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Variations in the management of diarrhoea induced by cancer therapy: results from an international, cross-sectional survey among European oncologists

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ABSTRACT

Background Chemotherapy-induced diarrhoea (CID) is a common side effect of cancer treatment. While cytotoxic agents are the main cause of CID, targeted drugs, immunotherapy and radiotherapy can also cause diarrhoea. Patients with severe CID often require hospital admission for intravenous fluid resuscitation and supportive treatment. In other patient populations, such as children with infectious diarrhoea, therapy is based on evidence from randomised-controlled clinical trials. In contrast, few trials have investigated CID management, and hence, treatment guidelines are largely based on expert opinion.

Methods We conducted an online survey on CID management and institutional routines across Europe to obtain a more detailed picture of current practice in CID treatment. We analysed the responses from a total of 156 clinicians from 83 different medical centres in 31 countries.

Results CID (any grade) is recognised as a common clinical problem in patients undergoing antitumoral treatment and it can require hospital admission in a substantial subgroup of patients. There is a strong consensus among clinicians as to the choice of resuscitation strategies and drug treatment for severe CID; 85.9% (n=134) of all respondents prefer intravenous crystalloid fluids and 95.5% (n=149) routinely use loperamide. In sharp contrast, we have identified disparities in the use of bowel rest in CID; approximately half of all participants (57.7%; n=90) consider bowel rest in initial CID management, while the remainder (42.3%; n=66) does not.

Conclusions As previous studies have shown that bowel rest is associated with adverse outcomes in diarrhoea due to causes other than chemotherapy, the results from this survey suggest that further research is needed as to its role in CID.

Key questions

What is already known about this subject?

► While treatment of infectious diarrhoea is based on clinical trials, there are limited data for the management of chemotherapy-induced diarrhoea (CID), and current practice guidelines are largely based on expert opinion.

What does this study add?

► Surveyed clinicians agree on resuscitation strategies and pharmacological management of CID. However, there is no consensus on bowel rest, while evidence from other patient populations suggests that fasting can have a potentially disadvantageous effect on the course of diarrhoea.

How might this impact on clinical practice?

► The results motivate prospective studies on the role of bowel rest in CID.

INTRODUCTION

Diarrhoea is a side effect of most anticancer agents, as they frequently affect the rapidly dividing cells of the intestinal epithelium.[1] For example, more than 10% of patients receiving fluoropyrimidins develop severe diarrhoea (≥ grade 3 according to the Common Terminology Criteria for Adverse Events (CTCAE)).[2]

Despite being commonly referred to as 'chemotherapy'-induced diarrhoea (CID), the term 'cancer-therapy'-induced diarrhoea would be more appropriate as classical cytotoxic drugs, targeted drugs such as tyrosine kinase inhibitors, radiotherapy and immunotherapy can all lead to severe CID. For example, depending on the regimen used, more than 30% of patients receiving immunotherapy develop diarrhoea due to immune-mediated enterocolitis, and approximately 1%–10% of these patients experience severe diarrhoea.[3] Several mechanisms can lead to CID, including enterocyte damage, cholinergic activation and autoimmune-induced mucosal impairment (summarised by Andreyev *et al* in the 2014 consensus paper on CID management).[2] CID is physically painful, socially debilitating and significantly affects the patient's quality of life.[4] In cases

of severe CID, cancer treatment is often temporarily, or permanently, discontinued, which may negatively affect oncological outcomes. In addition, CID can impose a significant economic burden on the healthcare system, with the length of the hospital stay being the most important cost factor.[5]

Several national and international guidelines for the management of CID exist, including those from the European Society for Medical Oncology (ESMO), and the US National Comprehensive Cancer Centre Network, complemented by published consensus papers.[2 6–8] Generally, the recommended initial approach to the patient with severe CID includes hospital admission, intravenous fluids and the opioid-receptor agonist, loperamide, to regulate gut motility.[2 4 5] However, evidence from randomised controlled trials for the use and dosage of loperamide is limited and recommendations are largely based on expert opinion and clinical experience, as well as extrapolated from data from the treatment of diarrhoea in other clinical settings, such as irritable bowel disease.[2 9] In therapy-refractory cases, the somatostatin analogue, octreotide, has been recommended based on a phase I trial as well as a small study conducted in the 1990s comparing octreotide to loperamide.[10 11] Beyond these evidence-based recommendations, data on CID management are sparse, and this is reflected in the limited overall strength of guideline recommendations.[6]

In most CID treatment guidelines, supportive therapy includes bowel rest, that is, complete avoidance of oral food or beverage intake, for varying degrees of CID severity.[6 7 12 13] It is likely that this concept stems from the observation that patients experience emptying of their bowels after food ingestion due the gastrocolic reflex (an increase in intestinal motility after food intake), as well as a consequence of malabsorption.[14] However, prospective studies on the benefit of bowel rest are lacking. By contrast, in the management of diarrhoea due to causes other than cancer therapy it is common practice to *avoid* fasting. The treatment of acute infectious diarrhoea is particularly well studied in children, who form a large patient group presenting with diarrhoea: trials from the late 1970s onwards have provided compelling evidence that bowel rest in this setting is associated with increased morbidity and mortality.[15 16]

Here, we report the results of a comprehensive international survey on CID management from 156 physicians, mainly oncologists at European medical centres. Our main aim was to identify the current treatment routines for patients with CID, to highlight areas of heterogeneity, and to assess the application of national or international guidelines. In particular, we were interested in the use of bowel rest for CID management in order to elucidate the feasibility and usefulness of a clinical trial to address its role in the treatment of CID.

METHODS

Participants

We conducted an international, web-based, cross-sectional survey on the management of CID among physicians involved in the medical treatment of malignant neoplasms. Physicians were contacted by email and invited to participate in the survey via an enclosed link to the survey website. We systematically searched public hospital websites for the contact details of eligible physicians. Searches were focused on, but not limited to, university hospitals and tertiary care providers. In addition, the survey was disseminated via national and international oncology associations, including the German Organisation for Medical Oncology, the Hellenic Society of Medical Oncology, the Danish Society for Clinical Oncology, the Young Hemato-Oncologist Group Austria, and via different email distribution lists of ESMO members. Participants were encouraged to forward the survey to other colleagues treating patients with CID. As a result of this distribution strategy, a response rate could not be calculated. Participants were informed that their involvement was voluntary, that the results were anonymised and that they would not receive any reward for their participation. The survey was conducted from March to May 2019.

Survey design

We created a web-based survey using the Swedish University computer Network Survey interface, *Survey&Report,* V.4.3.9.5. The questionnaire contained 20 questions designed to address three main areas: (1) Demographics of the participants (ie, clinical experience, (sub)specialisation, hospital, country). (2) Estimates of the clinical burden of CID in their practice. (3) The use of drugs, fluids and other supportive strategies used to manage CID (see online supplementary material). A draft survey was circulated among trainee oncologists at the Karolinska University Hospital and the final version of the survey was the result of several revisions of its structure, content and style. All questions, except estimates of the clinical burden of CID, were obligatory and participants could not complete the survey without answering them. We limited the possibility of repeatedly answering the survey from the same device to reduce the risk of multiple answers from the same individual.

Statistical analysis

Statistical analysis was performed using the IBM software package, SPSS V.25, and a graphical display of the results was generated with GraphPad prism V.6.0h. Descriptive statistics are given as percentages where applicable. Correlation was calculated using the Pearson correlation coefficient (Pearson's r).

RESULTS

A total of n=156 participants completed the survey (table 1). We received responses from 83 different

Table 1 Characteristics of surveyed physicians (n=156)

Country	
Sweden	47 (30.1%)
Germany	30 (19.2%)
UK	15 (9.6%)
Austria	10 (6.4%)
Italy	8 (5.1%)
Greece	8 (5.1%)
Other European	24 (15,5%)
Non-European	14 (9.0%)
Medical specialty	
Clinical oncology	71 (45.5%)
Gastroenterology	7 (4.5%)
Haematology	12 (7.7%)
Internal medicine	6 (3.8%)
Medical oncology	58 (37.2%)
Pulmonology	1 (0.6%)
Clinical role	
Professor	5 (3.2%)
Attending/senior physician	35 (22.4%)
Specialist	57 (36.5%)
Resident	48 (30.8%)
Intern	9 (5.8%)
Other	2 (1.3%)
Years of clinical experience	
0–2 years	17 (10.9%)
3–6 years	47 (30.1%)
>6 years	92 (59.0%)
Active involvement in clinical management of CID	
Yes	151 (96.8%)
No	5 (3.2%)

CID, chemotherapy-induced diarrhoea.

medical centres, 20 of which produced more than one respondent. The countries with most respondents were Sweden (n=47; 30.1%), Germany (n=30; 19.2%), the UK (n=15; 9.6%), Austria (n=10; 6.4%), Italy and Greece (n=8 each; 5.1%). Clinical (n=71; 45.5%) and medical oncologists (n=58; 37.2%) represented the majority of participants. Most participants had several years of clinical experience, with 89.1% (n=139) reporting at least 3 years of clinical activity and 59% (n=92) reporting more than 6 years. The vast majority (n=151; 96.8%) was actively involved in the clinical management of CID. A total of n=14 answers (9.0%) was received from outside Europe, including Canada, Japan, Ethiopia, Libya, India, Pakistan, Iraq, Kuwait, Bangladesh and Guatemala. These answers were included in the final evaluation.

When asked to estimate the number of admissions of patients with severe CID, the majority of participants reported 10 or fewer admissions per month to their centre (n=127, 88.2%; median, 4.0; IQR, 2–8; answers, n=144). In addition, participants estimated that CID (any grade) occurred in a fifth of patients with cancer receiving antitumoral treatment (median, 20%; IQR, 11%–36%; answers, n=135). While these data suggest that CID in general is a common problem in patients receiving cancer treatment, hospital admission rates among patients who develop CID were estimated to be only 1 in 10 (median, 10%; IQR, 5%–15%; answers, n=138).

Results from questions on the management of CID revealed a broad consensus on the drugs, as well as on the type of intravenous fluid, used to treat patients with CID (figure 1A and online supplementary table 1). In total, 95.5% (n=149) considered loperamide as the drug of choice for severe CID, followed by deodorised tincture of opium (n=55, 35.3%), octreotide (n=41, 26.3%) and oral antibiotics (n=36, 23.1%, multiple answers were permitted). Some variations in treatment approaches became evident when analysing results from countries with more than eight answers separately; however, loperamide was used by the majority of respondents in all six countries (see online supplementary table 1). A total of 85.9% (n=134) of all participants considered crystalloid fluids for resuscitation, with colloid fluids (n=17, 10.9%), sugar solutions (n=38, 24.4%) and oral rehydration solutions (n=37, 23.7%) each used by less than a quarter of all participants. Consensus on anti-inflammatory treatment in cases of immunotherapy-mediated CID was equally strong, with 87.8% (n=137) of participants considering steroids and 18.6% (n=29) using the tumour necrosis factor α (TNFα)-antibody, infliximab (figure 1A).

When asked to state the complications that are of greatest concern for patients with CID (multiple answers were permitted), the majority of respondents reported electrolyte imbalances (n=129, 82.7%,), while sepsis (n=107, 68.6%), neutropenic enterocolitis (n=70, 44.9%), *Clostridioides difficile*-associated colitis (n=66, 42.3%) and bowel perforation (n=62, 39.7%) were also frequently mentioned. Other complications included ileus, fat or carbohydrate malabsorption, small intestinal bacterial overgrowth, peritonitis and acute kidney failure.

When asked for strategies that the respondents regularly applied to reduce the risk of complications, answers were heterogeneous with 45.5% (n=71) of all participating colleagues using bowel rest, 34% (n=53) intravenous antibiotics, 19.9% (n=31) aggressive oral resuscitation and 17.9% (n=28) oral antibiotics (figure 1B). Asked directly whether they would consider bowel rest/fasting in the initial management of severe CID, 57.7% (n=90) answered that they would consider bowel rest, while 42.3% (n=66) would not (figure 1B). There was a strong positive correlation between those that answered in favour of using bowel rest to reduce the risk of complications and those that considered bowel rest for the initial treatment of CID (Pearson's r=0.626, p=2.2E^{-18}).

Institutional, national or international guidelines were used at the centres of 63.5% (n=99) of

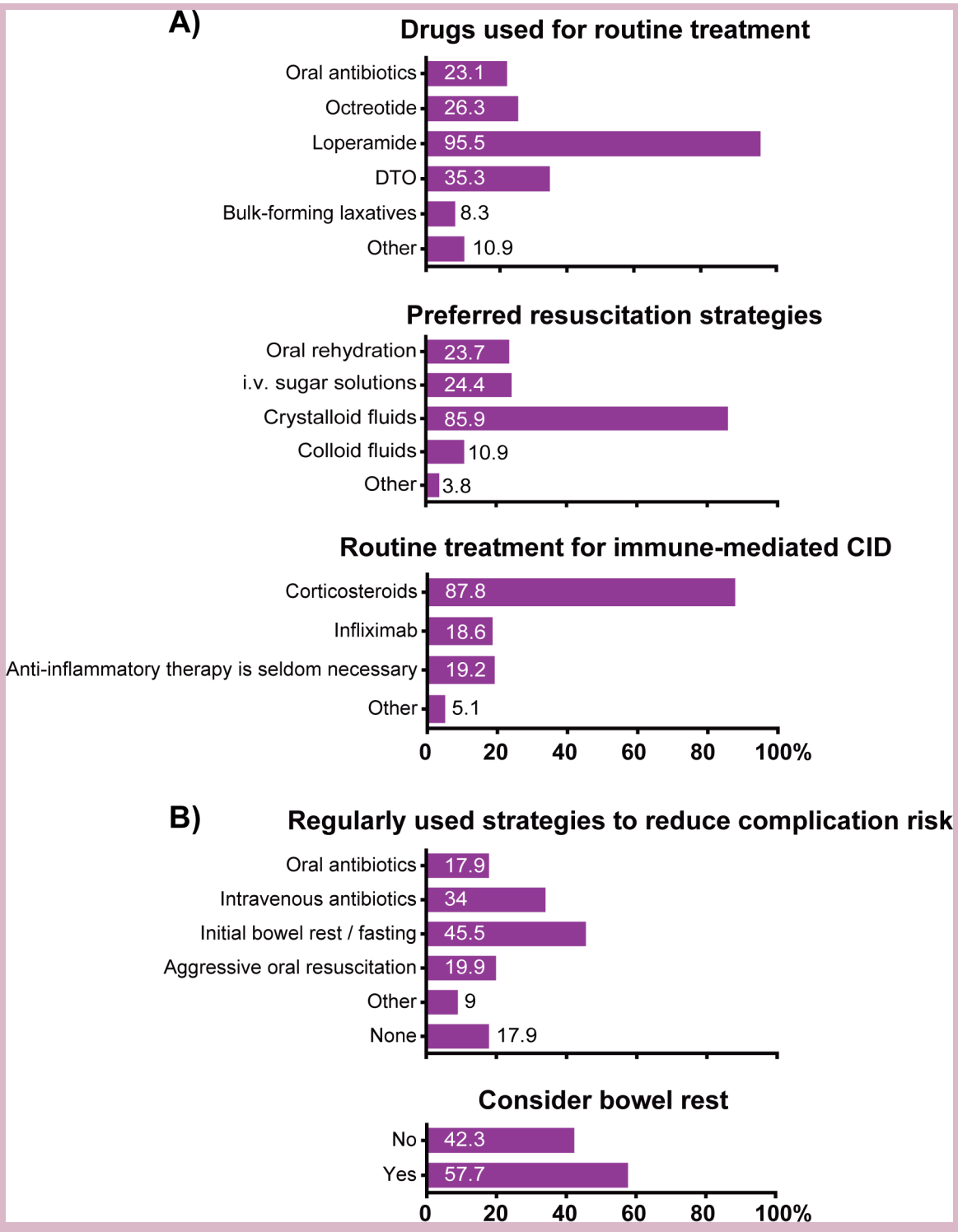

Figure 1 Results from treatment-related items. (A) Relative frequencies (as a percentage) for the indicated responses on drug treatment. (B) Relative frequencies (as a percentage) for the indicated responses on supportive strategies, including bowel rest. Total exceeds 100% as multiple answers were allowed; numbers in and next to bars give percentages. CID, chemotherapy-induced diarrhoea; DTO, deodorised tincture of opium.

participants, while 36.5% (n=57) reported to not use any guidelines.

DISCUSSION

This international survey identified areas of agreement between physicians treating patients with cancer for CID, and established aspects of treatment that differ substantially between different centres.

Overall, the survey participants estimated the prevalence of CID and severe CID at their respective centres in concordance with the available data that suggest frequencies of CTCAE grade 3 or 4 toxicity in 5%–47% of all patients, depending on the therapy regimen.[2]

Consensus among participants was highest when regarding the choice of intravenous fluids as well as the initial drug treatment (figure 1A). Both crystalloid fluids and loperamide were clearly favoured over all other options for CID treatment, which is in line with current guidelines[2 6] and for which there is at least some supporting evidence.[9 11] Octreotide, whose use in CID treatment is supported by older clinical trials,[10 11] is only considered by a quarter of all participants for routine use in cases of severe CID. This result could possibly be explained by the observation that symptoms in most patients resolve following loperamide and fluid resuscitation, but may also be influenced by the cost of octreotide, the requirement for parenteral application or by a lack of awareness of a role for somatostatin antagonists in CID treatment. The use of antibiotics was considered by more than a third of surveyed colleagues 'to reduce complication risk' (figure 1B). While this rate of antibiotics use is surprisingly high for CID, it cannot be excluded that some colleagues were referring to treating rather than preventing complications, as we did not explicitly ask the participants to disregard patients with proven or suspected bacterial translocation or other infectious complications.

Two questions were designed to address whether bowel rest is considered for CID treatment. Approximately half of all participants supported a role for bowel rest in CID management in both questions (figure 1B), indicating substantial discrepancies with respect to this strategy. In adult patients, the importance of enteral nutrition has been studied extensively in critically ill patients in intensive care units. Collectively, there is strong evidence to support early enteral feeding.[17 18] Similarly, treatment guidelines for children with infectious diarrhoea clearly support continuous enteral nutrition and discourage fasting.[19] An important scientific rationale for upholding enteral nutrition in enterocolitis is the way in which the intestinal epithelium receives nutrients: enterocytes require carbohydrates and short-chain fatty acids from the lumen, as the supply via the bloodstream is not sufficient.[20] Fasting, in contrast, reduces enterocyte renewal and hence increases intestinal permeability, facilitating bacterial translocation.[21] It is important to note that the main rationale for maintaining enteral nutrition (ie, nutrient supply for enterocytes) is independent of the mechanisms causing diarrhoea, and patients receiving cytotoxic therapy, targeted drugs or immunotherapy could benefit from an improved management of this serious complication. However, bowel rest would clearly be indicated for those patients anticipated to require surgery, for example, in the case of suspected or proven perforations, or ileus.

In summary, the results of this survey reveal high concordance among physicians treating patients with CID in the use of intravenous resuscitation strategies and loperamide. However, there is no consensus on the use of bowel rest versus continued enteral nutrition for CID treatment. Based on previous studies that demonstrated a detrimental effect of bowel rest in patients with diarrhoea due to causes other than cancer treatment, it is clear that further research on the role of continued enteral nutrition in CID is required.

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REFERENCES

1 Barker N, van de Wetering M, Clevers H. The intestinal stem cell. *Genes Dev* 2008;22:1856–64.
2 Andreyev J, Ross P, Donnellan C, *et al*. Guidance on the management of diarrhoea during cancer chemotherapy. *Lancet Oncol* 2014;15:e447–60.
3 Wang Y, Abu-Sbeih H, Mao E, *et al*. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *J Immunother Cancer* 2018;6.
4 Arbuckle RB, Huber SL, Zacker C. The consequences of diarrhea occurring during chemotherapy for colorectal cancer: a retrospective study. *Oncologist* 2000;5:250–9.
5 Dranitsaris G, Maroun J, Shah A. Estimating the cost of illness in colorectal cancer patients who were hospitalized for severe chemotherapy-induced diarrhea. *Can J Gastroenterol* 2005;19:83–7.
6 Bossi P, Antonuzzo A, Cherny NI, *et al*. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol* 2018;29:iv126–42.

7 Thompson JA. New NCCN guidelines: recognition and management of immunotherapy-related toxicity. *J Natl Compr Canc Netw* 2018;16:594–6.
8 Sharma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhoea. *Lancet Oncol* 2005;6:93–102.
9 Lavö B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome–a double-blind placebo controlled study. *Scand J Gastroenterol Suppl* 1987;130:77–80.
10 Wadler S, Haynes H, Wiernik PH. Phase I trial of the somatostatin analog octreotide acetate in the treatment of fluoropyrimidine-induced diarrhea. *J Clin Oncol* 1995;13:222–6.
11 Cascinu S, Fedeli A, Fedeli SL, *et al*. Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: a randomized trial. *J Clin Oncol* 1993;11:148–51.
12 Nationell vårdprogram akut onkologi. Available: www.cancercentrum.se/syd/cancerdiagnoser/overgripande-kunskapsstod/nationellt-vardprogram-akut-onkologi/ [Accessed 24 Sep 2019].
13 Pan Birmingham Cancer Network. Guideline for the management of chemotherapy induced diarrhoea in adult patients. Available: www.uhb.nhs.uk/Downloads/pdf/CancerPbChemotherapyInducedDiarrhoeaAdults.pdf [Accessed on 24 September 2019].
14 Brown KH, MacLean WC. Nutritional management of acute diarrhea: an appraisal of the alternatives. *Pediatrics* 1984;73:119–25.
15 Sack DA, Chowdhury AM, Eusof A, *et al*. Oral hydration rotavirus diarrhoea: a double blind comparison of sucrose with glucose electrolyte solution. *Lancet* 1978;2:280–3.
16 Brown KH, Gastañaduy AS, Saavedra JM, *et al*. Effect of continued oral feeding on clinical and nutritional outcomes of acute diarrhea in children. *J Pediatr* 1988;112:191–200.
17 Heyland DK, Dhaliwal R, Drover JW, *et al*. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003;27:355–73.
18 Nutrition under intensivvård, rutin för vårdpersonal, Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset. Available: alfresco.vgregion.se/afresco7service/vgr/storage7node/content/14613/nutrition under intensivvård.pdf [Accessed 24 Sep 2019].
19 The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/00018677.htm [Accessed 1 Aug 2019].
20 Roediger WE. The starved colon—diminished mucosal nutrition, diminished absorption, and colitis. *Dis Colon Rectum* 1990;33:858–62.
21 Isolauri E, Juntunen M, Wiren S, *et al*. Intestinal permeability changes in acute gastroenteritis: effects of clinical factors and nutritional management. *J Pediatr Gastroenterol Nutr* 1989;8:466–73.