Intestinal Absorption and Enteral Nutrition Support During Critical Illness

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Abstract

Malnutrition is common in critical illness and is related to gastrointestinal dysfunction. In critical illness, factors such as starvation, sepsis, reduced mesenteric blood flow, and medications can all contribute to altered gastrointestinal function. Adequate nutritional provision to critically ill is often impeded by delayed gastric emptying and feed intolerance, which is further aggravated by impaired small intestinal absorption of nutrients. In addition to factors that are important to luminal digestion such as gastrointestinal dysmotility and pancreatic insufficiency, recent data indicate that mucosal factors that mediate brush border enzymatic digestion, nutrient transporters, as well as mesenteric blood flow are also affected and adversely influenced by small intestinal nutrient absorption. Currently, timing of initiation of enteral nutrition appears to be important in intestinal absorption as early enteral feeding is associated with increased absorption of carbohydrate, improved mucosal integrity, and better clinical outcomes. This chapter will provide an overview of factors that are responsible for small intestinal malabsorption during critical illness and outline therapeutic strategies to manage and improve energy delivery, nutrient digestion, and intestinal absorption in these patients.

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List of Abbreviations

3-OMG	3-*O*-Methylglucose
AUC	Area under the curve
GLP1	Glucagon-like peptide 1
GLUT	Glucose transporter
ICU	Intensive care unit
LPS	Lipopolysaccharide
MMC	Migrating motor complex
PEPT1	Peptide transporter 1
PYY	Polypeptide YY
SGLT1	Sodium glucose transporter 1
SMA	Superior mesenteric artery
T1R	Type 1 taste receptor

Introduction

A combination of hypercatabolism and nutritional deprivation during critical illness culminates in a malnourished state, which is a risk factor for increased morbidity and mortality in these patients. The presence of malnutrition during critical illness has been shown to be associated with impaired immune function, increased risk of infectious complications, prolonged mechanical ventilation, and increased ICU and hospital length of stay (Giner et al. 1996; Fontes et al. 2013). Early provision of enteral nutrition to achieve daily energy requirement has, therefore, been advocated as one of the essential components of clinical care over the last 2 decades to improve the outcome of critically ill patients. There are, however, many potential barriers preventing optimal nutritional delivery, including a combination of feed intolerance, under-prescription, and disruption of feeds for nursing, diagnostic, and interventional procedures. Consequently, it has been consistently demonstrated that only 50 % of nutritional requirements is delivered. Delayed gastric emptying is the main cause of feed intolerance and occurs in approximately 50 % of patients in ICU, manifesting as nausea, vomiting, high nasogastric output, and increased gastric residual volume.

Even with measures to secure adequate nutrient delivery to the small intestine of critically ill patients, more recent data suggest that daily energy requirement remains insufficient for these patients due to impaired intestinal absorption and diarrhea is common (Strack van Schijndel et al. 2006; Casaer and Mesotten 2011; Deane et al. 2011; Burgstad et al. 2013). The aim of this chapter is to provide an overview of nutrient digestion and intestinal absorptive function during critical illness, as well as the potential pathophysiological factors underlying the malabsorption. This chapter will also outline strategies to manage and improve nutrient digestion and intestinal absorption and energy delivery to the critically ill patients.

Intestinal Digestion and Absorption in Health

In health, the alimentary tract is well adapted for efficient digestion and absorption of nutrients. Digestion and absorption can be divided into two phases: the "*luminal phase*," which comprises both mechanical and chemical digestion and the "*mucosal phase"* that involves mucosal digestion and subsequent absorption.

Luminal digestion involves both mechanical digestion and chemical digestion. Mechanical digestion commences in the oral cavity with mastication and continues in the stomach with mixing and grinding. Gastric emptying is critical in the digestive process, permitting chyme to enter the small intestine at a rate that optimizes mixing with pancreatic juices for proper digestion and absorption. Chemical digestion occurs through the action of enzymes secreted by the salivary glands, chief cells in the stomach, and exocrine cells of the pancreas. The digestive enzymes are summarized in Table 1. The digestion and absorption of carbohydrate, lipid, and protein will be described separately.

Digestive products formed in the luminal phase must first diffuse across the unstirred water layer to the surface of the enterocyte before traversing the intestinal epithelial cells and entering the bloodstream or lymphatic circulation. The thickness of the unstirred layer influences the absorption of monosaccharides, disaccharides, small peptides, long-chain fatty acids, and cholesterol (Read et al. 1977; Smithson et al. 1981).

Table 1 Enzymes that are important in the luminal phase of digestion of various types of nutrient

	Carbohydrate	Protein	Lipid
Oral cavity	Salivary amylase		Lingual lipase
Stomach		Pepsin	Gastric lipase
Pancreas	Pancreatic amylase	Trypsin	Pancreatic lipase
		Chymotrypsin	Pancreatic colipase
		Elastase	Phospholipase A_2
		Carboxypeptidase A	Cholesterol esterase
		Carboxypeptidase B	

Alterations in small intestinal contractility and intraluminal flow of chyme impact on the thickness of this diffusion barrier and subsequently attenuate intestinal absorption (Westergaard and Dietschy 1974; Levin 1994; Schwartz et al. 2002). The nutrients are further digested by hydrolysis by enzymes located on the small intestinal brush border. Finally, movement across the brush border membrane occurs by three mechanisms: (1) active transport, (2) facilitated diffusion, and (3) passive diffusion:

(i) *Digestion and absorption of carbohydrate.* Digestion of carbohydrate begins from the mouth by salivary α-amylase and continues in the small intestine by the action of pancreatic enzymes and oligosaccharidases (Table 2). The major end products after the digestive processes are glucose, fructose, and galactose, which are then transported across the brush border membrane by active transporters.

While glucose and galactose are transported across the lumen by the sodium glucose transporter 1 (SGLT1), fructose crosses the apical membrane by facilitated diffusion via glucose transporter 2 (GLUT2) and 5 (GLUT5) (Farrell 2010). GLUT5 has a lower affinity for glucose and is predominately involved in fructose transport (Goodman 2010). Glucose, galactose, and fructose can also be absorbed by facilitated diffusion across the intestinal mucosa by a concentration gradient that is maintained by continuous removal of sugars by the bloodstream. Once the monosaccharides have absorbed across the enterocytes, they diffuse into the portal circulation. The absorption of carbohydrates is summarized in Fig. 1.

Table 2 Enzymes involved in the digestion of carbohydrates on the brush border of the small intestine

Enzyme	Substrate	Monosaccharide products
Lactase	Lactose	Glucose
		Galactose
Trehalase	Trehalose	Glucose
Maltase (glucoamylase)	Maltose	Glucose
	Maltotriose	
	α-Limit dextrins	
Sucrase-isomaltase	Sucrose	Glucose
Sucrase	Maltose	Fructose
Isomaltase	Maltotriose	Glucose
	α-Limit dextrins	Glucose
	Maltose	
	Maltotriose	
	α-Limit dextrins	
	α-Limit dextrins	

The sensing of sugar in the intestinal lumen regulates intestinal glucose absorption, gut hormone release, and gastrointestinal motility. Similar to that seen in the tongue, the pathway involves two type 1G-protein-coupled receptors heterodimerized to form T1R2 + T1R3 sweet taste receptors. Intestinal sweet taste receptors are expressed on enteroendocrine cells, with preferential expression in the proximal small intestine (Margolskee et al. 2007; Young et al. 2013). Binding of sweet-tasting molecules to these

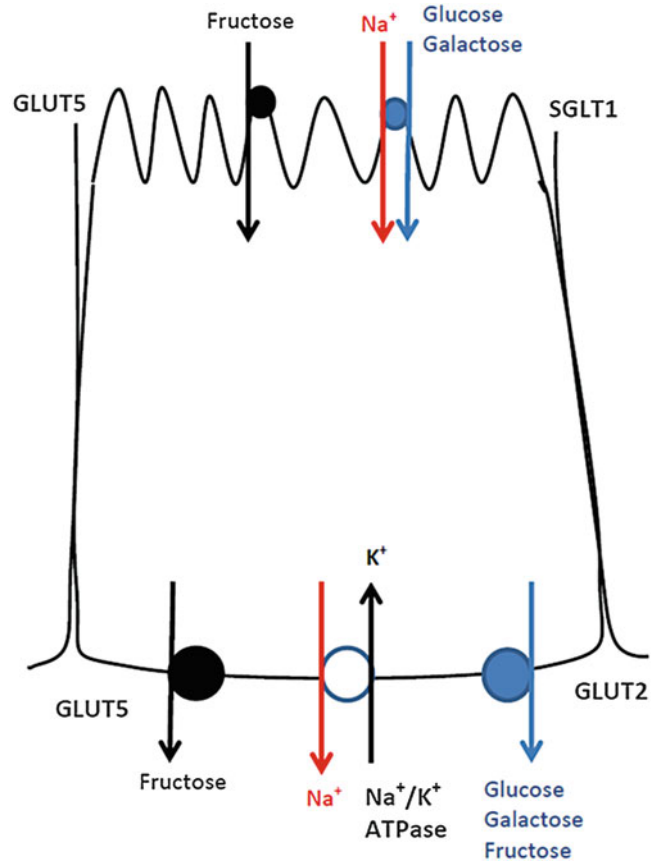

Fig. 1 Outline of mechanisms of carbohydrate absorption in the small intestine, which is mediated by both facilitated diffusion and active transport via GLUT5 and SGLT1

receptors activates a cascade of signaling molecules including the G-protein α-gustducin and transient receptor potential ion channel, TRPM5 (Young 2011). There is also evidence that these taste receptors regulate the expression of SGLT1. Expression of SGLT1 is enhanced in response to high luminal sugar levels, but unchanged in T1R3 or gustducin knockout mice (Margolskee et al. 2007). Intestinal sweet taste receptors are also involved in the secretion of satiation peptides (Jang et al. 2007). Blockade of the sweet taste receptor with lactisole is associated with reduced secretion of GLP1 and PYY (Gerspach et al. 2011)

(ii) *Digestion and absorption of protein.* The digestion of dietary proteins or polypeptides begins with the action of pepsin in the stomach. Pepsinogen is secreted by gastric chief cells and is activated by the low gastric pH to become pepsin. Pepsin preferentially cleaves peptide bonds involving aromatic amino acid (Johnson 2007). The majority of proteolysis occurs in the small intestine by the pancreatic enzymes that are secreted in response to the presence of intestinal chyme. The proteases fall into two groups: the endopeptidases that cleave interior peptide bonds and the exopeptidases that cleave one amino acid at a time at external peptide bonds. Pancreatic proteases are all secreted as inactive precursors. Trypsinogen is cleaved by enteropeptidase, a brush border enzyme, to form trypsin. Trypsin in turn activates other protease precursors. Oligopeptides remaining after endopeptidase and exopeptidase cleavage are further hydrolyzed to free amino acids, dipeptides, and tripeptides by

aminopeptidases located on the brush border membrane (Goodman 2010).

The diversity in amino acid substrates for transport across the apical and basolateral membrane of the enterocytes necessitates a broad range of carriers with broad specificity. Transport of amino acids across the apical membrane occurs by both active transport and facilitated diffusion. Transport across the basolateral membrane occurs by passive diffusion or carrier-mediated transport. Small peptides are transported by peptide transporter 1 (PEPT1) and undergo further hydrolysis by cytoplasmic peptidases (Barrett et al. 2006).

(iii) *Digestion and absorption of lipid.* The first important step in lipid digestion is emulsification in the stomach. While digestion can commence in the oral cavity with lingual lipase produced by glands in the tongue, lipolysis by lingual and gastric lipase only accounts for a minority of chemical digestion. The bulk of lipid digestion occurs in the intestine by bile salts and pancreatic enzymes. The coating of bile salts to phospholipids and cholesterol prevents the emulsified fat droplets from coalescing again. After activation by trypsin, colipase forms a complex with lipase to breakdown triglyceride, whereas activated phospholipase A_2 hydrolyzes phospholipids. In addition, cholesterol esterase hydrolyzes cholesterol esters as well as vitamin esters (A, D, and E) and triglycerides. These soluble breakdown products of dietary fats, also known as mixed micelles, are transported across the unstirred water layer to the enterocyte surface and then diffuse across the lipid bilayer.

Application to Critical Care

Recent evidence suggests that intestinal absorption of nutrition is impaired during critical illness (Chapman et al. 2009; Deane et al. 2011). Diarrhea is a frequent symptom in ICU patients receiving enteral nutrition (Wierdsma et al. 2011). Using fecal weight as a marker for intestinal malabsorption (Wierdsma et al. 2011), the presence of significant fecal energy loss has been shown to occur in almost half of enterally fed ICU patients (Heymsfield et al. 1981; Strack van Schijndel et al. 2006). Fecal examination in critically ill patients with diarrhea confirms significant fecal carbohydrate, fat, and protein loss (Wierdsma et al. 2011).

Carbohydrate Malabsorption

While impaired intestinal absorption is evidenced with all type of nutrients, carbohydrate absorption is the most extensively evaluated in the critically ill. Given 3-*O*-methylglucose (3-OMG) is a synthetic sugar which is actively absorbed by enterocytes, through SGLT1, but not metabolized (Fordtran et al. 1962), absorption of 3-OMG by measuring its plasma concentrations has been used as a marker of carbohydrate absorption. Compared to healthy controls, both the rate and the total amount of absorption of 3-OMG are reduced in critically ill patients (Hadfield et al. 1995), with an estimated 25–60 % reduction (Chapman et al. 2009; Deane et al. 2011). There is recent evidence that sucrose absorption malabsorption also occurs (Burgstad et al. 2013).

Fat Malabsorption

A number of studies have evaluated malabsorption of fat during critical illness, using either fecal fat content assessment or ^{13}C-triolein breath test. Overall, fat absorption is reduced by 30–50 % in ICU patients (Fraser et al. 2006; Nguyen et al. 2011) and has been shown to associate with altered intestinal motility and flow. As mixing of luminal fat content with bile acid and pancreatic enzymes is critical in the digestion and absorption of fat, these small intestinal motor disturbances are the most likely cause of maldigestion and malabsorption. In fact, as absorption of fat as assessed by ^{13}C-triolein breath test improved after, the small intestinal motility normalizes (Nguyen et al. 2011).

Protein Malabsorption

In experimental models of sepsis, amino acid absorption has been shown to be reduced (Gardiner et al. 1995; Abad et al. 2001). The assessment of protein absorption has not been extensively studied in human critical illness due to a lack of simple and reliable technique. Thus far, protein absorption has been quantified by determining both protein intake and fecal protein loss, which is cumbersome as determination of fecal nitrogen content is necessary (Jacobs 1959; Wierdsma et al. 2011).

Mechanisms Underlying Reduced Intestinal Absorption During Critical Illness

The mechanisms underlying impaired intestinal absorption of nutrients during critical illness are likely to be multifactorial and complex. Reduced carbohydrate absorption can occur even in the presence of normal mucosal histology and disaccharidase levels (Burgstad et al. 2013). Furthermore, disruption to the secretory and motor function of the stomach, biliary tract, or pancreas can lead to maldigestion and related malabsorption. Mechanical digestion in the oral cavity and stomach is clearly deficient in ICU patients, which can be partially overcome by enteral delivery of digested liquid feeding formulae. In enteral feeds, carbohydrates are in the partially or fully digested forms of dextrins, disaccharides, and monosaccharides while protein and fats are in the undigested form of whole protein and long-chain or medium-chain triglycerides. While gastric mixing is not essential for carbohydrate digestion as it is with lipid and protein digestion, gastric emptying determines the rate at which nutrient is delivered to the small intestine and therefore available for intestinal digestion and absorption. In ICU, proton pump inhibitors are frequently used and may contribute to maldigestion by increasing gastric pH and therefore impeding the activation of pepsinogen required for protein digestion. Other potential contributing factors to malabsorption during critical illness are mucosal dysfunction and pancreaticobiliary insufficiency. Even after absorption through the intestinal mucosa, a number factors present in critical illness can affect the removal of the absorbed nutrient by the lymphatic or vascular circulation, including intestinal ischemia related to altered mesenteric blood flow, and rarely vasculitis. Potential factors that mediate small intestinal maldigestion and malabsorption are summarized in Fig. 2:

(i) ***Luminal nutritional deprivation***. The small intestine is sensitive to deprivation of luminal nutrients with rapid alteration to

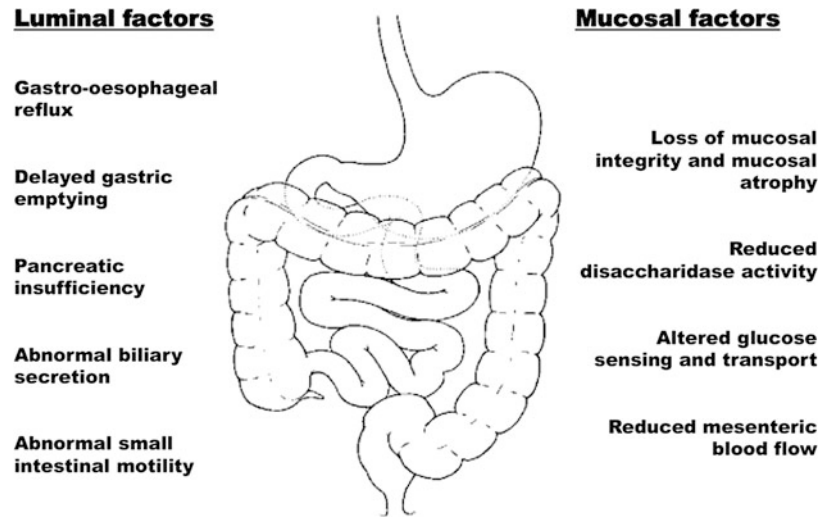

Fig. 2 Potential mechanisms underlying reduced intestinal absorption during critical illness

structure and function, which is not prevented by parenteral delivery of nutrition. As nutritional support has not been well integrated into the overall management of critically ill patients in many ICU around the world, nutritional deprivation is common in the first few days of ICU admission. Even in the recent survey (Quenot et al. 2010), where nutritional care is part of the standard care, the median prescribed/required energy ratio was only 43 % on day 1 and increased to 80 % on day 4. In humans, nutritional deprivation for 4 days leads to mucosal atrophy, impaired intestinal permeability, reduced absorptive surface area (Hernandez et al. 1999), as well as reduced disaccharidase activity (Levine et al. 1974), promoted by increased intestinal epithelial apoptosis (Boza et al. 1999). Thus, timing of the nutritional support is important as early administration of enteral nutrition would prevent these complications (Maxton et al. 1989). As a proof of concept, glucose absorption in critically ill patients who were fed early (within 24 h of ICU admission) is significantly better than those had delayed enteral feeding (after 72 h of admission) (Nguyen et al. 2008b, 2012). Together, these findings highlight the importance of early initiation of enteral nutrition, which has become the standard of care in most, if not all, critical care units.

(ii) ***Mesenteric blood flow***. Intestinal ischemic and reperfusion injury can impair mucosal integrity but also attenuates mucosal absorption. In critical illness, mesenteric ischemia is common due to the imbalance between increased oxygen requirement related to hypermetabolism and decreased supply from mesenteric hypoperfusion, leading to ischemic injury. Conditions such as hemorrhage, cardiogenic shock, and sepsis are risk factors for intestinal ischemia. In critically ill patients, fasting SMA flow is greater than in healthy controls. However, postprandial increase in SMA flow is attenuated (Sim et al. 2013) Changes in mesenteric blood flow during glucose infusion is directly associated with glucose absorption both in critical illness and in health (Sim et al. 2013).

Decrease in small intestinal blood flow can also reduce glucose absorption by a number of other mechanisms. Given active transport of glucose by SGLT1 is driven by the Na + gradient across the apical membrane, reduced activity of Na + K + ATPase will reduce glucose transport and thus absorption. Furthermore, as the exit of glucose across the basolateral membrane into the bloodstream is by facilitated diffusion, the reduced mesenteric perfusion would further compromise the absorption by lower the concentration gradient.

(iii) ***Sepsis***. Apart from the alterations in mesenteric perfusion seen in sepsis, sepsis itself has been associated with gastrointestinal dysfunction and impaired intestinal absorption. Lipopolysaccharides (LPS) are a major constituent of the outer membrane of gram-negative bacteria. It is an endotoxin recognized as a causative agent of sepsis. Exposure of LPS to immune cells evokes an inflammatory response with release of cytokines. Excessive production and release of cytokines is involved in the pathogenesis of sepsis. The proinflammatory cytokines most strongly linked to sepsis are TNFα, IL-1β, Il-6, and IL-8. In experimental models, LPS has been associated with reduction in intestinal amino acid absorption (Abad et al. 2001). Intestinal fructose and galactose absorption also is reduced by intravenous injection of LPS in animal models of sepsis. Both TNFα and IL-1β have been linked with reduction in fructose and galactose absorption. The inhibitory effect of endotoxins and proinflammatory cytokines on nutrient absorption appears in part to be related to alteration in nutrient transport across the enterocyte. LPS-induced reduction in fructose absorption is associated with decreased GLUT5 protein levels (Garcia-Herrera et al. 2008). However, altered galactose absorption in sepsis is not related to SGLT1 levels (Amador et al. 2008).

(iv) ***Glucose sensing and transport***. In animal models of critical illness, levels of the SGLT1 are reduced (Amador et al. 2007), suggesting that defective glucose transport by enterocytes may play a role in carbohydrate malabsorption in critical illness. There is emerging evidence that the molecular basis for decreased intestinal absorption of glucose in humans is also related to markedly reduced transcript levels of the glucose transporter SGLT1. Compared to healthy controls, the expressions of intestinal sweet taste receptor (T1R2) and glucose transporters (SLGT1 and GLUT2) are reduced in ICU patients during fasting and duodenal glucose stimulation (Deane et al. 2013).

(v) ***Gastrointestinal dysmotility***. There is a close relationship between gastric emptying and glucose absorption. Slow gastric emptying occurs in up to 50 % of mechanically ventilated patients (Nguyen et al. 2007c, 2008a, b; Chapman et al. 2011), and it is associated with reduction in the rate of glucose absorption following intragastric nutrient infusion (Chapman et al. 2009). Risk factors for delayed gastric emptying include age, illness severity, reduced Glasgow coma score, multi-trauma, traumatic brain injury, and raised intracranial pressure (McArthur et al. 1995; Nguyen et al. 2007c). Factors associated with delayed gastric emptying are summarized in Table 3. Delayed gastric emptying alone, however, does not account for the extent of glucose malabsorption, with reduced glucose absorption seen in critically ill patients with normal gastric emptying (Chapman et al. 2009). Furthermore, reduction in glucose absorption is evident even when nutrient or 3-OMG is administered into the small bowel. This suggests that factors other than gastric emptying, such as mucosal dysfunction or reduced glucose transporters, contribute to glucose malabsorption during critical illness.

Alteration in small intestinal motility and transit can also influence intestinal absorption of lipid and protein (Bryant et al. 2004). Given non-propulsive contractions are important for the mixing of luminal nutrients whereas transit of luminal contents impacts on the time for digestion and absorption, the disruption of intestinal motor function during enteral feeding can impair lipid absorption (Dive et al. 1994). Major non-gastrointestinal surgery is associated with disruption in small intestinal motility with initial reduction in both lipid and glucose absorptions, but fat malabsorption persisted even after normalization of glucose absorption and intestinal motor function (Nguyen et al. 2011). In critical illness, small intestinal transit does not appear to be altered, and a relationship between transit and glucose absorption has not been demonstrated (Deane et al. 2011).

(vi) ***Pancreatic insufficiency***. Impaired exocrine pancreatic function has also been reported during critical illness and can contribute substantially to reduced absorption of

Table 3 Factors contributing to altered gastric emptying in critically ill patients

Premorbid diagnosis
Diabetes mellitus
Previous vagotomy
Systemic sclerosis
Chronic intestinal pseudo-obstruction
Myopathies/dermatomyositis
Admission diagnosis
Head injury
Burns
Extensive abdominal surgery
Multi-trauma
Spinal cord injury
Pancreatitis
Severe sepsis
Biochemical abnormalities
Hyperglycemia
Hypokalemia
Drugs
Opiates
Benzodiazepines
Anticholinergics
Erythromycin
Calcium channel blockers
Pain

protein and lipid. In patients without preexisting pancreatic disease, the prevalence of pancreatic exocrine insufficiency is over 50 % when assessed using fecal elastase-1 (Wang et al. 2013). In septic shock, aspirated duodenal fluid volume and amylase, trypsin, and chymotrypsin content are reduced compared to non-septic patients (Tribl et al. 2000). Exocrine pancreatic insufficiency is also evident in severe trauma and improves with early initiation of polymeric enteral nutrition (Senkal et al. 2008). Other risk factors for pancreatic insufficiency include diabetes, cardiac arrest, hyperlactacidemia, invasive mechanical ventilation, and hemodialysis (Wang et al. 2013). The clinical consequence of pancreatic insufficiency has not been evaluated, but it may contribute to the increased diarrhea and fecal fat loss seen in critical illness.

(vii) ***Abnormal biliary secretion***. In addition to pancreatic exocrine insufficiency, biliary secretion is also abnormal. In critical illness, not only is there a reduction in the total bile volume but also the individual constituents. Compared to healthy controls, bile salt, phospholipid, and cholesterol are reduced before initiation of enteral nutrition (de Vree et al. 1999). This is in part due to enteral fasting, with impaired bile flow also seen with total parenteral nutrition in several animal studies (Das et al. 1996; Duerksen et al. 1996). In the critically ill, enteral feeding partially restores but does not normalize biliary secretion (de Vree et al. 1999).

Applications to Other Conditions

As with critical illness, alterations in gastrointestinal integrity and function have been described in other anorectic conditions including liver cirrhosis and the elderly. While inadequate oral intake is one of the major causes of malnutrition in these patients, gastrointestinal dysmotility, malabsorption, and increased intestinal permeability have also been described.

Delayed gastric emptying is common in patients with cirrhosis and has been associated with postprandial fullness and bloating (Kalaitzakis et al. 2009). The relationship between delayed gastric emptying and intestinal absorption has not been extensively evaluated in liver cirrhosis, but given the similarities between this group of patient and the critically ill, it is anticipated that carbohydrate absorption would be reduced. In experimental models of cirrhosis, sugar, fat, and amino acid absorption have all been shown to be decreased (Castilla-Cortazar et al. 1997, Pascual et al. 2000). While there is paucity of corresponding human data on carbohydrate absorption, fat malabsorption occurs in up to two thirds of patients (Linscheer 1970). Fat malabsorption in liver cirrhosis may result from inadequate mixing with digestive secretions, decreased bile acid secretion, defective luminal hydrolysis secondary to pancreatic exocrine insufficiency, or small bowel bacterial overgrowth.

Similarly, slow gastric emptying of solids (Evans et al. 1981; Di Francesco et al. 2005), altered levels of gut hormones (Di Francesco et al. 2005), and increased intestinal permeability (Bolin et al. 2010) are commonly present in the elderly. Given the underlying pathologies in the gastrointestinal tract are similar between the elderly, patients with liver cirrhosis, and the critically ill, the same therapeutic strategies for nutritional management could be applied.

Guidelines and Protocols

Feeding guidelines and protocols have been introduced to improve the delivery of nutrients in the intensive care setting. The implementation of feeding protocols has reduced the time to commencement of nutritional support, the time to reach target nutrition rate, and overall energy delivery (Singer et al. 2009; Soguel et al. 2012). However, these improvements thus far have not been shown to confidently reduce mortality. Current guidelines and protocols predominately focus on adequate energy and protein delivery. Figure 3 is an example of an enteral feeding protocol

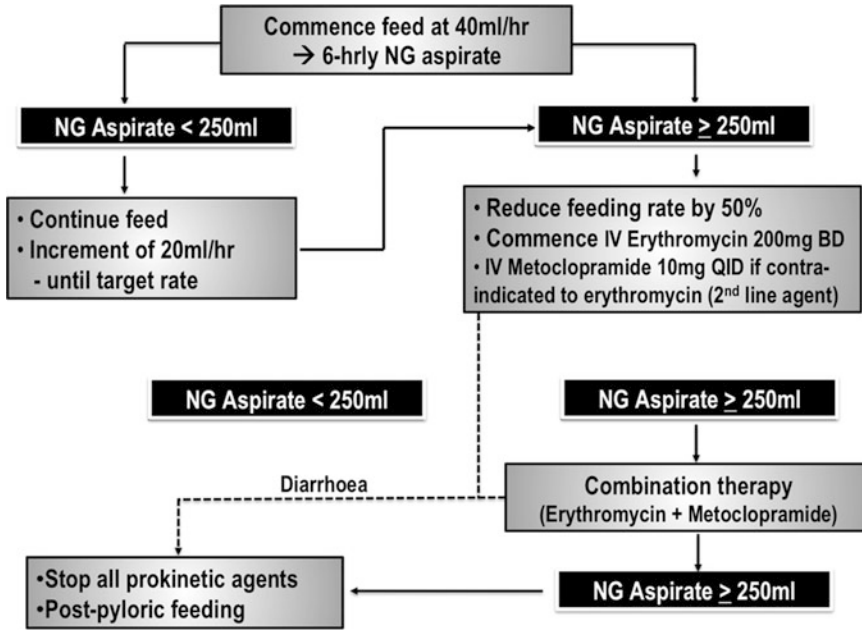

Fig. 3 An example of a feeding protocol that is aimed to maximize the delivery of enteral feeding

adopted at our hospital to optimize the amount of feed to be given to critically ill patients.

Even with the optimization of nutrient delivery, malnutrition may remain a problem in critically ill patients due to the impaired nutrient absorption described in this chapter. Unfortunately, the available guidelines do not take into account the absorptive capacity of the small intestine, and the impact of such factor needs to be further evaluated and integrated in the future guidelines.

Route of Nutritional Support

Enteral nutrition is the preferred route of nutrient delivery. The advantages of enteral nutrition over parenteral nutrition are the preservation of gut function, mucosal integrity, and mucosal immunity (Hadfield et al. 1995; Kudsk 2003; McClave and Heyland 2009). The reduction in infectious complications seen with enteral nutrition compared with parenteral nutrition may be attributed to improved gut barrier function. This potentially reduces translocation of bacteria and their toxins, thereby reducing the risk of sepsis, and septic inflammatory response syndrome (SIRS). Enteral feeding improves mucosal integrity as reflected by a decrease in intestinal permeability, whereas parenteral nutrition is associated with a continued increase in intestinal permeability from baseline (Hadfield et al. 1995).

Route of feeding also influences mesenteric blood flow, which has effects on the intestinal mucosa integrity. It has been demonstrated that total parenteral nutrition reduces postprandial superior mesenteric artery flow whereas intraluminal nutrients increase SMA flow in both healthy controls and those enterally fed (Gatt et al. 2009). The increase in SMA flow in response to luminal nutrient is more attenuated during critical illness (Sim et al. 2013), which may influence glucose absorption. In these patients, luminal nutrient-stimulated SMA blood flow has been shown to correlate with glucose absorption (Sim et al. 2013).

Intragastric feeding is most commonly employed due to convenience and ease of insertion of nasogastric tubes. Given the high prevalence of gastroparesis, post-pyloric feeding has been proposed as better feeding approach in patients with feed intolerance. Unfortunately,

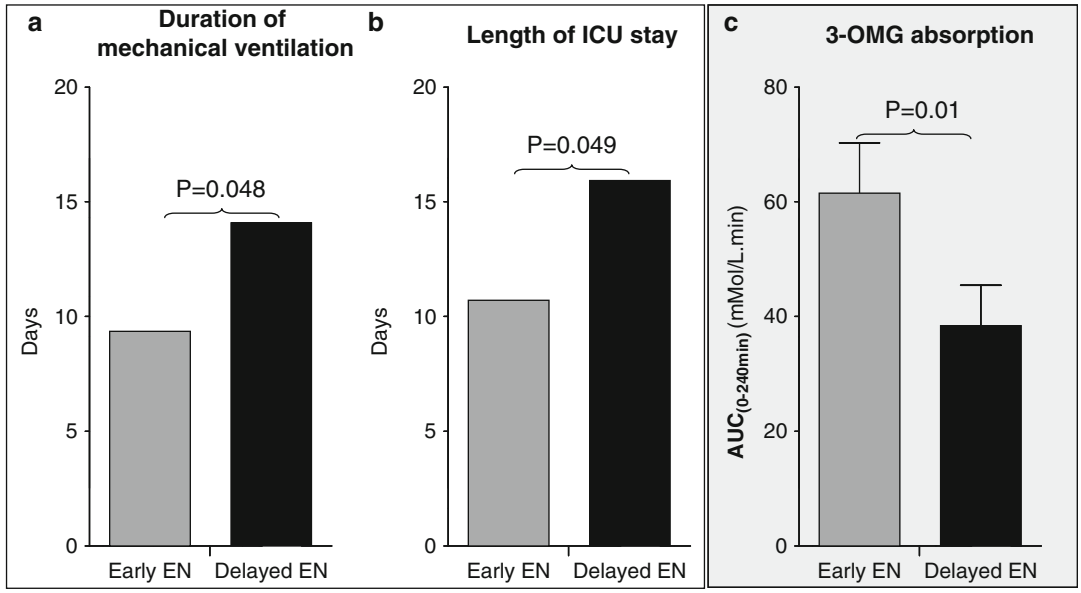

Fig. 4 Impact of early enteral feeding on clinical outcomes and absorption of carbohydrates

naso-jejunal feeding has not been consistently shown to improve nutrient delivery nor reduce the rates of aspiration (Davies et al. 2012). Furthermore, whether nutrient is delivered via a gastric tube or post-pyloric tube, there is no difference in overall glucose absorption, though the rate of glucose absorption in the initial period is more rapid with post-pyloric feeding (Di Bartolomeo et al. 2012).

Timing of Nutritional Support

Timing of initiation of enteral nutrition impacts on gastrointestinal structure and function as well as clinical outcomes. Delayed enteral nutrition is associated with prolonged duration of mechanical ventilation and hospital length of stay (Nguyen et al. 2008b) (Fig. 4a, b). It is also associated with mucosal atrophy and increased intestinal permeability (Hernandez et al. 1999). When patients are enterally fed within the first 24 h of admission, glucose absorption is increased compared to those where feeding was delayed for 4 days (Nguyen et al. 2012) (Fig. 4c).

Prokinetics

Given the high prevalence of delayed gastric emptying and feed intolerance, prokinetics are frequently used to improve nutrient delivery. The use of prokinetics improves feed tolerances, increases the daily caloric delivery, and lowers the need for post-pyloric feeding (Nguyen et al. 2007a, b). Combination therapy with erythromycin and metoclopramide is superior to monotherapy and enables the achievement of energy delivery to 72 % of targeted goal (Nguyen, Chapman et al. 2007a) (Fig. 5), which appears to be within the ideal range for calorie delivery in recent trials (Rice et al. 2011; The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network 2012). Delayed gastric emptying is associated with reduction in the rate of carbohydrate absorption (Chapman et al. 2009). Use of prokinetics would be anticipated to increase the rate of glucose absorption, but its impact on intestinal absorption was not known until recently. A single intravenous dose of erythromycin is associated with increased glucose absorption when nutrient was

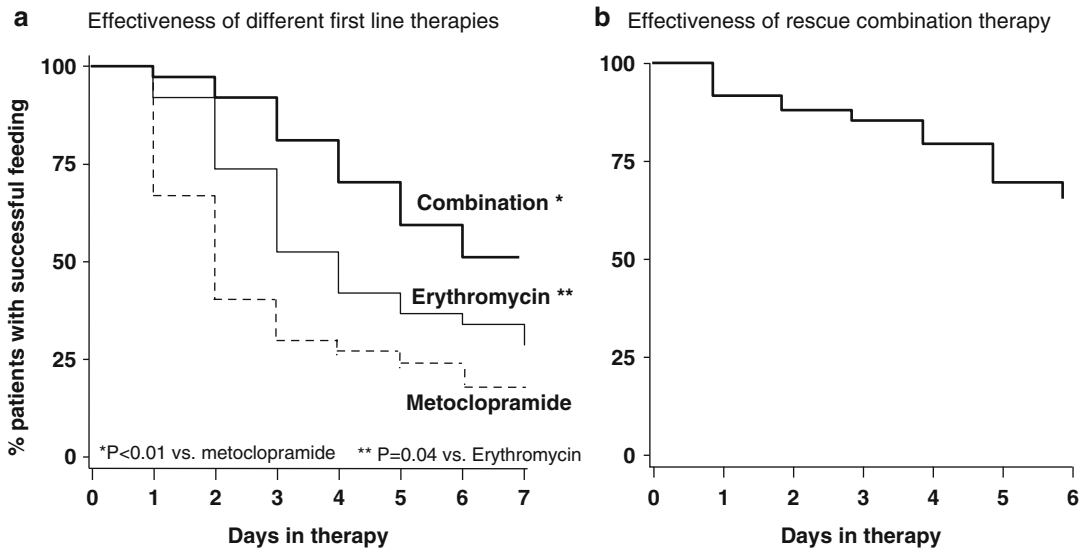

Fig. 5 Impact of prokinetic therapy on the success of enteral feeding during critical illness

infused directly into the small intestine. However, erythromycin may reduce lipid absorption (Bryant et al. 2004; Deane et al. 2012).

When to Consider Parenteral Nutrition?

Given that enteral nutrition alone often fails to deliver the recommended daily caloric requirements, the role of parenteral nutrition (PN) for nutritional support, either alone or in addition to enteral feeds, in critically ill patients has been much debated. The use of early supplementation of PN to increase caloric and protein provision has not been shown to improve survival (Kutsogiannis et al. 2011) and, more worrisome, is associated with prolonged mechanical ventilation, ICU length of stay, hospital length of stay, and mortality when compared to enteral nutrition alone (Kutsogiannis et al. 2011). Similarly, compared to late supplemental PN, early supplementary PN is also associated with longer duration of mechanical ventilation, longer hospital length of stay, more ICU infections, and increased duration of renal replacement therapy (Casaer et al. 2011). Together, these data indicated that early supplementary PN during critical illness is harmful and should not be used.

Conclusions

Malnutrition is common in critical illness and is related to gastrointestinal dysfunction. Nutrient delivery is hampered by delayed gastric emptying and feed intolerance, but malabsorption also impedes nutrient assimilation. The factors contributing to reduced absorption include gastrointestinal dysmotility, pancreatic insufficiency, reduced effective mucosal surface area, impaired disaccharidase activity, reduced nutrient transport, and mesenteric blood flow. The timing of initiation of enteral feeding appears to be important as early enteral nutrition is associated with increased intestinal absorption, better mucosal integrity, and better clinical outcomes. Therefore, in addition to managing impaired gastrointestinal motility with prokinetics or small intestinal feeding, early initiation of enteral feeding should also be adopted routinely to improve the mucosal factors involving in nutritional absorption. Currently, the use of supplementary parenteral nutrition to enteral

feeding during critical illness is associated with poorer outcomes and is not recommended.

Summary Points

Gastric emptying impairs the rate of carbohydrate absorption but does not account for the extent of malabsorption.

Carbohydrate malabsorption is evident even with normal gastric emptying.

Carbohydrate absorption is not related to small intestinal transit.

Small intestinal dysmotility is associated with lipid malabsorption but not glucose malabsorption.

Mesenteric blood flow is attenuated in critical illness and is associated with reduced carbohydrate absorption.

While therapeutic strategies such as post-pyloric feeding and prokinetics may improve the delivery of nutrients, it does not equate to increase intestinal absorption.

Glucose absorption does not differ with intragastric versus post-pyloric feeding.

Erythromycin increases glucose absorption but may reduce lipid absorption.

Early initiation of enteral nutrition within the first 24 h of admission is associated with increased carbohydrate absorption and decreased intestinal permeability.

The use of supplementary parenteral nutrition to enteral feeding during critical illness is associated with poorer outcomes and is not recommended.

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