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EDITORIAL

Tube feeding, the microbiota, and *Clostridium difficile* infection

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Abstract

Clostridium difficile (*C. difficile*) is now the leading cause of nosocomial diarrhea in the USA, accounting for 30% of patients with antibiotic-associated diarrhea, 70% of those with antibiotic-associated colitis, and most cases of pseudomembranous colitis. The organism has evolved over the last 8 years to become more virulent and resistant to antimicrobials (NAP1/027 strain) causing a more severe form of the disease that has increased mortality and healthcare costs. While it is generally accepted that the problem results from the overuse of antibiotics, and in particular second and third generation cephalosporins, fluoroquinolones and macrolides, recent studies suggest that acid suppression with proton pump inhibitors (PPIs) may be equally culpable. A further common, but less recognized, etiological factor is the prolonged use of elemental diets. Such diets are totally absorbed within the small intestine and therefore deprive the colonic microbiota of their source of nutrition, namely dietary fiber, fructose oligosaccharides, and resistant starch. The resultant suppression of colonic fermentation leads to suppression of the "good" bacteria, such as butyrate-producers (butyrate being essential for colonic mucosal health), and bifidobacteria and the creation of a "permissive" environment for *C. difficile* colonization and subsequent infection. Based on this analysis, the best chance of suppressing the emerging *C. difficile* epidemic is to adopt a 3-pronged attack consisting of (1) avoidance of the use of prophylactic antibiotics, (2) the avoidance of prophylactic PPIs, and (3) the conversion of elemental diet feeding to a diet containing adequate indigestible carbohydrate after the first week of critical illness. In this review, we highlight the rising worldwide incidence of *C. difficile* associated diarrhea and the role played by non-residue diets in destabilizing the colonic microbiota.

Key words: *Clostridium difficile*; Elemental diets; Enteral nutrition; Microbiota

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INTRODUCTION

In under 10 years, *Clostridium difficile* (*C. difficile*) has risen from an obscure anaerobic bacterium to a notorious "superbug" responsible for epidemics of hospital-acquired infections worldwide, attracting major media concern (e.g. "Stomach Bug Crystallizes an Antibiotic Threat", New York Times, April 13, 2009). It is now the leading cause of nosocomial diarrhea in the USA, accounting for 30% of patients with antibiotic-associated diarrhea, 70% of those with antibiotic-associated colitis, and most cases of pseudomembranous colitis[1]. Furthermore, the organism has evolved over the last 8 years to become more virulent and resistant to antimicrobials

(NAP1/027 strain) causing a severe form of the disease that prolongs hospitalization and increases mortality, creating substantial increases in health service and economic burdens[2]. USA estimates report an additional annual cost to health care of $1.1 billion[3]. Mortality rates have increased concomitantly with these epidemic outbreaks. For example, a report from Quebec, Canada, noted that mortality from infection associated with the use of prophylactic antibiotics for surgical procedures increased from 0.7 cases per 1000 procedures in 2002 to 14.9 in 2005[4]. Subsequent studies on bacterial isolates revealed strain changes that increased the production of toxins and made the organism resistant to a wider range of broad-spectrum antibiotics[5]. Second and third generation cephalosporins, fluoroquinolones and macrolides have been shown to increase the development of virulence and adherence enhancing colonization. It is therefore understandable that the observed recent exponential increases in incidence, morbidity, mortality and associated healthcare costs are of extreme national and international concern, as they threaten our current ability to support survival in septic critically ill hospitalized patients with the latest generation of potent antibiotics.

HOSPITAL CONTROL

There is no consensus on how the problem can be solved. Despite increasing resistance, the organism is still generally sensitive to both oral metronidazole and vancomycin, and yet mortality continues to increase. Thus greater effort is being directed at prevention. Of the considered 3 most powerful risk factors, age, antimicrobials and exposure to healthcare facilities, the third should be the most controllable. The mode of transmission is thought to be chiefly due to contamination from the hospital environment and from the hands of healthcare workers. Most hospitals now impose strict isolation and hygiene control to detected cases, but the ability of the organism to form spores makes it difficult to control. Although the spores are easily washed down the drain with soap and water, *C. difficile* is not killed by most routinely used hospital germicides. Only 1:10 bleach used with a 10-min contact time serves as a *C. difficile* sporicide[6] and doing this routinely is logistically impossible.

PROTON PUMP INHIBITORS

However, the overuse of broad-spectrum antibiotics cannot alone explain the *C. difficile* crisis. Recent studies have suggested that the increase in incidence is better correlated with the use of gastric acid suppressing proton pump inhibitors (PPIs) than with antibiotic usage[7]. While spores are resistant to acid, the vegetative form is killed by gastric acid but has been shown to survive passage through the stomachs of patients on PPIs[8]. As the vegetative form can theoretically survive on damp surfaces for short spaces of time, it is possible that colonic infection may be propagated from patient-to-patient through the use of equipment such as bedpans. The use of PPIs may also promote the expansion and colonization of *C. difficile* by its recognized potential to induce small bowel bacterial overgrowth with anaerobic colonic organisms[9].

ELEMENTAL DIETS

In addition, there is the commonly overlooked question of enteral feeding. While there is irrefutable evidence that conventional enteral tube feeding reduces respiratory and bloodstream infectious morbidity[10], the technique has been associated with increased risk of *C. difficile* infection[11]. Although this is usually explained by enteral feeding providing a high-frequency portal for inoculation of *C. difficile* spores deep into the gut by healthcare workers, it could simply be explained by the fact that patients requiring enteral feeding are usually sicker, at higher risk of any complication, and more often on antibiotics. Patients receiving percutaneous endoscopic gastrostomies (PEGs) may be at even higher risk due to their higher grades of chronic illness and the conventional use of prophylactic antibiotics to prevent placement infections[12]. Enteral feeding associated *C. difficile* infections may also be related to the fact that research has focused on the importance of luminal nutrition on the upper gastrointestinal (GI) tract - and not on the colon. Critically ill patients commonly have impaired upper GI function with poor motility and ileus. Studies have shown that feeding tolerance by such patients can be remarkably good if the feed is given in a residue-free predigested, or "elemental" form, and delivered beyond the stomach into the jejunum because it is totally absorbed within the upper small intestine[13]. Unfortunately, modification of normal eating in this way has some potentially deleterious effects. Firstly, the jejunal elemental diets suppress bacteriostatic gastric and pancreobiliary secretions[14,15] and also motility. These effects together promote colonization of the small intestine with colonic microbiota, leading to small bowel bacterial overgrowth. Secondly, experimental studies have shown that elemental diets are a perfect culture medium for *C. difficile* organisms[16]. Thirdly, elemental diets contain no complex carbohydrate residues, such as fiber or "resistant" starch that escape digestion in the small intestine and enter the colon to provide a fermentable food source for the colonic microbiota.

THE CRITICAL IMPORTANCE OF COLONIC NUTRITION ON THE MICROBIOTA

The absence of fiber and resistant starches not only disturbs microbiotal balance further, but also deprives the colonic epithelium of its chief energy source and proliferation regulator, butyrate, a short chain fatty acid that is synthesized by the microbiota during the fermentation process[17]. A further twist to the story is that it

has been shown that butyrate deficiency in the colon potentiates the growth and toxin production of *C. difficile* organisms[18]. It is reasonable to thus speculate that the prolonged use of non-residue tube feeds will enhance *C. difficile* colonization and subsequent *C. difficile* associated colitis by reducing mucosal health and therefore resistance to pathogen adherence and subsequent cytotoxic injury. It has been shown experimentally that colony adherence results in mucosal inflammation induced by the transference of cytotoxic and enterotoxic factors, disrupting the epithelial barrier[19]. Toxins A and B enter the colonic cells and kill the cells by multiple mechanisms, including catalysis of the transfer of glucose to GTPases. This may be critically important as in the absence of butyrate, colonic cell survival will be totally dependent on efficient glucose utilization. The suggestion that pre-existing mucosal injury predisposes to *C. difficile* colonization and cytotoxicity is supported by the observation that patients with chronic ulcerative colitis are at dramatically increased risk of developing severe *C. difficile* associated colitis, and that many are resistant to antimicrobial treatment, with 20% requiring total colectomy and an overall mortality rate of 50%[20]. To date, fiber supplementation of enteral feeds has not been systematically tested in the critically-ill, but it is noteworthy that Lewis *et al*[21] found that oligosaccharide supplementation (12 g/d) increased bifidobacteria counts and decreased diarrhea in patients with chronic relapsing *C. difficile* infection.

CONCLUSION

So what can we do to reduce the incidence of *C. difficile* infection and its progression to colitis? Survival in the ICU is commonly dependent on the protracted use of broad-spectrum antibiotics, and so withholding their use is not an option. However, prophylactic antibiotics post-operatively and in conditions, such as severe pancreatitis where they are of unproven benefit, should be avoided[22]. Secondly, PPIs are grossly overprescribed in the ICU usually with the intent of preventing stress ulceration, but there is poor correlation between this and gastric acidity. One study looking at the association between *C. difficile* associated colitis and PPIs, showed that 63% of patients had no valid indication for acid suppression[23]. Not only would restriction of PPI use likely decrease the incidence of *C. difficile* associated colitis but it would also have enormous heath care savings worldwide. PPIs now account for 10% of the annual prescribing costs in the UK; more judicious use would save the National Health Service at least £100 million/year[24]. Finally, the use of non-residue tube feeds should be restricted to those critically-ill patients with ileus and borderline gut function and since, in practice, ileus usually resolves and function returns with the slow progression of tube feeding over three or 4 d[13], even in these patients a change can often be made to a fiber or "prebiotic" containing formula after the first week.

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