg/min
  - Dopamine >10 mcg/kg/min
  - Vasopressin >0.04 units/min
  - Milrinone >0.375 mcg/kg/min

formulas may result in GI toxins that could damage the mucosa and initiate or contribute to NOMI.

The case reports raise a final point with respect to the importance of monitoring for clinical signs of intestinal distress. Please refer to Table 2 for clinical and radiographic signs of non-occlusive bowel ischemia. Clinically, initial signs of EN intolerance may be nonspecific, and often the severity of the ischemia will dictate the symptoms. Patients able to communicate may describe bloating, cramps, and nausea. If unable to communicate, clinical signs can include abdominal distension, obstipation, constipation, ileus, increased or high nasogastric tube output. In this clinical setting, it is important to monitor for hypotensive or hypovolemic episodes, as these can potentially precede bowel ischemia. A more advanced, dire process presents with oliguria, an acute abdomen, or metabolic acidosis (8). Unfortunately, laboratory studies are often nonspecific, but may include leukocytosis, low bicarbonate, elevated lactic acid or electrolyte abnormalities, including hyperkalemia or hyperphosphatemia.

Radiographically, plain abdominal films may be normal 25%–30% of the time (8). Alternatively, abdominal x-rays may show signs of an ileus, including dilated loops of bowel, thickened loops, pneumatosis intestinalis, or potentially portal venous gas (8). A computed tomography (CT) scan would likely reveal a similar picture and might not provide much additional information except to allow the clinician to rule out other causes of abdominal pathology. An even more precipitous clinical deterioration can suggest long-segment bowel infarction or intestinal perforation. Serial abdominal exams no less frequent than every eight hours may be the best method to alert the clinician to the development of an acute abdomen; early involvement of a surgical team adept in managing these acute problems can be life-saving. From the moment the potential diagnosis of bowel infarction or perforation is suspected, a surgical consult is warranted.

Overall, adopting a methodical approach to EN management in patients on vasopressors will help optimize their care. Inappropriate candidates for EN include those with active bleeding requiring ongoing transfusions, a mean arterial blood pressure consistently less than 60 mmHg, or an increasing requirement for vasoactive agents (Table 3). Occasionally, "trophic" EN at a rate of 10–20 mL/hour is utilized in patients deemed to be at increased risk, with most of their nutritional needs provided parenterally. While the use of low-dose EN with supplemental PN may intuitively seem the best of both worlds, a retrospective review reported that trauma patients that received early supplementation with PN had increased nosocomial infections compared to patients that received EN alone (16). Randomized trials are necessary to establish if there are populations of critically ill patients at high-risk of GI compromise that may benefit from combined EN and PN support.

CONCLUSIONS

Although certain factors may predispose a patient to non-occlusive bowel ischemia, predicting who will suffer this complication is not clear cut. However,

because EN may benefit many critically ill patients on vasopressors, the risks and benefits should be weighed carefully for the individual patient. Consideration should be given to the existing nutritional status of the patient in the context of potential for harm from temporary withholding EN or initiating PN. Close monitoring of clinical signs and symptoms is vital in those begun on EN to intercept signs of gastrointestinal distress and NOMI. Critically ill patients requiring vasopressors will benefit in many respects from EN, and therefore each should be individually assessed and fed when the risk is acceptable. ■

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