Diarrhoea in the critically ill

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Purpose of review

The purpose of this review is to update the knowledge on diarrhoea, a common problem in critically ill patients. Epidemiological data will be discussed, with special emphasis on diarrhoea in tube-fed patients and during antibiotic therapy. The possible preventive and therapeutic measures will be presented.

Recent findings

The need for concise definitions of diarrhoea was recently re-emphasized. The use of pump-driven continuous instead of intermittent enteral feeding is less often associated with diarrhoea. The discontinuation of enteral feeding during diarrhoea is not justified. *Clostridium difficile*-associated diarrhoea is frequent during antibiotic therapy with quinolones and cephalosporins. Formulas enriched with water-soluble fibres are probably effective to prevent diarrhoea, and promising data on the modulation of gut microflora with probiotics and prebiotics were recently released.

Summary

Diarrhoea is common in critically ill patients, especially when sepsis and hypoalbuminaemia are present, and during enteral feeding and antibiotic therapy. The management of diarrhoea includes generous hydration, compensation for the loss of electrolytes, antidiarrheal oral medications, the continuation of enteral feeding, and metronidazole or glycopeptides in the case of moderate to severe *C. difficile* colitis. The place of enteral formulas enriched with water-soluble fibres, probiotics and prebiotics is not yet fully defined.

Keywords

artificial nutrition, *Clostridium difficile* colitis, critically ill, enteral feeding, gastrointestinal tract

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Abbreviations

ICU	intensive care unit
SCFA	short-chain fatty acid

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Introduction

Diarrhoea is a common finding in critically ill patients, whatever the initial cause of admission into the intensive care unit (ICU). Although several risk factors have been identified, the pathogenesis, incidence and management of diarrhoea in critically ill patients are loosely defined. Not surprisingly, the approach to enteral feeding-associated diarrhoea, the commonest form observed in critically ill patients, is quite variable, from the discontinuation of nutrition to the use of antidiarrhoeal medications along with the infusion of the enteral solution at the same rate [1,2]. Nevertheless, a concise and standardized diagnostic approach to diarrhoea is mandatory because the cause can require a specific treatment in addition to supportive measures [3]. Some advances in the understanding and management of diarrhoea in critically ill patients have been reported during the past few years. These advances encompass a refined assessment of the epidemiology, and a better definition of the risk factors and of the clinical impact of diarrhoea. Importantly, new therapeutic and preventive modalities have been assessed and will be reviewed in this article.

Definition and epidemiology

Reported incidences of diarrhoea may vary over a very wide range (from 2 to 95%) [4••], namely because of the lack of standardization in the definition of diarrhoea. For example, in a recent survey among nurses who were asked to inspect faeces, they agreed on the presence or absence of diarrhoea on only 75% of occasions [5]. If the concept of diarrhoea being defined as the emission of frequent (≥ 3 to > 5 per day) and soft stools (200–300 g/day or volume > 250 ml/day) is universally accepted, the use of more accurate descriptors of the frequency, consistency and quantity of faeces is desirable [4••] to improve the management of this condition. 'Stool charts' have been developed to standardize the description of diarrhoea [4••,5,6].

In ICUs, the reported frequencies of diarrhoea are also very variable. For example, in an observational multicentre study performed in 37 Spanish ICUs where a cohort of 400 patients was followed prospectively over one month to assess the rate of gastrointestinal complications related to enteral nutrition, the total frequency of complications was 62.8%, whereas diarrhoea represented 15.7% of these complications [2], much less often than delays in gastric emptying. In other recently published descriptive studies, Elpern *et al.* [7] still found an incidence of 38% of diarrhoea (data recorded over 3 months

in a medical ICU), whereas in severely burned children diarrhoea was observed in 18 out of the 19 patients [8•]. Taken together, as in older studies [9], the prevalence of diarrhoea depends on the definition used. Diarrhoea is, however, definitely a common and significant problem in critically ill patients, and can impede the delivery of an adequate amount of nutrients by the enteral route [7,10].

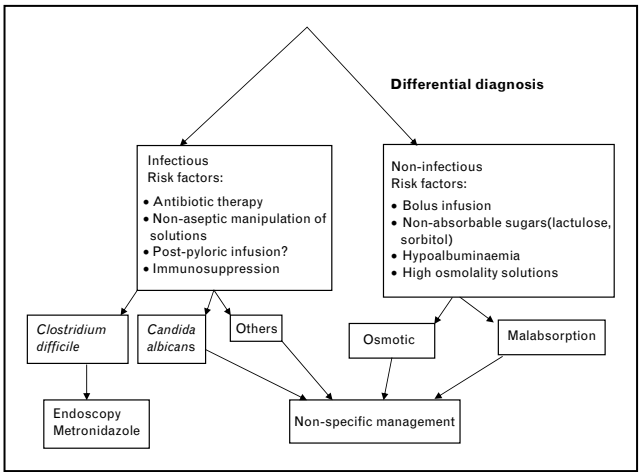
Pathogenesis and risk factors

Once diarrhoea has been diagnosed, it can be further characterized using a pathophysiological or a diagnostic approach. A pathophysiological definition relies on the mechanisms that can synergize to increase the faecal content of water. A diagnostic definition aims at the differentiation between infectious and non-infectious causes, implying different therapeutic approaches. The most common categories of diarrhoea found in ICUs are summarized in Table 1. An example of the diagnostic algorithm useful for enteral feeding-associated diarrhoea is shown in Fig. 1 [10]. The clinical management also differs when diarrhoea occurs during enteral feeding or antibiotic therapy. Therefore, even though the presence and persistence of diarrhoea can seriously influence the outcome of critically ill patients, whatever its cause, these common risk factors will be treated separately.

Enteral feeding-associated diarrhoea

The commonly reported presence of diarrhoea during the enteral infusion of feeds can be explained by the composition of enteral formulas, as well as by the characteristics of administration, including the site and the mode of infusion. Interestingly, in a recent meta-analysis comparing the risks of parenteral and enteral nutrition [11•], enteral feeding was not found to increase the risk of diarrhoea, perhaps suggesting that the modalities of administration can influence the incidence of diarrhoea more than the route of administration itself. Enteral feeding is sometimes interrupted or its infusion rate is decreased, in contradiction with current recommendations and with the available evidence [1,2,10]. Many experimental and clinical studies have demonstrated that, in comparison with total parenteral nutrition, enteral nutrition can actually reduce the incidence of diarrhoea via a better preservation of the gastrointestinal mucosal structure and function. Even in the case of circulatory compromise, early enteral nutrition seems to be more useful than harmful, once managed cautiously to minimize the risk of non-occlusive bowel necrosis [12].

Figure 1 Proposed algorithm for the differential diagnosis and management of diarrhoea in critically ill patients



Adapted from Preiser *et al.* [10], with the permission of the publisher, Remedica.

Site of infusion

In a large multicentre prospective randomized study, Montejo *et al.* [13] compared the efficacy and rate of complications associated with the early gastric versus the early jejunal route in 101 patients. The incidence of diarrhoea was identical (14%) in both groups, although the total number of gastrointestinal complications (mainly high gastric residues) was lower in the group fed in the jejunum than in the group fed in the stomach. Similarly, in another study comparing gastric versus small bowel feeding in critically ill children receiving mechanical ventilation [14•], there was no difference in the incidence of diarrhoea between the two groups. These two recent findings somewhat challenge previous beliefs

Table 1 Common aetiologies of diarrhoea in critically ill patients

Pathophysiological	Diagnostic		
Secretory	Reduced absorption or increased secretion of electrolytes. Bright stools and reduction in osmotic gap	Infectious	Microorganisms (especially during antibiotherapy)
Motor	Reduced area of contact or gut hypermotility with decreased time of contact between gut content and intestinal mucosa		Bacterial Mainly *Clostridium difficile* Anaerobes
Exudative	Release of colloids, liquids, electrolytes, desquamated cells (mainly polymorphonuclear neutrophil) and necrotic membranes	Non-infectious	Other causes Gut ischaemia or hypoperfusion Hypoalbuminaemia
Osmotic	Reduced water absorption due to luminal non-absorbable molecules. Bright stools with increased osmotic gap		Drug-associated Gut dysmotility

that intragastric infusion favours diarrhoea via the stimulation of fluid secretion into the ascending colon, or of intrajejunal infusion favouring diarrhoea via hyperosmolarity (> 400 mosm/l) in the small intestine or via a neurohumoral reflex implying the release of peptide YY [4••].

Mode of administration

The administration of enteral feeding can be pump-driven or controlled by gravity, continuous or intermittent. These aspects also affect the incidence of diarrhoea. For example, the use of pump-assisted infusion dramatically reduced the incidence of diarrhoea compared with gravity-controlled infusion [15]. Similarly, new data recently recorded in trauma and elderly patients confirmed a better prevention of diarrhoea with the use of continuous rather than intermittent enteral infusion of feeds, although the advantage of the continuous mode was no longer observed during diarrhoea [16,17].

Composition of enteral formulas

Several characteristics of enteral formulas have been associated with an increased incidence of diarrhoea, including the amount of carbohydrates, fat, high osmolarity and bacterial contamination (bacterial count $> 10^2$ colonies/ml) [4••]. Presumably, the presence of a high concentration of non-absorbable carbohydrates or an acquired intolerance of lactose will increase the osmolarity of the solutions. Recent data recorded from burned children, however, failed to correlate the daily intake of carbohydrates (over a range from 168 to 1191 g) with the faecal output assessed by the stools' weight [9]. A similar correlation between maldigested fat and bowel osmolarity is suspected but has not been investigated in critically ill patients. Of note is the fact that most of the osmotic effects of macronutrients could be attenuated by the incorporation of non-absorbable fibres (see below).

Antibiotic-associated diarrhoea

Although the changes in gut microflora are not specific and the associated diarrhoea usually resolves spontaneously, only the finding of *Clostridium difficile* colitis requires a specific therapy. Therefore, we will review the recent advances in this topic.

C. difficile is an anaerobic toxin-producing Gram-positive bacillus. The toxin triggers inflammation, necrosis of the bowel mucosa, and even colon dilatation up to perforation. The diagnosis of *C. difficile* colitis is confirmed by the presence of the toxin in the stools. *C. difficile* is the most common cause of infectious nosocomial diarrhoea, and can be found in up to 30% of asymptomatic hospitalized patients [18••]. Clostridial colitis actually occurs when the equilibrium of gut flora is severely perturbed, thereby allowing the growth of *C. difficile*. Risk factors for the development of *C. difficile*-related diarrhoea include recent or current antibiotic therapy, a prolonged stay in the ICU [18••], treatment with a proton pump inhibitor [19], sex (more frequent in women than in men) [20], the severity of the underlying disease as evaluated by Horn's index [21••,22], and enteral nutrition [23]. In a study of 150 non-critically ill patients, a larger proportion of tube-fed than non-tube-fed patients acquired *C. difficile*-associated diarrhoea, especially in the case of postpyloric feeding [23]. Among antibiotic agents, there are striking differences in the prevalence of *Clostridium*-associated diarrhoea. In particular, the use of quinolones and cephalosporins are commonly associated with an increased risk, whereas the use of macrolides was found to be less risky [18••,24].

Once diagnosed, if symptoms are mild, no specific treatment is required in addition to the discontinuation of antibiotic therapy. Metronidazole is presently recommended in moderate to severe *C. difficile*-associated diarrhoea. In the case of failure of metronidazole treatment, oral vancomycin can be given. In a recent retrospective analysis of 119 patients [25•], metronidazole-resistant *C. difficile*-associated diarrhoea was found to be more frequent in hypoalbuminaemia (< 25 g/l) and after a recent or current ICU stay [25•]. In a large retrospective study (1991–2003), Pepin *et al.* [26] found a greater rate of colon-related complications in patients receiving metronidazole than in those initially receiving vancomycin. In contrast, a Cochrane database systematic review of nine randomized controlled trials [27••], involving patients with clostridial diarrhoea related to previous antibiotic therapy, found a similar efficacy of metronidazole, bacitracin, fucidic acid, vancomycin and teicoplanin. This latter agent, which is rarely used could be slightly more effective [27••].

Other risk factors

In a multicentre study published in 1997, Bleichner and colleagues [28] identified the following risk factors for diarrhoea among 11 tested variables: fever or hypothermia, the presence of an infection site, malnutrition, hypoalbuminaemia (< 26 g/l), sepsis syndrome, multiple organ failures, open feed container, and previous total parenteral nutrition. In the multivariate analysis carried out with the same data, fever or hypothermia, malnutrition, hypoalbuminaemia, the previous suspension of oral feeding, and the presence of an infection site were associated with an increased prevalence of diarrhoea [28]. In the available literature [4••,5,28,29••], hypoalbuminaemia and malnutrition were the risk factors most often quoted, whereas malnutrition could be a cause as well as a consequence of diarrhoea. Other risk factors include the presence of faecaloma associated with pseudodiarrhoea, drugs (mainly laxatives, H_2 receptor antagonists, antibiotics, sorbitol or magnesium-containing oral medications) and gut hypoperfusion [30].

Consequences of diarrhoea

In adult ICUs in western countries, diarrhoea is more often a cause than a consequence of malnutrition, in contrast to less developed areas, where the opposite holds true [31••]. If left untreated, diarrhoea-induced malnutrition can increase morbidity. The management of diarrhoea-induced malnutrition can be complicated by the poor absorption of nutrients given enterally; in this case the adjunction of parenteral support may be justified.

Besides malnutrition, critically ill patients presenting with severe diarrhoea are particularly at risk of haemodynamic instability, as a result of sudden shifts in the blood circulating volume related to diarrhoea itself, and abundant perfusions are required. Similarly, metabolic acidosis is often observed as a consequence of massive digestive losses of electrolytes and bicarbonate ions. Not surprisingly, the mineral balance is always altered when diarrhoea persists over a few hours; accordingly, the stores of potassium, magnesium and zinc can be significantly depleted and must be compensated, because of their roles in the prevention of arrhythmias, membrane stability, and wound healing. The contamination of wounds and pressure sores must also be taken into account when there are large abdominal sutures or seat burning, and in extreme cases colostomy could be considered [4••,9].

Preventive and therapeutic measures

Therapeutic management algorithms have been proposed [2,10]. In addition to generous hydration with sodium and sugar-containing solutions, oral opioids or anticholinergic medications can be considered. The effects of different antidiarrhoeal medications have recently been reviewed [30,31••]. Basically, the use of opioids including loperamide can induce a paralytic ileus when used with other drugs, impairing gut motility [32]. Racecadotril could be preferable to loperamide as it may induce less secondary ileus [33•]. A non-absorbable antibiotic agent, rifaximin, was recently reported to have an appropriate activity against enteropathogens and could be useful for infectious diarrhoea [31••].

Besides this general scheme, the use of a continuous mode of administration and rigorous hygiene efficiently prevent diarrhoea. Alterations in the composition of enteral feeding formulas and therapies designed to modulate the gut microflora are currently being studied and will be reviewed.

Composition of enteral formulas

Enteral feeding formulas of low osmolarity and enriched with fibres should be preferred. Dietary fibres (non-digestible plant cell wall constituents) have been added to enteral nutrition formulas to normalize bowel function and actually improve feeding tolerance. The beneficial effect on bowel function results from the release of short-chain fatty acids (SCFAs) after the fermentation of carbohydrates of fibres in the colon. SCFAs (butyrate, propionate and acetate) play an important role in salt and water absorption in the colon, with butyrate being the main energetic fuel for colonocytes [4••]. Soy polysaccharides, which contain 94% insoluble fibre, are the most common source of fibre in enteral formulas, but can be less efficient for the prevention of diarrhoea than water-soluble fibres. Water-soluble fibres, such as pectin and guar gum, have better potential trophic effects, increase the viscosity of the solutions, can delay gastric emptying and absorption in the small intestine, and reduce luminal flow by causing resistance to the propulsive action of intestinal contractions. These effects of fibres have been confirmed in experimental studies that have shown a better colon mucosal trophicity and a lower rate of bacterial translocation. Fibre-enriched formulas are now frequently used in critically ill patients to prevent diarrhoea and to treat constipation [34,35]. In a recent study in critically ill tube-fed patients receiving antibiotics [36], pectin tended to prevent diarrhoea more efficiently than placebo. The beneficial effects of a solution enriched with water-soluble fibres have been confirmed in elderly patients [34]. In contrast, a recent meta-analysis on the randomized trials of enteral solutions enriched with fibres [37•] found no benefit in the subset of critically ill patients. Clearly, larger studies are warranted to edict recommendations for the use of fibres.

Modulation of gut microflora

The use of probiotics, prebiotics and synbiotics is an area of intense investigation, namely in critically ill patients. The gut flora is profoundly disturbed during critical illness [38], and this could profoundly alter the interaction and physiology of the gut mucosa [39•]. Therefore, attempting to restore the normal microflora with probiotics (a preparation or a product containing viable defined microorganisms in sufficient numbers, which alter the microflora by implantation or colonization in a compartment of the host and that exert beneficial effects in the host), prebiotics (a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon, and thus improving host health) or synbiotics (a combination of prebiotics and probiotics able to modulate gut immunity and facilitate nutrient/factor interaction necessary for gut recovery) was recently suggested, and the relevance for critically ill patients was extensively reviewed [40,41••].

Of particular interest, *Saccharomyces boulardii* seems to be effective in controlling the growth of *Salmonella enterica*, Serovars *typhimurium* or *Escherichia coli in vitro*, and to increase the synthesis of SCFAs [42]. The best available

evidence for using *S. boulardii* is the maintenance of remission in ulcerative colitis, the treatment and prevention of infectious diarrhoea (mainly in children), and the prevention of antibiotic-induced diarrhoea [28]. It could also be useful after liver transplantation and during acute pancreatitis. In critically ill tube-fed patients, treatment with *S. boulardii* reduced by 25% the mean percentage of days with diarrhoea (from 18.9 to 14.2%). This relative reduction reached 52% when a risk factor for diarrhoea other than enteral feeding was present [28]. The use of *S. boulardii* in 128 ICU patients with enteral feeding reduced the number of patient days with diarrhoea by 25% [43]. A cautious use of *S. boulardii* in patients at risk of gut mucosal atrophy is warranted, as some cases of bloodstream infection with this strain have been reported [44].

Other probiotics, such as bifidobacteria or lactobacilli, are able to prevent or alleviate diarrhoea in intensive care patients through their effects on the immune system and resistance to colonization by pathogens [41••,45••]. The mechanisms of action of the different strains of bifidobacteria are still poorly understood, and the comparison of efficiency for diarrhoea prevention are still awaited. *Bifidobacterium longum* seems particularly promising for the prevention of antibiotic-associated diarrhoea [46••]. The combination of lactobacillus and bifidobacterium reduced the number of samples positive for *C. difficile* from 7.25% (placebo group) to 2.9% (probiotic group) in a study of over 150 patients with antibiotic-associated diarrhoea [45••]. Another prospective randomized trial consisting of the enteral administration of *Lactobacillus plantarum* to critically ill patients [47] showed a late attenuation of the systemic inflammatory response, but was not accompanied by any significant changes in the intestinal microflora, intestinal permeability, endotoxin exposure, septic morbidity or mortality. The effects of this strain are presently unknown.

No data on the effects of prebiotics alone in critically ill patients are available now, to the best of our knowledge. The addition of various amounts of fructo-oligosaccharides is, however, able to influence the population of bifidobacteria considerably [4••].

Symbiotics (a combination of prebiotics and probiotics) can potentially reduce or eliminate gut pathogens or toxins. Among symbiotic treatments, a recently conducted study [48] showed that the administration of a solution containing *Lactobacillus acidophilus* and *bulgaricus*, *Bifidobacterium lactis*, *Streptococcus thermophilus* with oligofructose in critically ill patients favourably altered the microbial composition of the upper gastrointestinal tract, but had no effect on intestinal permeability, and was not associated with significant clinical benefit, although the frequency of diarrhoea was not reported.

Conclusion

A more concise definition of diarrhoea is required for a better assessment of the risk factors and of the preventive and therapeutic modalities. Pump-driven continuous infusion of enteral feeding and the judicious and limited use of antibiotics are recommended to prevent the most common causes of diarrhoea in critically ill patients. New antidiarrhoeal medications, the use of fibres, and the administration of selected probiotics represent promising preventive or therapeutic approaches.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 186).

1 Preiser JC, Berre J, Carpentier Y, *et al.* Management of nutrition in European intensive care units: results of a questionnaire. Working Group on Metabolism and Nutrition of the European Society of Intensive Care Medicine. Intens Care Med 1999; 25:95–101.

2 Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med 1999; 27:1447–1453.

3 Preiser JC, Ledoux D. The use of protocols for nutritional support is definitely needed in the intensive care unit. Crit Care Med 2004; 32:2354–2355.

4 •• Whelan K, Judd PA, Preedy VR, Taylor MA. Enteral feeding: the effect on faecal output, the faecal microflora and SCFA concentrations. Proc Nutr Soc 2004; 63:105–113.
A useful review paper with special focus on the definition of diarrhoea, the pathogenesis of enteral feeding-related diarrhoea and the role of the colonic microflora.

5 Whelan K, Judd PA, Taylor MA. Defining and reporting diarrhoea during enteral tube feeding: do health professionals agree? J Hum Nutr Diet 2003; 16:21–26.

6 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997; 32:920–924.

7 Elpern EH, Stutz L, Peterson S, *et al.* Outcomes associated with enteral tube feedings in a medical intensive care unit. Am J Crit Care 2004; 13:221–227.
A paper that conclusively reports the adverse effects of precautionary interruptions in enteral feedings on nutritional intake.

8 • Thakkar K, Kien CL, Rosenblatt JI, Herndon DN. Diarrhea in severely burned children. J Parenter Enter Nutr 2005; 29:8–11.
This interesting study performed in burned children challenges the concept of diarrhoea being caused by hyperosmolar enteral formulas.

9 Kelly TW, Patrick MR, Hillman KM. Study of diarrhea in critically ill patients. Crit Care Med 1983; 11:7–9.

10 Preiser JC, Leverve X, Noordally O. Nutrition in critical care. London, UK: Remedica; 2005.

11 • Gramlich L, Kichian K, Pinilla J, *et al.* Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. Nutrition 2004; 20:843–848.
This systematic literature review confirms the advantageous risk/benefit ratio of enteral nutrition over parenteral nutrition.

12 Rokyta R Jr, Matejovic M, Krouzecky A, Novak I. Enteral nutrition and hepatosplanchnic region in critically ill patients – friends or foes? Physiol Res 2003; 52:31–37.

13 Montejo JC, Grau T, Acosta J, *et al.* Multicenter prospective randomized single-blind study comparing the efficacy and gastrointestinal complications of early jejunal feeding with early gastric feeding in critically ill patients. Crit Care Med 2002; 30:796–800.

14 Meert KL, Daphtary KM, Metheny NA. Gastric versus small-bowel feeding in • critically ill children receiving mechanical ventilation: a randomized controlled trial. Chest 2004; 126:872–878.
A nice demonstration of the nutritional efficiency of small bowel feeds in mechanically ventilated children, without increasing the incidence of diarrhoea.

15 Shang E, Geiger N, Sturm W, Post S. Pump-assisted versus gravity-controlled enteral nutrition in long-term percutaneous endoscopic gastrostomy patients: a prospective controlled trial. J Parenter Enter Nutr 2003; 27:216–219.

16 Steevens EC, Lipscomb AF, Poole GV, Sacks GS. Comparison of continuous vs intermittent nasogastric enteral feeding in trauma patients: perceptions and practice. Nutr Clin Pract 2002; 17:118–122.

17 Lee JS, Auyeung TW. A comparison of two feeding methods in the alleviation of diarrhoea in older tube-fed patients: a randomised controlled trial. Age Ageing 2003; 32:388–393.

18 Modena S, Bearelly D, Swartz K, Friedenberg FK. *Clostridium difficile* among •• hospitalized patients receiving antibiotics: a case–control study. Infect Control Hosp Epidemiol 2005; 26:685–690.
A case–control study that emphasizes the protective and risk factors of developing *C. difficile*-associated diarrhoea.

19 Dial S, Alrasadi K, Manoukian C, *et al.* Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case–control studies. Can Med Assoc 2004; 171:33–38.

20 Crabtree TD, Pelletier SJ, Gleason TG, *et al.* Clinical characteristics and antibiotic utilization in surgical patients with *Clostridium difficile*-associated diarrhea. Am Surg 1999; 65:507–511.

21 Vesta KA, Wells PG, Gentry CA, Stipek WJ. Specific risk factors for •• *Clostridium difficile*-associated diarrhea: a prospective, multicenter, case control evaluation. Am J Infect Control 2005; 33:469–472.
A prospective observational case–control study of the specific risk factors for the development of *C. difficile*-associated diarrhoea.

22 Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. Infect Control Hosp Epidemiol 2002; 23:653–659.

23 Bliss DZ, Johnson S, Savik K, *et al.* Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalized patients receiving tube feeding. Ann Intern Med 1998; 129:1012–1019.

24 Yip C, Loeb M, Salama S, *et al.* Quinolone use as a risk factor for nosocomial *Clostridium difficile*-associated diarrhea. Infect Control Hosp Epidemiol 2001; 22:572–575.

25 Fernandez A, Anand G, Friedenberg F. Factors associated with failure of • metronidazole in *Clostridium difficile*-associated disease. J Clin Gastroenterol 2004; 38:414–418.
A retrospective review clearly identifying hyopalbuminaemia and stay in the ICU as risk factors for the failure of metronidazole therapy for *C. difficile*-associated diarrhoea.

26 Pepin J, Valiquette L, Alary ME, *et al. Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. Can Med Assoc J 2004; 171:466–472.

27 Bricker E, Garg R, Nelson R, *et al.* Antibiotic treatment for Clostridium difficile-•• associated diarrhea in adults. Cochrane Database Syst Rev 2005; (1):CD004610.
A large systematic review of published therapeutic trials for *C. difficile*-associated diarrhoea.

28 Bleichner G, Blehaut M, Mentec H, Moyse D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial. Intens Care Med 1997; 23:517–523.

29 Mechanick JI, Brett EM. Nutrition and the chronically critically ill patient. Curr •• Opin Clin Nutr Metab Care 2005; 8:33–39.
A nice review paper of the effects of nutritional support in chronically critically ill patients on several issues, including the incidence and consequences of diarrhoea.

30 Urbain D, Belaiche J, De Vos M, *et al.* Treatment of acute diarrhoea: update of guidelines based on a critical interuniversity assessment of medications and current practices. Acta Gastroenterol Belg 2003; 66:218–226.

31 Gadewar S, Fasano A. Current concepts in the evaluation, diagnosis and •• management of acute infectious diarrhea. Curr Opin Pharmacol 2005; 5:559–565.
A nice update on the pathogenesis and pharmacological therapy of diarrhoea.

32 Mutlu EM, Mutlu GA, Factor P. GI complications in patients receiving mechanical ventilation. Chest 2001; 119:1222–1241.

33 Wang HH, Shieh MJ, Liao KF. A blind, randomized comparison of racecadotril • and loperamide for stopping acute diarrhea in adults. World J Gastroenterol 2005; 11:1540–1543.
This study showed in outpatients that racecadotril is an effective antihypersecretory agent, which causes less consecutive reactional constipation than loperamide.

34 Nakao M, Ogura Y, Satake S, *et al.* Usefulness of soluble dietary fiber for the treatment of diarrhea during enteral nutrition in elderly patients. Nutrition 2002; 18:35–39.

35 Schneider SM, Girard-Pipau F, Anty R, *et al.* Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota. Clin Nutr 2005; 24 October 2005. [E-pub ahead of print].

36 Schultz AA, Ashby-Hughes B, Taylor R, *et al.* Effects of pectin on diarrhea in critically ill tube-fed patients receiving antibiotics. Am J Crit Care 2000; 9:403–411.

37 Yang G, Wu XT, Zhou Y, Wang YL. Application of dietary fiber in clinical • enteral nutrition: a meta-analysis of randomized controlled trials. World J Gastroenterol 2005; 11:3935–3938.
A thorough meta-analysis showing that fibres have not been proved to be efficient in ICU patients, in contrast to other hospitalized patients.

38 Marshall JC. Gastrointestinal flora and its alterations in critical illness. Curr Opin Clin Nutr Metab Care 1999; 2:405–411.

39 Alverdy J, Zaborina O, Wu L. The impact of stress and nutrition on bacterial– • host interactions at the intestinal epithelial surface. Curr Opin Clin Nutr Metab Care 2005; 8:205–209.
This review examines new concepts on the interaction between bacteria and the host, the complex relationship that make them beneficial in healthy subjects and modification during illness.

40 Bengmark S. Gut microbial ecology in critical illness: is there a role for prebiotics, probiotics, and synbiotics? Curr Opin Crit Care 2002; 8:145–151.

41 Meier R, Steuerwald M. Place of probiotics. Curr Opin Crit Care 2005; •• 11:318–325.
An excellent update on the current understanding of the potential therapeutic roles of probiotics.

42 Schneider SM, Girard-Pipau F, Filippi J, *et al.* Effects of *Saccharomyces boulardii* on fecal short-chain fatty acids and microflora in patients on long-term total enteral nutrition. World J Gastroenterol 2005; 11:6165–6169.

43 Spapen H, Diltoer M, Van Malderen C, *et al.* Soluble fiber reduces the incidence of diarrhea in septic patients receiving total enteral nutrition: a prospective, double-blind, randomized, and controlled trial. Clin Nutr 2001; 20:301–305.

44 Munoz P, Bouza E, Cuenca-Estrella M, *et al. Saccharomyces cerevisiae* fungemia: an emerging infectious disease. Clin Infect Dis 2005; 40: 1625–1634.

45 Jenkins B, Holsten S, Bengmark S, Martindale R. Probiotics: a practical •• review of their role in specific clinical scenarios. Nutr Clin Pract 2005; 20:262–270.
A comparative overview of the effects of different strains of probiotics in various circumstances.

46 Picard C, Fioramonti J, Francois A, *et al.* Review article: bifidobacteria as •• probiotic agents – physiological effects and clinical benefits. Aliment Pharmacol Ther 2005; 22:495–512.
An updated review that focuses on the preventive and alleviating effect of bifidobacteria on diarrhoea through their effect on the immune system and resistance to colonization by pathogens.

47 McNaught CE, Woodcock NP, Anderson AD, MacFie J. A prospective randomised trial of probiotics in critically ill patients. Clin Nutr 2005; 24:211–219.

48 Jain PK, McNaught CE, Anderson AD, *et al.* Influence of synbiotic containing *Lactobacillus acidophilus* La5, *Bifidobacterium lactis* Bb 12, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and oligofructose on gut barrier function and sepsis in critically ill patients: a randomised controlled trial. Clin Nutr 2004; 23:467–475.