Carol Rees Parrish, R.D., M.S., Series Editor

Enteral Feeding: Should It Be Continued in the Patient with *Clostridium Difficile* Enterocolitis?

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***Clostridium difficile* (*C. diff*) enterocolitis is a common cause of diarrhea in the hospital setting, responsible for significant increases in healthcare costs. The medical management of this disease is well understood, yet, controversy exists on how to provide nutrition to infected patients that require enteral nutrition (EN) support. EN delivers many benefits to the gastrointestinal tract, including gut mucosal protection and gut immune stimulation. In order to make reasonable clinical decisions regarding the potential efficacy of EN in patients with *C. diff* infection, one needs to understand the contributory effects of EN on the gastrointestinal system; this includes the impact on small bowel motility, small bowel secretions, colonic motility and colonic secretions. To date there is no evidence suggesting that EN is contraindicated in this patient population. This paper will briefly describe the definition, diagnosis, pathophysiology and treatment of *C. diff* enterocolitis. It will also focus on the influence of EN on gastrointestinal motility and secretions as a mechanism for supporting the use of EN in patients with active *C. diff* when nutrition support is required.**

INTRODUCTION

A *Clostridium difficile* enterocolitis infection is commonly acquired in the hospital setting. It is the leading cause of hospital acquired diarrhea and is responsible for over one billion dollars in healthcare costs annually (1). Fifty percent of patients with hospital stays over four weeks acquire *C. diff* and their average hospital stays are approximately 3.6 days longer (1). The incidence of *C. diff* in acute care hospitals has dramatically increased in the last decade. During the mid-to-late 1990s, reported cases of *C. diff* were 30–40 per 100,000 patients; as of 2005 reported cases have increased to 84 per 100,000 (2). In England, *C. diff* was listed as the pri-

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mary cause of death for 3,393 patients in 2006 (2). Although *C. diff* is primarily a colonic infection, it can also be present in the distal ileum in patients who have had a total colectomy (3-5). The medical management of this disease is well understood; however, how to feed patients with active infection is an area of debate. Enteral nutrition (EN) delivers many benefits to the gastrointestinal tract, including gut mucosal protection and gut immune stimulation. Currently there are no prospective, retrospective or case series regarding the use of EN in patients with *C. diff* enterocolitis. No current standard of care exists on the use of nutrition support; hence, the clinician is left with clinical judgment to guide decisions. In order to make reasonable clinical decisions regarding the potential efficacy of EN in patients with *C. diff*, an understanding of the effects of EN on the gastrointestinal system is helpful.

Beliefs on how to feed patients with active *C. diff* infection varies considerably. See Table 1 for results of a recent informal survey from the American Society of Parenteral and Enteral Nutrition listserv (ASPENet) in the fall of 2008. Some clinicians feel that it is necessary to impose an NPO order for oral intake and EN in the setting of *C. diff* induced enterocolitis; fear of toxic megacolon and bowel ischemia are often cited as the reason. However, these same practitioners often do not hold oral or enteral feeding during other episodes of infectious diarrhea. Withholding of EN can lead to the use of parenteral nutrition (PN), a therapy with known risks and complications. The question that needs to be asked is: "what evidence is there to support withholding of enteral feeding in the patient with *C. diff*?"

Table 1
Clinician's Response on How to Feed Patients with Active *Clostridium difficile* Enterocolitis*

- No changes to enteral regimen (po or TF)
- Lactose Free diet
- Addition of Benefiber
- Addition of Banana Flakes
- Addition of Probiotics (Lactinex, Florastor, Bacid)
- Change TF to Fiber-Free
- Change TF to Fiber-containing
- Hold Enteral Nutrition (if prolonged, begin PN)
- NPO, PN
- Clear liquid, high protein

*Responses from ASPENet Listserv September 2007

DEFINITION AND PATHOPHYSIOLOGY

Clostridium difficile is an anaerobic bacterium that exists primarily in the colon in two forms: a vegetative state where the bacteria can be treated with antibiotics, and a dormant spore state unable to be eradicated by antibiotics. Once the dormant state becomes activated to the vegetative state it can produce toxins which result in the disease's common symptoms; the vegetative state will also produce more spores (6). The bacteria produce toxins known as endotoxin A and B; endotoxin A, the more potent of the two, is the cause of mucosal cell damage and apoptosis (7).

The increasing use of antibiotics, specifically broad spectrum antibiotics such as cephalosporins, penicillins, and clindamycin, alters normal gut flora allowing *C. diff* to thrive (6). Other risk factors include age >60 years, intensive care settings and malnutrition (Table 2) (8–10). The clinical features of a *C. diff* infection can range from no symptoms to diffuse peritonitis. Peritonitis can develop as a result of bacterial translocation (11) and/or bowel perforation. The most common symptom is a profuse, watery diarrhea. This is generally a high volume diarrhea. In fulminant

Table 2
Risk Factors for *Clostridium difficile* Infection

- Increasing use of antibiotics, specifically broad spectrum antibiotics such as:
  - Cephalosporins
  - Penicillins
  - Clindamycin
- Age >60 years
- Residence in extended care facility
- Radiation therapy to the gut
- Intensive care settings
- HIV
- Malnutrition
- Nasogastric intubation
- Use of medications to suppress gastric acid
- Immunosuppressive medications

Table 3
Examples of Secretory Versus Osmotic Diarrhea

Secretory	*Osmotic*
An increase in active secretion and/or inhibition of absorption.	Osmotic substances draw too much water into the bowel
Clostridium difficile infection	Laxative use • Magnesium containing • Lactulose
Enteric Pathogens	Pancreatic enzyme deficiency
Vasoactive intestinal peptide (VIP) excreting adenomas	Bile salt deficiency
Zollinger-Ellison	Lactose intolerance
Metastatic carcinoid tumors	Sorbitol

cases, such as toxic megacolon, bloody diarrhea and sepsis may develop. Fortunately, toxic megacolon and perforation are unusual presentations of *C. diff* with a reported incidence of 0.4%–3% (12).

C. diff toxins increase the mucosal production of IL-8 and ICAM-1, cytokines leading to neutrophil chemoattraction and mucosal inflammation (13). This leads to cellular necrosis and protein loss through increased intestinal peristalsis and permeability. Ultimately, colonic mucosal ischemia and ulcerations may develop. Binding of the *C. diff* toxin to the colonic mucosa is important to initiate its toxic effects. This binding leads to a relaxation of the tight cellular junctions of the colonic mucosa (14). As a result of cytokine production mast cells degranulate and promote a heightened inflammatory environment. The combination of the relaxation of tight cellular junctions, as well as the associated inflammatory reaction that ensues, a secretory, often high volume diarrhea results (15).

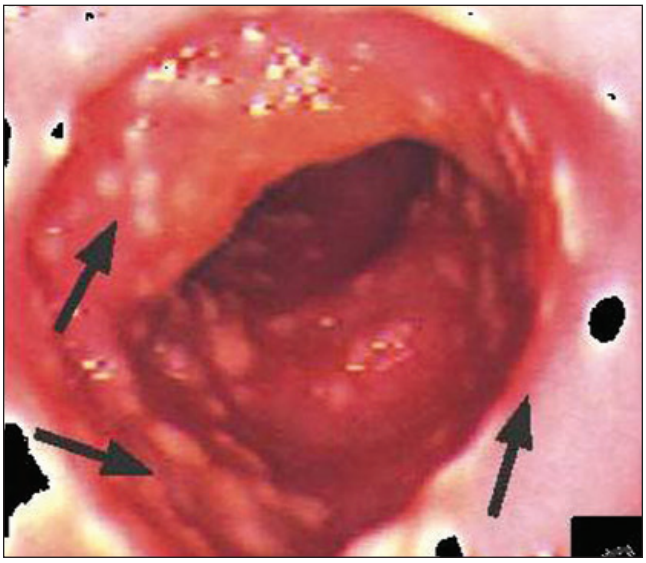

Figure 1. Endoscopic Image of *Clostridium Difficile* Pseudomembranes on the Colon Mucosa

Secretory vs Osmotic Diarrhea

After 24 hours of fasting, patients with secretory diarrhea will continue to experience a large volume of liquid stools (16), patients with *C. diff* may secrete several liters per day of stool. In contrast, osmotic diarrhea is often lower in volume and is triggered by an osmotically active substance; diarrhea from osmotic causes will resolve when oral intake or EN is discontinued (Table 3).

Diagnosis

The gold standard for the diagnosis of infection is the isolation of the toxin from the stool. White blood cells (WBC) in the stool may also be seen. It is common to have an elevated serum WBC count and elevated serum acute phase reactants, such as C reactive protein (CRP). The development of metabolic acidosis is an ominous sign potentially signaling ischemia of the gut. The diag-

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nosis of *C. diff* can also be made by visualizing pseudomembranes on the colonic mucosa with either flexible sigmoidoscopy or colonoscopy (Figure 1).

TREATMENT

The management of *C. diff* is focused around supportive care. This includes: a) hydration, b) correction of electrolyte imbalance, c) pain and nausea control, and d) monitoring for signs and symptoms of sepsis. However, the mainstay of treatment is the use of specific antibiotics to kill the vegetative state of the bacteria. The most commonly prescribed antibiotics are metronidazole (intravenous or oral) and vancomycin (oral) (17). One study found that in patients with *C. diff* infection, WBC over 30,000 cells/mm^3 and a 50% increase in Cr above baseline predicted complications, such as colonic resection and death, related to *C. diff* (18). These authors concluded these patients would benefit from earlier and possibly surgical intervention. Surgery is usually reserved for patients with toxic megacolon or perforation.

PREVENTION

The best treatment for *C. diff* is prevention, including fastidious hand washing (Table 4, Ref. 19). Some have theorized that the use of fiber supplements can help protect the bowel from the alterations of microflora that occurs during critical illness (20–22). Fiber produces short chain fatty acids (SCFA) in the large intestine from fermentation of carbohydrates. These SCFA (butyrate, propionate and acetate) create a more acidic environment and provide fuel for colonocytes. Experimental studies have shown improved trophic effects on colonic mucosa and a lower rate of bacterial translocation with the use of water soluble fibers, such as guar gum and pectin (20). More recently, there has been a focus on the use of probiotics, specifically *Saccharomyces boulardii*, in the treatment and prevention of *C. diff* (7,20–22).

NUTRITION SUPPORT

As mentioned earlier, toxic megacolon is reported to occur in only 0.4%–3% of *C. diff* cases (12). Unless an ileus is present, toxic megacolon or colonic perforation occurs, there is no known contraindication to the use of EN. Severe abdominal distention, extreme tenderness, severe constipation, high fevers, hypotension and tachycardia can signal onset of toxic megacolon (12). Abdominal CT scans are very useful in making the diagnosis of toxic megacolon or colonic perforation. In these instances, EN is clearly contraindicated. However, as toxic megacolon and perforation is the exception rather than the rule in the disease spectrum of *C. diff*, it is unlikely that EN should be withheld in the majority of patients with this disease.

When using EN in any patient one needs to assess gastrointestinal tolerance. In essence, the question of whether EN would result in a worsening of diarrhea that might pose undue risk in a patient with *C. diff* has yet to be answered. These questions are focused on factors which could increase stool output and include:

1. Does the use of EN (food/tube feeding) increase colonic motility?
2. Does the use of EN increase colon secretions?
3. Does the use of EN increase small bowel motility?
4. Does the use of EN increase small bowel secretions?
5. If EN is delivered, is a specialty formulation beneficial?

COLONIC MOTILITY

Changes in colonic contractility follow food ingestion, previously referred to as the "gastro-colonic reflex" (23).

Table 4
Prevention of *Clostridium difficile* Infection (19)

- WASH HANDS (with soap and water)
- Do not use alcohol rub—does not kill the spores!
- Identify patients at risk for *C. diff* to diagnose and treat early
- Isolate with contact precautions as soon as *C. diff* is identified:
  - Require gown and gloves for all that come in contact with the patient or the patient's environment
  - Hand washing before gowning, as well as after discarding gown and gloves
- Thoroughly cleaning the room and all equipment that comes in contact with a *C. diff* patient

It starts within one-to-three minutes of food ingestion and lasts for several hours. The response of colonic contractions to food is dependent also on the macronutrient content. Fat is the main stimulus of the colon's contractile response (24). Carbohydrates have a stimulatory effect on the colon when consumed in large amounts. Amino acids have an inhibitory effect on colonic motility (25). This response is created by direct gastroduodenal receptor stimulation as the intravenous injection of fat does not stimulate the colon (26). Interestingly, studies evaluating the effect of EN specifically noted that an intragastric infusion of a low calorie enteral formulation had minimal impact on colonic motility (27). Infusion of a calorie dense enteral formulation, either intragastrically or intraduodenally, resulted in a significant stimulation of colonic motor activity (28).

COLONIC SECRETIONS

A series of experiments were designed to evaluate the response of the large intestine to enteral feeding (29–32). In these studies a low-load (standard polymeric) or high-load (concentrated) tube feeding was delivered intragastrically or intraduodenally. Increased water and electrolyte secretion into the colon occurred during intragastric feedings of a low load (standard) or high load (concentrated) enteral formula and during the intraduodenal infusion of a high load (concentrated) enteral formula (32). This accounted for volumes of approximately 120 mL/hr produced in the ascending colon, most of which was absorbed in the descending colon (33). More interestingly, when short-chain fatty acids, by-products of carbohydrate fermentation, were infused directly into the cecum and ascending colon, water and electrolyte secretion was reduced significantly, if not completely reversed (28). The colon, at peak efficiency, has the ability to absorb up to 5.2 L of fluid daily (34).

SMALL INTESTINE MOTILITY

The small intestinal motor activity post-feeding is influenced by several control mechanisms. A cephalic phase of small bowel motility takes place before food is even ingested and is caused by the simple sight and smell of food (35). Gastric distention disrupts the normal contractile pattern of the small intestine and changes it to a "fed pattern" where small bowel motility is decreased. Movement of nutrients from the stomach into the small intestine also results in a reduction in small bowel motility. Increased distention of the small intestine further decreases the speed of movement of material through the small intestine.

SMALL INTESTINE SECRETIONS

Secretion in the small intestine occurs from the intervillious spaces. In the animal model, little or no secretion into the small intestine occurs in the fasting state. In the dog-model, basal small bowel secretions are approximately 1–2 mL/hr which increases to 5–8 mL/hr with feeding (36). Both neural and hormonal causes of the increased secretions have been identified. Secretagogues such as vasointestinal peptide, bile acids and fatty acids may also markedly increase small bowel secretions through the activity of cyclic-AMP (36).

FEASIBILITY OF ENTERAL NUTRITION IN PATIENTS WITH *CLOSTRIDIUM DIFFICILE* ENTEROCOLITIS

It is widely accepted that EN maintains gut mucosal integrity which leads to decreased intestinal permeability, decreased infections, and an improved immunological status (38). Alternatively, starvation causes gastrointestinal mucosal atrophy. A study looking at various compositions of nutrients in the diet to see what was best absorbed demonstrated that no matter the composition of the diet, 100% of carbohydrate, fat, and protein were absorbed well before entering the colon (39). Studies have shown that during acute diarrhea, 78%–95% of carbohydrate, 65% of fat and 75% of protein are absorbed from mixed diets (40,41); however, the belief that enteric infections can increase mucosal permeability and that an oral diet exacerbates infectious diarrhea persists (42). The theory is based on the concept that diet is the cause of symptoms, in this case, profuse diarrhea: "starvation leads to decreased stool output while feeding exacerbates malabsorption." To rule out this hypothesis, stool reducing substances (unabsorbed sugars) and fecal fat can be checked in this patient population during EN.

Table 5
Authors Suggested Guidelines for Enteral Nutrition Provision in the Setting of *Clostridium Difficile* Infection

- Check for *C. diff* in any patient on enteral feeding with diarrhea
- Always be on the lookout for *C. diff* in unexplained diarrhea in hospitalized patients or in those who do not respond to appropriate interventions
- Do not use gut slowing agents (Imodium, lomotil, narcotics, etc) until *C. diff* infection has been ruled out and then cleared
- Continue enteral feedings as previously ordered unless clinical judgment dictates otherwise:
  - Abdominal distention/pain/fever
  - If you are unable to keep up with fluid losses (e.g. >3 liters of stool/day)
  - If output looks the same as tube feeding
- No evidence to avoid fiber content in setting of positive *C. diff* culture
- Addition of *Saccharomyces boulardii* may be of benefit—may have best effect if initiated prior to *C. diff* infection
- No literature supporting lactose free diet in colonic infectious episodes

Clinically it makes sense to feed the gut during periods of secretory diarrhea such as *C. diff* (Table 5). Feeding during acute diarrhea has been shown to improve enterocyte healing and maintenance of enzyme activity (43,44). Early EN in critically ill patients has shown positive effects of down-regulating the systemic inflammatory response and decreasing the duration of illness. Isolori, et al. noted that fasting during acute diarrhea prolongs increased intestinal permeability to sugars such as mannitol and lactulose. They concluded that early enteral feeding promotes optimal absorption (45).

Is it possible that the use of EN increases a patient's risk for developing *C. diff*? The acquisition of *C. diff*-associated diarrhea in tube-fed patients has been briefly addressed. Bliss, et al evaluated 76 tube-fed and non-tube-fed hospital patients for the development of *C. diff*-associated diarrhea (46). Patients were controlled for age, severity of illness and duration of hospitalization. Patients who were tube-fed were statistically more likely to develop *C. diff*-associated diarrhea (20% versus 8% p = 0.03). Post-pyloric EN was identified as a covariate that markedly increased the risk of developing *C. diff*-associated diarrhea (OR 3.14). The use of antibiotics was frequent and similar in both groups. The rationale for this finding can only be hypothesized. The EN formulas used did not contain fiber. One study has shown that the use of a fiber-free formula results in less short-chain fatty acids in the colon and a less acidic pH (47); short-chain fatty acid content and an acidic pH contribute to the resistance of the colon to *C. diff* colonization (48). Another hypothesis postulates that tube-fed patients require more frequent handling by caregivers thus leading to more body contact time and an increased risk of developing *C. diff*-associated diarrhea. Ibrahim, et al demonstrated that ICU patients with a higher Clinical Pulmonary Infection Score (CPIS) had a higher incidence of ventilator associated pneumonia, which led to more antibiotic days and subsequently an increased incidence of *C. diff* diarrhea (49).

Does the type of EN provided have any effect on the incidence or development of *C. diff* infection? IIzuka, et al and colleagues have evaluated this topic. They originally reported that *C. diff* toxin was frequently detected in the stool of patients being fed an elemental diet while not receiving antibiotics (41.2%). Fecal *C. diff* toxin disappeared from the stool soon after the elemental diet was stopped (50). In a follow-up in vitro study, this group cultured *C. diff* in various culture mediums and monitored growth. The combination of an elemental formula plus a standard culture medium resulted in a significant increase in growth of the *C. diff* bacteria as compared to the same bacteria grown in a standard culture medium alone or with the combination of a polymeric enteral formula plus a standard culture medium (51).

CONCLUSION

In summary, we are still left with clinical judgment with how best to feed patients with active *C. diff* infections. However, our review of the literature would suggest that a polymeric enteral formulation is reasonable to use in this patient population. Fiber containing formulations may be important based on their ability to

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stimulate the development of short-chain fatty acids resulting in colonic mucosal trophic effects. There is no literature available to suggest that withholding EN is beneficial. Feeding the gut maintains mucosal integrity, decreases bacterial translocation, decreases severity of illness and leads to increased absorption of nutrients. The presence of nutrients in the intestinal lumen does not lead to exacerbation of a secretory diarrhea. Our practice is to provide oral/EN and monitor tolerance as we would in any patient with or without the presence of *C. diff* infection. A prospective study would be helpful to not only determine whether oral intake/EN is safe, or even beneficial in these patients. One could just as easily ask the opposite question: where is the data that EN should be stopped in this patient population? For now, there is no good physiologic reason that EN should be withheld in patients with active *C. diff* enterocolitis without clinical signs indicating that the clinician should do so. ■

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