Diarrhoea in the critically ill

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**Purpose of review**
To summarize existing evidence on definition, epidemiology, mechanisms, risk factors, consequences, outcome and management of diarrhoea in the critically ill.

**Recent findings**
In health, diarrhoea is defined as the passage of three or more loose or liquid stools per day. In the critically ill, the diagnosis is yet to be formalized and reported prevalence of diarrhoea varies according to the definition used. Recent studies estimate the prevalence between 14 and 21\% and describe risk factors for diarrhoea in critically ill patients. The precipitant of diarrhoea always needs to be identified, as targeted therapies are important for several causes. Although the majority of patients with diarrhoea require only supportive care, it is always essential to exclude, or confirm and treat infectious diarrhoea. There is little evidence to support delaying or withdrawing provision of enteral nutrition in patients with diarrhoea, and we recommend continuing enteral nutrition whenever possible. However, the consequences of diarrhoea – hypovolaemia, electrolyte disturbances, malnutrition, skin lesions and contamination of wounds – should be avoided or at least recognized promptly.

**Summary**
A definition of diarrhoea and a practical approach to identify the precipitant and to manage diarrhoea in critically ill patients are proposed.

**Keywords**
Clostridium difficile, diarrhoea, enteral nutrition, infectious diarrhoea

**INTRODUCTION**
Our review summarizes existing evidence regarding the definition, epidemiology, mechanisms, risk factors, consequences and outcomes of diarrhoea. We propose a practical approach to identify the cause and thereby treat patients with diarrhoea.

**DEFINITION**
The World Health Organization definition of diarrhoea is the passage of three or more loose or liquid stools per day \cite{1}. However, other experts recommend that rather three criteria must be met: stool frequency, stool weight and stool consistency \cite{2–4}.

Stool frequency three stools or more per day, or a more frequent passage than is normal for the individual, defines this component of the diagnosis \cite{4}. Normal gastrointestinal transit times are considered to be around 48 h \cite{4}.

Stool weight 200 g/day or above or volume 250 ml/day or above is considered abnormally high \cite{4}. The average stool weight of healthy meat-eating adults is 105–140 g/24 h, being greater in vegetarians \cite{4}.

The Bristol Stool Chart is probably the most widely used description of stool consistency \cite{5}, with loose or watery stools (Bristol Stool Chart type 5–7) required to constitute diarrhoea \cite{5}.

In a survey, nursing staff found faecal frequency more important than consistency and quantity, whereas agreeing that diarrhoea was present in only three-fourths of cases, suggesting moderate
reliability between observers when it comes to making the diagnosis [6].

For patients with colostomy, grading of chemotherapy-induced diarrhoea but not other forms has been proposed [7].

Extrapolating from data in health, we suggest that diarrhoea in the critically ill be defined as the simultaneous presence of stool frequencies three stools per day or more, with stool weights 200 g/day or higher and consistency of stools categorized as 5–7 on the Bristol Stool Chart.

EPIDEMIOLOGY
Recent studies have estimated the prevalence of diarrhoea in critically ill patients as between 14 and 21% [8,9,10], slightly higher when only patients with enteral nutrition were studied [11] (Table 1) [8,9,10,11], with the median onset of symptoms occurring 6 days after ICU admission [10]. However, none of these studies used a strict definition such as the one proposed above. Moreover, selected patients were studied and/or a limited period of observation used. Taken together, the true overall prevalence of diarrhoea in ICU population is unknown.

Diarrhoea is frequently occurring in critically ill patients during enteral nutrition, with prevalences reported varying from 10 to 78% [11–14]. Importantly, Ferrie and East [11] recently reported a reduction in the prevalence of diarrhoea from 36 to 23% ($P = 0.0002$) in severely ill tube-fed patients with the introduction of a bowel management protocol. However, the mean APACHE II score was significantly lower during the second phase of the study (22 vs. 29%, $P < 0.001$), and this raises the possibility that diarrhoea occurred more frequently in those patients that were more severely ill and represents a type I error. Such a hypothesis is supported by recent observational data in which patients with diarrhoea had greater illness severity scores [10].

PATHOPHYSIOLOGICAL MECHANISMS OF DIARRHOEA
Four different pathophysiological mechanisms underlying diarrhoea have been described: motoric, osmotic, secretory and exudative [3]. According to a more recent review [15], we suggest narrowing the focus to distinguish only between two pathophysiological processes: osmotic, reduced water absorption because of osmotically active substances intraluminally or short passage time; and secretory, imbalance between absorption and secretion of electrolytes leading to increased water secretion.

RISK FACTORS
Enteral nutrition may be mistakenly considered a common precipitant of diarrhoea. Interestingly, a meta-analysis suggested that the risk of developing diarrhoea was similar in patients receiving enteral or parenteral nutrition [16]. In contrast, a recent study reported that the enteral delivery of more than 60% of energy targets increased the risk of diarrhoea by 1.75 (1.02–3.01), whereas just the presence of enteral nutrition had no impact [10]. These latter data suggest that there may be a small intestinal threshold of nutrient absorption [17] and beyond such a level, malabsorption and diarrhoea occur. Another factor that appears to be associated with the risk of diarrhoea is exposure to antimicrobial drugs [10].

Proven risk factors for diarrhoea in general ICU population are enteral nutrition more than 60% of energy target and exposure to antimicrobial drugs.

CLASSIFICATIONS OF DIARRHOEA
Diarrhoea can be described by its severity, duration and cause.

Severity
Severe diarrhoea requires treatment (e.g. fluids), whereas mild is self-limiting (Fig. 1). However, the term ‘mild’ does not exclude the need for interventions, as mild diarrhoea might be infectious and therefore require treatment.

Duration
Acute diarrhoea lasts for less than 2 weeks and chronic diarrhoea more than 4 weeks. The majority
Table 1. Summary of recent larger studies reporting prevalence of diarrhoea in critically ill patients

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Definition</th>
<th>Design</th>
<th>Study patients</th>
<th>Main inclusion criteria</th>
<th>Main exclusion criteria</th>
<th>Prevalence</th>
<th>Association with outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrie and East, 2007 [11]</td>
<td>Bowel activity exceeding three stools of any consistency per day, or at least three unformed stools (or 300 ml) per day, for two consecutive days</td>
<td>Prospective, single-centre, before and after introduction of bowel management protocol</td>
<td>656</td>
<td>Length of stay &gt; 3 days + enteral nutrition</td>
<td>No enteral nutrition</td>
<td>36% before, 23% after the introduction of a bowel management protocol</td>
<td>No</td>
</tr>
<tr>
<td>Reintam et al., 2009 [8]</td>
<td>Not formed stools at least three times per day</td>
<td>Prospective, single-centre</td>
<td>1312</td>
<td>All patients admitted to the ICU</td>
<td>None</td>
<td>14%</td>
<td>No</td>
</tr>
<tr>
<td>Reintam Blaser et al., 2013 [9]</td>
<td>Not formed stools at least three times per day</td>
<td>Prospective, multicentre</td>
<td>377</td>
<td>Mechanical ventilation at admission continued for &gt; 6 h</td>
<td>Spontaneous breathing at admission, no bladder catheter (for IAP measurements)</td>
<td>21.5</td>
<td>No</td>
</tr>
<tr>
<td>Thibault et al., 2013 [10]</td>
<td>At least three liquid stools per day</td>
<td>Prospective, single-centre</td>
<td>278</td>
<td>All patients staying for &gt; 24 h</td>
<td>No admission diagnosis of gastrointestinal bleeding, and without enterostomy or colostomy</td>
<td>14%</td>
<td>NA</td>
</tr>
</tbody>
</table>
of critically ill patients have acute diarrhoea, with 89% of diarrhoea episodes in critically ill patients lasting for 4 days or less [10*, 18].

**Cause**

It is our opinion that differentiation between disease-related, medication-related and diet-related diarrhoea is useful.

**Infectious vs. noninfectious**

Because of differences in management, it is very important to distinguish additionally between infectious and noninfectious diarrhoea. Causes and management of noninfectious diarrhoea are presented in Table 2 [15, 19] and of infectious diarrhoea in Table 3 [20**, 21–23].

We wish to emphasize that diarrhoea is a symptom. Accordingly, only diagnosing and then treating the underlying cause may solve the problem.

**DISEASE-RELATED DIARRHOEA**

Underlying or concomitant disease or acute condition can cause disease-related diarrhoea. Assessment of specific intolerances, like lactose or sorbitol intolerance and fructose malabsorption, requires accurate anamnesis.

Pancreatic exocrine insufficiency and bile salt malabsorption-associated diarrhoea may occur without preexisting diagnosis and stops immediately when pancreatic enzymes or cholestyramine are added [24–26]. Wang *et al.* [24] reported moderate steatorrhoea in more than half of the patients in the ICU. Steatorrhoea was graded severe in almost 20% and the occurrence of steatorrhoea was closely associated with shock, sepsis, diabetes, cardiac arrest, hyperlactacidemia, invasive mechanical ventilation and haemodialysis. Although the assessment of duodenal enzyme output is complicated and not applicable at bedside, a sophisticated study of a small cohort reported that the content of amylase, chymotrypsin and trypsin in aspirated duodenal fluid was significantly reduced in patients with septic shock when compared with nonseptic patients as well as healthy subjects (*P* < 0.01) [25], consistent with the concept that pancreatic insufficiency is likely to contribute to diarrhoea in a proportion of ICU patients.

It has been proposed that hypoalbuminaemia (<2.5 g/dl), leading to reduced oncotic pressure, can be associated with reduced reabsorption of water from the gut lumen [2].

Severe infections, organ rejections after transplantation, endocrine disorders (thyroid diseases, diabetes among others), gastrointestinal tumours and malassimilation, for example, in short bowel syndrome or chronic inflammatory bowel disease are also associated with diarrhoea.

Disease-related diarrhoea resolves only when the trigger is eliminated.
**Table 2. Causes and specific management of noninfectious diarrhoea**

<table>
<thead>
<tr>
<th>Etiologic classification group</th>
<th>Specific pathology/condition/drug</th>
<th>Management</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-related</td>
<td>Specific intolerances (lactose, sorbitol, fructose, celiac disease)</td>
<td>Avoiding the trigger</td>
<td>Anamnesis is essential</td>
</tr>
<tr>
<td></td>
<td>Pancreatic exocrine insufficiency</td>
<td>Pancreatic enzymes (cave different administration rules via gastric and postpyloric tube) [19]</td>
<td>Can also occur in critically ill patients without previous pancreatic disease</td>
</tr>
<tr>
<td></td>
<td>Endocrine disorders (thyroid disease, diabetes, Zollinger-Ellison syndrome)</td>
<td>Treating the trigger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumours (gastrointestinal, pheochromocytoma)</td>
<td>Treating the trigger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic malassimilation states (short bowel syndrome, chronic inflammatory bowel disease)</td>
<td>Treating the trigger where possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bile acid malabsorption (cholestasis, postcholecystectomy)</td>
<td>Cholestyramine can be considered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intoxications (heavy metal poisoning)</td>
<td>Gastrointestinal decontamination and chelation therapy</td>
<td></td>
</tr>
<tr>
<td>Medication-related</td>
<td>Laxatives</td>
<td>Stop when no indication any more</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prokinetics</td>
<td>Stop when no indication any more</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperosmolar oral liquid preparations</td>
<td>Alternative preparations where possible</td>
<td>Detailed list elsewhere [15] Cave oral preparations via tube, especially postpyloric</td>
</tr>
<tr>
<td></td>
<td>Preparations with significant amount of poorly absorbed large carbohydrates (sorbitol, xylitol) Antibiotics</td>
<td>Alternative preparations where possible</td>
<td>Detailed list elsewhere [15] Antibiotic-associated diarrhoea with colitis is addressed under infectious diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
<td>In case of neutropenic colitis broad-spectrum antibiotics are recommended, rarely surgery may be needed</td>
<td>Cell fragments and membranes in stool support the diagnosis</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td></td>
<td>Cell fragments and membranes in stool support the diagnosis</td>
</tr>
<tr>
<td>Diet-related</td>
<td>Tube-feeding</td>
<td>Iso-osmolar formula with fibres, continuous administration. If severe diarrhoea persists after excluding other causes, changing formula and excluding contamination of the feeds, rate of enteral nutrition could be reduced.</td>
<td>Enteral nutrition should not be stopped because of diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Oral diet</td>
<td>Isotonic fluids, frequent small meals, avoidance of hypo- or hyperosmolaric fluids, gradual return to normal diet</td>
<td></td>
</tr>
</tbody>
</table>

**MEDICATION-RELATED DIARRHOEA**

Laxatives are frequently administered to critically ill patients, and their prophylactic use is thought to reduce the occurrence of gastrointestinal paralysis/paralytic ileus [27]. The implementation of a bowel management protocol should alert clinicians to promptly cease laxatives if diarrhoea occurs. Diarrhoea resolves in about 25% of all cases when laxatives are ceased [11].

Prokinetics are frequently implicated as causing diarrhoea with motor effects reducing gastrointestinal transit time. However, in the critically ill, the
Table 3. Miscellaneous pathogens causing infectious diarrhoea [20**,21–23]

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Characteristics</th>
<th>Special aspects</th>
<th>Diagnostics</th>
<th>Antimicrobial treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Large bowel, toxin-producing, dysentery, antibiotic-associated, recurrence-prone</td>
<td>Offending antibiotic should be withdrawn if possible. Unfavourable prognostic factors: WBC count &gt;15 000 cells/μl or albumin &lt;30 g/l or &gt;50% rise in baseline creatinine [20**]. Risk of toxic megacolon.</td>
<td>Fecal test for toxin A and B. Search in all ICU patients with diarrhoea</td>
<td>Choice of regimen depending on severity and recurrence. Metronidazol, Vancomycin enterally. Fidaxomicin, Rifaximin enterally</td>
</tr>
<tr>
<td>Escherichia coli-producing</td>
<td>Large bowel, toxin-producing, consider when nonfebrile bloody diarrhoea</td>
<td>Sporadic diarrhoea, 5–10% develop haemolytic uremic syndrome</td>
<td>Stool culture, test for Shiga toxin</td>
<td>No treatment with antimicrobials</td>
</tr>
<tr>
<td>Shigalike toxin (EHEC s. E. coli O157:H7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli (ETEC, EPEC, EAggEC, EIEC)</td>
<td>Small bowel (EIEC in large bowel), toxin-producing</td>
<td>Sporadic diarrhoea, traveller’s diarrhoea</td>
<td>Stool culture</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>Salmonella typhus</td>
<td>Small and large bowel, toxin-producing, dysentery, sometimes bloody diarrhoea</td>
<td>Food poisoning, sporadic diarrhoea, traveller’s diarrhoea. Risk of intestinal perforation, osteomyelitis, septic arthritis and mycotic aneurysm</td>
<td>Stool culture, blood culture if high fever</td>
<td>Fluoroquinolone. Ceftriaxone if acquired in Asia. Longer treatment in immunocompromised patients</td>
</tr>
<tr>
<td>Salmonella nontyphoidal</td>
<td>Small and large bowel, dysentery, sometimes bloody diarrhoea</td>
<td>Sporadic diarrhoea, traveller’s diarrhoea</td>
<td>Stool culture, blood culture if high fever (bacteraemia in 2–4%)</td>
<td>Antibiotics only if age &gt;50 y, bacteraemic, severely ill or immunocompromised patient, vascular graft, prosthetic joints or haemoglobinopathy, Fluoroquinolone</td>
</tr>
<tr>
<td>Shigella</td>
<td>Large bowel, toxin-producing, dysentery, sometimes bloody diarrhoea</td>
<td>Sporadic diarrhoea, traveller’s diarrhoea</td>
<td>Stool culture</td>
<td>Fluoroquinolone in immunocompromised</td>
</tr>
<tr>
<td>Campylobacter species</td>
<td>Large and small bowel, dysentery, sometimes bloody diarrhoea</td>
<td>Sporadic diarrhoea, traveller’s diarrhoea, self-limited in normal host, associated with Guillain-Barré Syndrome (in 15% of cases) or reactive arthritis</td>
<td>Stool culture</td>
<td>Azithromycin, for Campylobacter fetus gentamicin</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Small bowel, toxin-producing</td>
<td>Food poisoning</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Small bowel, toxin-producing</td>
<td>Food poisoning</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>Large bowel, toxin-producing, bloody diarrhoea, antibiotic-associated</td>
<td>Rare</td>
<td>Responds to stopping offending antibiotic</td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td>Large bowel, dysentery</td>
<td></td>
<td>Antibiotics only if severe, doxycycline plus aminoglycoside</td>
<td></td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Large bowel, toxin-producing</td>
<td>Food poisoning, traveller’s diarrhoea. Rehydration is essential.</td>
<td>Stool culture</td>
<td>Doxycycline, azithromycin, tetracycline</td>
</tr>
</tbody>
</table>

(Continued)
Table 3 (Continued)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Characteristics</th>
<th>Special aspects</th>
<th>Diagnostics</th>
<th>Antimicrobial treatment options</th>
</tr>
</thead>
</table>
| *Vibrio parahaemolyticus* and *vulnificus* | Large bowel, toxin-producing | Food poisoning, traveller’s diarrhoea. V. *vulnificus*: skin lesions and bacteraemia, life-threatening | Stool culture                | *V. parahaemolyticus*: treat if severe disease. Fluoroquinolone  
*V. vulnificus*: treat early. Ceftriaxone plus doxycycline |
| *Aeromonas/Plesiomonas*         | Small bowel                       | Food poisoning, traveller’s diarrhoea                | Stool culture                | Fluoroquinolone                                                        |
| *Norovirus*                     | Small bowel, nausea and vomiting  | Highly contagious, majority of outbreaks of nonbacterial gastroenteritis | Stool or emesis for PCR      | None                                                                   |
| *Rotavirus*                     | Small bowel, nausea               | Mainly in small children                            | Stool for rapid antigen test  | None                                                                   |
| *Adenovirus*                    | Small bowel                       |                                                     | Stool for rapid antigen test  | None                                                                   |
| *Cytomegalovirus*               | Large bowel, dysentery            | Search in case of immunosuppression                  | Mucosal biopsy for histology, plasma PCR | Ganciclovir                                                          |
| *Herpes simplex virus*          | Large bowel                       | Search in case of immunosuppression                  | Mucosal biopsy for histology and PCR | Valacyclovir                                                          |
| *Protozoa*                      |                                    |                                                     |                              |                                                                        |
| *Entamoeba histolytica*         | Large bowel, dysentery, bloody diarrhoea | Risk factors: anoreceptive intercourse and colonic irritation | Stool for enzyme immunoassay or PCR | Metronidazole                                                        |
| *Cryptosporidium parvum*        | Small bowel                       | Search if HIV-infected (with immunodeficiency) and diarrhoea > 10 days | Stool for enzyme immunoassay | Nitazoxanide                                                          |
| *Microsporidium species*        | Small bowel                       | Search if HIV-infected (with immunodeficiency) and diarrhoea > 10 days | Stool for enzyme immunoassay | Albendazole                                                          |
| *Isospora belli*                | Small bowel                       | Search if HIV-infected (with immunodeficiency) and diarrhoea > 10 days | Stool for enzyme immunoassay | Trimethoprim/sulfamethoxazole                                          |
| *Cyclosporacayatanensis*        | Small bowel                       | Search if HIV-infected (with immunodeficiency) and diarrhoea > 10 days | Stool for enzyme immunoassay | Trimethoprim/sulfamethoxazole                                          |
| *Giardia lamblia*               | Small bowel                       | Search if chronic traveller’s diarrhoea             | Stool for microscopy or enzyme immunoassay | Tinidazole, nitazoxanide, albendazole                                    |

EAggEC, enteroaggregative Escherichia coli; EHEC, enterohemorrhagic Escherichia coli; EIEC, enteroinvasive enteroaggregative Escherichia coli; EPEC, enteropathogenic Escherichia coli; ETEC, enterotoxigenic Escherichia coli; WBC, white blood cell.
motilin agonist erythromycin at a dose of 200 mg acutely slows rather than accelerating small intestinal transit time [28]. When prokinetic drugs are used during intragastric feeding in the critically ill, metoclopramide was associated with diarrhea in 32%, erythromycin in 30% and their combination in 49% [29]. In all patients included in the latter study, diarrhea was mild and stopped immediately after discontinuing prokinetic therapy.

Hyperosmotic preparations containing lactose, sorbitol or other osmotically active components (e.g. magnesium) can induce osmotic diarrhea [15], especially in patients with respective intolerance. Medications causing osmotic diarrhea are listed elsewhere [15].

Laxatives and prokinetics should be stopped immediately when the indication is not present anymore. All prescribed substances need to be checked for their indication and ingredients, and alternative preparations need to be considered where possible.

Antibiotic-associated diarrhea
Incidence of antibiotic-associated diarrhea (AAD) is up to 25% and depends on the antibiotic drug used and can be classified as follows [30–32]:

AAD without colitis is usually mild and self-limiting with different underlying causes:

1. Direct prokinetic effect of antibiotics on gastrointestinal motility (e.g. erythromycin, azithromycin)
2. Microbial modification with unmetabolized carbohydrates causing osmotic diarrhea [33,34].
3. Unmetabolized dihydroxy bile acids owing to disturbed microbiota induce secretory diarrhea [30,35].

AAD with colitis is induced by bacterial overgrowth of gut microbiota by Clostridium difficile or rarely Klebsiella oxytoca (see section INFECTIOUS DIARRHOEA).

Diarrhoea in the immunocompromised patient
Diarrhoea in immunocompromised and/or neutropenic patients (commonly both disease-related and medication-related diarrhea) is severe in up to 10% and has a specific etiologic spectrum [36,37].

Neutropenic enterocolitis is a combination of pyrexia (>38.5°) and abdominal symptoms (pain in right iliac fosse, abdominal distension, diarrhea) along with typical radiologic findings (gross thickening of ileal and caecal wall with surrounding inflammatory changes) in neutropenic patients (absolute neutrophil count <500 cells/mm²) [38].

DIET-RELATED DIARRHOEA
Diarrhoea as a complication of enteral nutrition is often reported, whereas less associated with oral diet in hospitalized patients.

Enteral feeding
Long-time enteral nutrition, but also high-osmolality and/or low-fibre formula, bolus feeding and/or too fast increase to the target, and postpyloric enteral nutrition have been associated with increased prevalence of diarrhea in stroke unit patients [39]. The latter is not confirmed in critically ill patients [40,41].

Bacterial contamination of the enteral formulas is rarely seen. More frequently, retrograde bacterial overgrowth of tube feeding systems with Enterococcus, Enterobacter cloacae and Klebsiella oxytoca was found, whereas bacterial count correlated directly with severity of illness, and the time the systems were used [42,43].

In case of diet-related diarrhea, soluble fibres added to the meal exert positive effects; when being fermented by gut microbiota to gas and short-chain fatty acids they can increase transit time, reduce stool frequency and improve consistency [15].

Oral diet
A significantly increased amount of oral fluids, increased amounts of ingested fibres or nutrients with a high amount of fructose or sorbitol may induce diarrhea. Extubated patients require a gradual return to normal diet using isotonic fluids, and frequent small meals, with hypoosmolaric or hyperosmolaric fluids avoided [44].

INFECTIOUS DIARRHOEA
To exclude infectious diarrhea in all patients with severe diarrhea, anamnesis is important, completed by a clinical examination and laboratory values. When infectious diarrhea is presumed, determination of the pathogen - either via culture or PCR of toxin or antigen - is essential (Table 3).

Bacterial diarrhea
Different strains of Escherichia coli (Table 3) cause diarrhea, but most of them are not relevant for the ICU. Different is enterohemorrhagic E. coli
(EHEC), which in up to 10% leads to a haemolytic uremic syndrome (HUS), characterized by acute renal failure, haemolytic anaemia and thrombocytopenia [45]. The EHEC toxins are similar to the toxins produced by *Shigella dysenteriae*. The incubation period ranges from 3 to 8 days, and symptoms include bloody diarrhoea, abdominal cramps, fever and vomiting. Antibiotics and antimotility drugs are contraindicated because they may enhance toxin release. In patients with HUS, plasma exchange is recommended, and immunosuppressive therapy with eculizumab can be considered [46,47].

**Antibiotic-associated diarrhoea with colitis**

*C. difficile* is a gram-positive spore-forming anaerobe that was identified as the leading cause of toxin-positive AAD with pseudomembranous colitis in the late 1970s [48,49]. Severe colitis, toxic megacolon and death have all been reported. Recently, a considerable increase in the incidence of *C. difficile* infections (CDI) was reported [50]. The cause was a new *C. difficile* strain (NAP1/BI/027) that produces about 20 times the amount of the toxins A and B. The new strain is associated with a more severe course of disease, higher morbidity and mortality, a greater likelihood for ICU admission and higher healthcare costs [50]. Independent risk factors include antimicrobials (most notably quinolones, clindamycin, ampicillin and cephalosporines), age above 60 years, proton pump inhibitors (PPIs) [51], exposure to other patients with CDI, residence in a chronic care facility and severe underlying disease [52]. Relapses occur in up to 30% [53].

*Klebsiella oxytoca* AAD occurs after antibiotic treatment with penicillins, quinolones and cephalosporines and responds to cessation of antibiotic treatment [54]. Main symptoms are bloody diarrhoea and severe abdominal cramps; endoscopic findings are longish ulcers predominantly in the right colon [54].

**Viral, fungal and parasitic diarrhoea**

In patients who are immunocompromised, the presence of severe diarrhoea necessitates specific investigations for opportunistic pathogens (Table 3).

**MANAGEMENT**

Differential diagnosis and management algorithm is presented in Fig. 2.

Prevention is the desired management strategy of diarrhoea, but several factors that may promote diarrhoea (e.g. antibiotics) are unavoidable in critically ill patients. However, indication for each medication, including PPI [55], should be carefully considered.

To prevent feeding-associated diarrhoea, administration rules for enteral nutrition are important. Generally accepted options to reduce diarrhoea in enterally fed patients are iso-osmolar solutions and continuous infusion. In case of intolerances, lactose-free diets, and in patients with fat malabsorption, low fat or medium-chain triglyceride containing diets are recommended [56]. Some fibres (e.g. pectin and partially hydrolysed guar gum) have been reported to reduce the incidence of diarrhoea [56,57]. There are no data to support elemental diet for prevention or treatment of diarrhoea.

Specific treatment is available for pancreatic exocrine insufficiency and some forms of infectious diarrhoea (Table 3), whereas efforts to identify and treat the underlying cause and provision of supportive care are required for all patients with diarrhoea.

Supportive care with replacement of fluids and electrolytes and close monitoring of laboratory values and organ function are essential. Avoidance or early detection and treatment of consequences (skin lesions among others) is also important (see Fig. 2).

Isolation precautions to prevent nosocomial transmission are required for all symptomatic patients with infectious diarrhoea in the ICU because of their bedriddenness and to great extent incontinence.

**Nonspecific treatment options**

Opioids as antimotility drugs (loperamide) are not recommended as primary therapy and should be avoided in patients with acute dysentery characterized by blood in the stools and high fever, acute ulcerative colitis, bacterial enterocolitis caused by invasive organisms or AAD with colitis.

Cholestyramine may be considered in diarrhoea caused by bile acid malabsorption (patients with cholestasis, short bowel syndrome, terminal ileum resection and following cholecystectomy) [15]. It needs to be remembered that cholestyramine can reduce the absorption of enterally administered medications, including metronidazole used for CDI [15].

Probiotics and prebiotics can possibly reduce diarrhoea, but there are not enough data to recommend their routine use in critically ill patients [58,59]. Important is that in critically ill patients and immunocompromised patients, *Saccharomyces boulardii* is not recommended because of several reported cases of fungemia [60,61]. Faecal transplantation is recommended in case of multiple recurrent
CDI [20**,62], but not studied in the critically ill patients.

**CONSEQUENCES AND OUTCOME**

There are several systemic (water and electrolyte dysbalance, haemodynamic instability, metabolic acidosis, malabsorption and malnutrition) and local (skin lesions and contamination of wounds) consequences of diarrhoea that need to be avoided or, at least, recognized early.

Higher disease severity scores at admission and longer ICU length of stay in patients with diarrhoea have been described [10*,14], but it has not been demonstrated that diarrhoea itself is an independent risk factor for adverse outcome in critically ill patients [8,9,10*]. Nonetheless, a greater incidence of bedsores occurs in patients with diarrhoea [63]. Although not definitively proven, it is very likely that diarrhoea has an impact on the risk of complications in ICU patients, as well as on the workload and costs [10*].

**CONCLUSION**

We propose that diarrhoea in the critically ill patients be defined as the simultaneous presence of stool frequencies three or more stools per day, stool weights 200 g/day or more and consistency of stools categorized as 5–7 on the Bristol Stool Chart. We propose a practical approach for differential diagnosis and management of diarrhoea based on

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**FIGURE 2.** Differential diagnosis and management of diarrhoea.
existing evidence. However, further studies on epidemiology, risk factors, management and outcome of diarrhoea in critically ill patients are warranted.

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Conflicts of interest

None.

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

11. This is the first study specifically addressing prevalence and risk factors of diarrhoea in critically ill patients independent of provision of enteral nutrition.
47. This is a nice update on this severe complication associated with infectious diarrhoea.


56. Blumenstein I, Shastri YM, Stein J. Gastrointestinal tube feeding: techniques, problems and solutions. World J Gastroenterol 2014; 20:8505–8524. This is a nice review article summarizing current evidence on the problems of tube feeding.


