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Review Article

Diarrhea in Critically Ill Patient

Sanaa AlKhawaja*

Senior Critical Care Consultant, Intensive Care and Anesthesia Department, Salmaniya Medical Center, Bahrain

***Corresponding Author**: Sanaa AlKhawaja, Senior Critical Care Consultant, Intensive Care and Anesthesia Department, Salmaniya Medical Center, Bahrain.

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Abstract

Diarrhea is one of the major problems that may complicate the hospitalization of a critically ill patient. Diarrhea may result in a number of negative clinical sequelae, including fluid and electrolyte abnormalities, dehydration, fecal incontinence, and pressure sores. This may result in the cessation of enteral nutrition, which increases the risk of energy and protein deficit and can exacerbate under nutrition. Diarrhea was found to be associated with increased crude ICU length of stay and mortality. There is no consensus on the definition of diarrhea among the critically ill patients which result in difficulties in reporting its incidence. Blaser., *et al*. [1] define diarrhea in the critically ill 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. This definition is comprehensive and easy to apply in practice and can be standardized among health care professionals.

Diarrhea in general can be classified according to the duration, severity, mechanism, or the cause. In the critical care setting, it is practical to divide diarrhea according to the cause into two main categories, either a life threating conditions or non-life threatening. Life threating can be caused by intestinal ischemia or *Clostridium difficile* infection (CDI). Non-life threatening can be caused by critical illness related diarrhea, drugs and enteral feeding associated diarrhea. Once diarrhea is recognized, clearly defined protocols should be implemented which identify the cause, reduce risk of transmission of infectious agents, and treat reversible etiology. The treatment of diarrhea should start with providing supportive care while the underlying causes of diarrhea are investigated and treated.

Keywords: *Diarrhea; Critical Ill; Bowel Ischemia; Drug Causing Diarrhea; Life Threatening Causes of Diarrhea; Diarrhea in Enteral Feeding Patient; Clostridium Difficile Infection; Laxatives; Prokinetics; Antibiotics Associated Diarrhea*

Introduction

Diarrhea is one of the major problems that may complicate the hospitalization of a critically ill patient. The cause is usually multifactorial, including medication, enteral feeding and *Clostridium difficile* infection. Diarrhea may result in a number of negative clinical sequelae, including fluid and electrolyte abnormalities, dehydration, fecal incontinence, and pressure sores. This may result in the cessation of enteral nutrition, which increases the risk of energy and protein deficit and can exacerbate undernutrition [1,2]. Diarrhea was found to be associated with increased crude ICU length of stay and mortality [3]. Diarrhea is distressing for the patients and their families, and increase burdensome for both patients and their care givers [4].

Definition

There is no consensus on the definition of diarrhea among the critically ill patients; this difference is clearly observed in the literature, which shows great variability in the definition of diarrhea, Bliss., *et al.* [5] found about 14 different definitions. Lordani., *et al*. [6] conducted a study regarding the knowledge of intensive care professionals about diarrhea; he found big variations among professionals working at the same hospital and among professionals of the same category, which makes the standardization of practices more difficult.

The variety of definitions of diarrhea has led to difficulties in developing evidence based treatment studies. In 2012, the European Society of Intensive Care Medicine (ESICM) working group on abdominal problems sought to standardize the definitions, they define diarrhea as having three or more loose or liquid stools per day with a stool weight greater than 200 - 250 g/day (or greater than 250 ml/day) [7]. However, some experts recommend that rather three criteria must be met for diarrhea: stool frequency, stool weight and stool consistency [8-10]. A comprehensive definition which met the three criteria was proposed by Blaser [11], he define diarrhea in the critically ill 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. This definition is comprehensive and easy to apply in practice and can be standardized among health care professionals.

Epidemiology

Diarrhea is frequently observed in ICU patients; the reported prevalence varies from 2 to 95% [1,12-15]. This inconsistency of reported incidence may be a result of variations in diarrhea definition and the application of these definitions in the clinical setting. The median onset of symptoms occurring 6 days after ICU admission and 89% of diarrhea episodes in critically ill patients lasting for 4 days or less [16].

Classification and Etiology of Diarrhea

Diarrhea in general can be classified according to the duration, severity, mechanism, or the cause. According to the duration diarrhea may be acute if the duration is less than 2 weeks, persistent if the duration varies from 2 to 4 weeks, and chronic if it lasts more than 4 weeks in duration [17]. The severity can be either mild or sever according to absence or presence of major fluid loss and electrolyte disturbances respectively [11].

According to the mechanism, no single cause of diarrhea is truly unifactorial but broadly spoken; the two main underlying mechanisms are osmotic and secretory diarrhea [11,18]. Osmotic diarrhea caused by presence of unabsorbed substance that draws water from the plasma into the intestinal lumen along osmotic gradients like osmotic laxatives and antacids which contains magnesium, phosphate, sulfate [19]. Secretory diarrhea caused by an imbalance between absorption and secretion of electrolytes with a net balance of decreased absorption. The driving force for intestinal ion secretion can arise from the gut lumen as with infectious diarrhea (enterotoxins), luminal secretagogues (such as bile acids or fatty acid), circulating secretagogues (such as various hormones and drugs), and intestinal motility disorders [20].

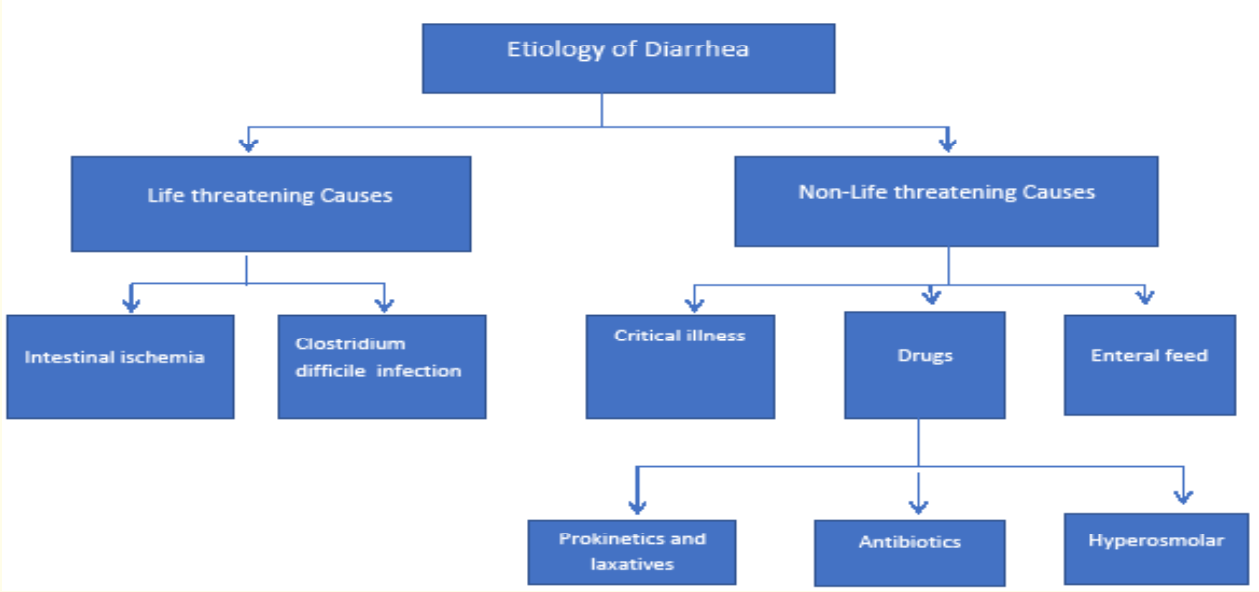

Figure 1: *Causes of Diarrhea in critically ill patient.*

In the critical care setting, it is practical to divide diarrhea according to the cause into two main categories, either a life threating conditions or non-life threatening. Life threating can be caused by intestinal ischemia or *Clostridium difficile* infection (CDI). Non-life threatening can be caused by critical illness related diarrhea, drugs and enteral feeding associated diarrhea. Detailed classification in (Figure 1).

Life Threatening Diarrhea

Intestinal Ischemia

Ischemia results from inadequate blood flow to the bowel. The etiology of intestinal ischemia can be divided into three general categories pre-splanchnic; splanchnic and post-splanchnic.

Syndrome	Risk factor	Clinical presentation	Diagnosis	Treatment
Acute mesenteric ischemia	• Atrial fibrillation • Recent myocardial infarction • Diffuse atherosclerotic disease • Sepsis • Cardiogenic shock	Acute onset of mid-abdominal pain that is disproportional to the physical exam, associated with diarrhea.	Computed tomography angiography (CTA)	Non-occlusive is treated medically, whereas occlusive is corrected with surgery and resection of non-viable intestine.
Chronic Mesenteric Ischemia (CMI)	• long-standing atherosclerotic disease • Connective tissue disease • Abdominal radiation	Insidious onset of crampy, postprandial abdominal pain (intestinal angina) with weight loss diarrhea	Computed tomography angiography (CTA)	Restoration of arterial perfusion by relieving proximal stenosis or occlusions either by open surgical reconstruction or catheter-directed endovascular angioplasty.
Mesenteric Venous Thrombosis (MVT)	• Hypercoagulable state like cancer, oral contraceptive use • Recent surgery (especially splenectomy). • Abdominal trauma. • portal hypertension	vague abdominal pain that fluctuate over time	Computed tomography angiography (CTA)	systemic anticoagulation with resection of necrotic bowel
Ischemic colitis	• Shock state • Major arterial occlusion like aortic dissection. • Small artery occlusion (diabetes, atherosclerosis). • Vasculitis (systemic lupus erythematosus, polyarteritis nodosa, sickle cell disease). • Inflammatory like pancreatitis, diverticulitis. • Hypercoagulable states • Colonic obstruction.	acute onset of mild, crampy abdominal pain and bloody diarrhea	• Colonoscopy • CT scan • The role of contrast angiography is limited being that most ischemic colitis is the result of non-occlusive or venous disease rather than arterial insufficiency.	Conservative management in non-sever form and surgical intervention in case of colonic ischemia

Table 1: *Clinical presentation of intestinal ischemia.*

Pre-splanchnic usually result from decreased mesenteric blood flow secondary to heart failure, hypovolemia or hemorrhage. Splanchnic, caused by local decreased in blood flow due to thrombosis, embolus, trauma, compression, or medications. Postsplanchnic, which occur in cases of venous disease, hypercoagulable syndromes, and cirrhosis [21].

Injury to the gut occurs by both ischemia and reperfusion injury and results in four distinct clinical presentations [21-24]: acute mesenteric ischemia, chronic mesenteric ischemia, mesenteric venous thrombosis, and ischemic colitis (Table 1).

Clostridium difficile Colitis

Clostridium difficile is a gram-positive, anaerobic, spore-forming bacillus that is responsible for the development of colitis in antibiotic treated patients. Although modern studies found a lower incidence of *C. difficile* infection in ICU population compared to the older ones [16,25,26]. However, because of its potentially complication risk of transmission, *C. difficile* infection has to be taken seriously if suspected as a case of diarrhea in ICU patients.

Use of antibiotics results in the disturbance of the normal bacterial flora of the colon, which lead to colonization by C difficile, and the release of toxins that cause mucosal inflammation; damage and result in diarrhea. The clinical presentation ranging from asymptomatic carrier state to severe diarrhea and pseudomembranous colitis and can result in severe life-threatening fulminant colitis with perforation [27]. In simple colitis patient complaining of abdominal pain and watery diarrhea. The presence of systemic manifestation like fever, hypotension, abdominal distention, and leukocytosis should rise the suspicious of fulminant colitis [28].

The primary risk factor for developing *C. difficile*–associated diarrhea (CDAD) is previous exposure to antibiotics. The antibiotics most frequently implicated in predisposition to CDAD include fluoroquinolones, clindamycin, and broad-spectrum penicillins and cephalosporins [28-31].

However, any antibiotic can predispose to colonization by *C. difficile*, including metronidazole and vancomycin, which are the major antibiotics used to treat *C. difficil*e infection [32]. The use of broad-spectrum antimicrobials, use of multiple antibiotic agents, and increased duration of antibiotic therapy all contribute to the incidence of CDAD [33,34].

Another important risk factor include the use of gastric acid suppression [35,36]. The US Food and Drug Administration issued a drug safety communication in 2012 following a review of published literature of recent studies which found that CDAD was higher among patients with PPI exposure compared with those without PPI exposure [37]. Additional risk factors include enteral feeding, gastrointestinal surgery, obesity, cancer chemotherapy, and hematopoietic stem cell transplantation [38-41].

The diagnosis of *C. difficile* infection should be suspected in any patients with clinically significant diarrhea or ileus in the setting of relevant risk factors (including recent antibiotic use, hospitalization, and advanced age).

The gold standard for *C. difficile* diagnosis is a stool cytotoxic assay [42]. The most important step in the management of *C. difficile* colitis is the cessation of the inciting antibiotic as soon as possible.

Non-Life Threatening Diarrhea

Critical illness Related Diarrhea

Patient with critical illness commonly have pancreatic enzyme deficiency and bile salt malabsorption [43-45]. Wang., *et al.* [43] found that more than 50% of critically ill patients had exocrine pancreatic insufficiency without the presence of primary pancreatic diseases. He reported that the presence of shock, sepsis, diabetes, cardiac arrest, hyperlactacidemia, invasive mechanical ventilation and haemodialysis to be risk factors for this insufficiency [43]. Hypoalbuminaemia is another cause of diarrhea in critically ill patient, as it can result in decreasing the absorption of water from the gut secondary to decrease in oncotic pressure [8].

Diarrhea usually improved with the improvement of the general condition of the patient.

Drug Related Diarrhea

Several medication which are commonly used in ICU can precipitate diarrhea, these medication can be broadly classified into three mail group laxatives and prokinetics; antibiotics; and hypoerosmolar oral liquid medication.

Laxatives and prokinetics

Decreased gastrointestinal motility and constipation and are common problems in critically ill patients; accordingly, a lot of these patients are on laxatives and prokinetic agents. Several studies found that significant number of patients suffering diarrhoea had received laxatives or enemas/suppositories immediately prior to diarrhea onset [46,47]. Two-year prospective audit in Australian ICU showed that discontinuation of laxatives result in resolving of diarrhea in 25% of all cases [12].

The two main prokinetics medication used in the critical care are metoclopramide and erythromycin, they cause diarrhea by increasing small bowel transit time [48]. Study by Nguyen., *et al*. [26] found that diarrhea was more common with the use of metoclopramide alone (32%) than with erythromycin alone (30%) and their combination result in higher incidence of diarrhea rate (49%). Diarrhea associated with the use of laxatives and prokinetics are short term with an average duration of 3.6 +/- 1.2 days [26]. The most important step in the management is to stop these agents with the early onset of diarrhea. The prophylactic use of these agents should be strictly avoided [26], and if they are used for gastroparesis they should be stopped immediately when the indication is not present anymore.

Antibiotics

Diarrhea is one of the most frequent side effects of antibiotic treatment, it occurs in about 5-30% of patients, it can be as early as after the first dose or late up to two months after the end of the treatment [49-52]. Clinical presentations range from mild abdominal discomfort with diarrhea to sever colitis. The median time from the starting of antibiotic and the occurrence of symptoms is 9 days [49]. A number of factors contribute to the development of antibiotic associated diarrhea (AAD), a very important factor it include the disruption of the normal enteric flora by antibiotic which can lead to overgrowth of pathogens. Another factor is the functional disturbance of the intestinal carbohydrates and bile acid metabolism by the antibiotics, which can result in osmotic diarrhea. Finally, antibiotics may also affect the intestinal mucosa and motility by allergic or toxic mechanism [53].

Almost all antibiotics can cause AAD, but certain antibiotics carry a higher risk. Higher risk could be related to the spectrum of the antimicrobial, with higher rate of AAD among antibiotics with activities against anaerobes. Another important factors is concentration of the antibiotic in the stool, and the prolonged course of the treatment for more than 3 days [49].

Antibiotics with high risk of AAD include broad spectrum penicillins, like amoxicillin and pipercillin, combination of aminopenicillins and clavulanate, cephalosporins, and clindamycin. Lower risk antibiotics include quinolones, co-trimoxazole and tetracycline constituted a lower risk [52].

High risk patient for developing AAD include those who are admitted to nephrology units or are residents of long term facilities [52], this could be related to the present of multiple co-morbidities in these population.

Hyperosmolar oral liquid medication

Many of the oral liquid medications which are used in the ICU are hyperosmolar [54] and/or contain sorbitol [55-57], these medications, especially when given undiluted and in large amount, directly into the bowel can cause osmotic diarrhea. Sorbitol is a sugar alcohol that is used as a sweetener in many oral liquid medications, adding the sorbitol increase the osmolality of the drug and causes osmotic diarrhea with abdominal cramps and bloating. A sorbitol intake of as little as 10 - 20 g/d has been shown to produce these gastrointestinal effects [58] especially when given undiluted and in large amount, directly into the small bowel.

Other type of medication that can cause diarrhea include oral electrolyte supplements (eg, magnesium, phosphates) and magnesium-containing antacids [47].

Enteral Feeding associated diarrhea

Enteral nutrition (EN) has become the standard of care for nutritional support in modern intensive care unit when the gastrointestinal tract is functional. The role of EN the onset of diarrhea has long been suspected [59]. Different studies reach to different conclusion about the relation of enteral feeding and diarrhea [16,60-62]. A recent prospective study by Thibault., et al. [16] among ICU patients in Switzerland found that the enteral feed per se was not a risk factor for diarrhea. However, delivering of more than 60% of energy target by enteral feed increased the risk of diarrhea, which signify the type, volume, outflow, and the amount of feed as a major factor for diarrhea in theses group of patient.

The alleged factors associated with diarrhea in EN patients is complicated and multifactorial. It include altered physiological response, concomitant use of antibiotics, microbial contamination, feeding rate and hyper osmolality of certain formulas [63-65].

During enteral feeding, there is altered physiological response to the direct feeding into the stomach, which could result in abnormal water secretion into the ascending colon and suppression of the gastrocolic response with reduces the opportunity for water absorption and diarrhea [39].

One of the important factors which could play a significant role for diarrhea in EN could be related to the concomitant use of antibiotics in these patients. It is not clear whether this is merely antibiotic-associated diarrhea, or there is a particular interaction between antibiotics, enteral nutrition, and diarrhea. Thibault., *et al.* found that the combination of EN covering > 60% of energy target with the use antibiotics or antifungal drugs result in increasing in the incidence of diarrhea [16]. This finding supports the presence of interaction between these two factors.

The risk of enteropathogenic infection in patients receiving EN cannot be under estimated. Feeding formulas are excellent environment for rapid microbial growth because of their compositing and their administered at room temperature. Bacteria can gain access to the feed during preparation and mixing of ingredients, the dilution, decanting of feeds or from the enteral tube hub which can colonies the external surfaces of the administration set [20,66,67]. Bliss., *et al*. in his case –control study found, that *Clostridium difficile* colonization was three-fold higher, and *C. difficile* associated diarrhea (CDAD) was nine-fold higher, in patients receiving EN, despite similar antibiotic use in both groups [66].

The EN formulas with high osmolality may cause diarrhea, especially when feeding into the small intestine. Changing to a lower osmolality formula may solve this problem [8,68].

EN should be considered as the cause of diarrhea in critically ill patient only after all other causes of diarrhea have been ruled out. If EN is considered the primary cause of diarrhea, an assessment of the enteral feeding regimen should be considered with possible changing in the administration flow rate or replacement of the EN solution with other formula. EN should not be discontinuing as this might result in increase the risk for EN of protein-energy deficit and can aggravate the problem [68,69].

Treatment

Diarrhea in the critically ill is usually multifactorial. Once diarrhea is recognized, clearly defined protocols should be implemented which identify the cause, reduce risk of transmission of infectious agents, and treat reversible etiology. The treatment of diarrhea should start with providing supportive care while the underlying causes of diarrhea are investigated and treated. Suggested management algorithm is presented in Figure 2.

Antimotility medications like loperamide lead to slow in the intestinal motility and may aggravate toxic megacolon (acute toxic colitis with colon dilatation). These medications should be used cautiously, they are contraindicated in acute ulcerative colitis, bacterial enterocolitis and active intestinal C difficile infection.

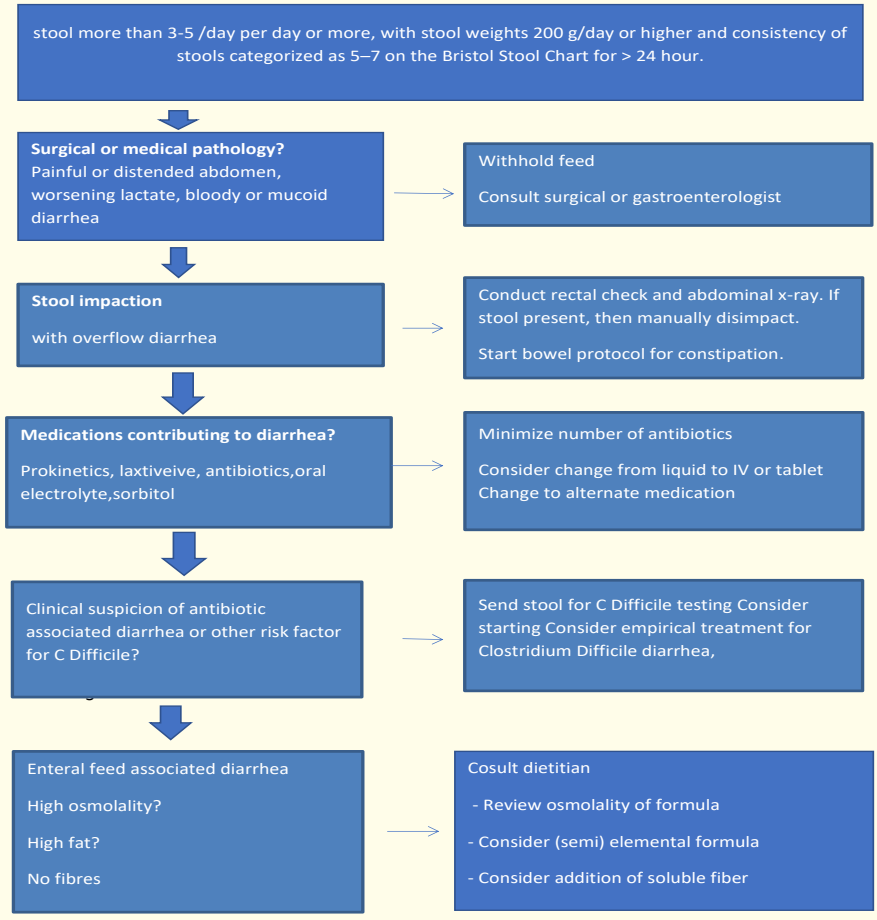

Figure 2: *Management Algorithm for diarrhea.*

Cholestyramine may be considered in diarrhea caused by bile acid malabsorption (patients with cholestasis, short bowel syndrome, terminal ileum resection and following cholecystectomy [68].

Probiotics and prebiotics can possibly reduce diarrhea, but there are not enough data to recommend their routine use in critically ill patients [69,70].

Conclusion

Diarrhea is common problem in critically ill patient, the cause is usually multifactorial. Early recognition of this problem with appropriate investigation and prompt treatment are necessary to reduce the burden of diarrhea on the already fragile ICU patient. The importance of excluding life-threatening causes should be a priority.

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