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MINIREVIEWS

Clinical approach to diarrheal disorders in allogeneic hematopoietic stem cell transplant recipients

Shadi Hamdeh, Abd Almonem M Abdelrahman, Osama Elsallabi, Ranjan Pathak, Smith Giri, Kailash Mosalpuria, Vijaya Raj Bhatt

Shadi Hamdeh, Abd Almonem M Abdelrahman, Osama Elsallabi, Department of Internal Medicine, Creighton University School of Medicine, Omaha, NE 68131, United States

Ranjan Pathak, Department of Medicine, Reading Health System, Reading, PA 19612, United States

Smith Giri, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, United States

Kailash Mosalpuria, Vijaya Raj Bhatt, Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, Omaha, NE 68198, United States

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Correspondence to: Kailash Mosalpuria, MD, MPH, Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE 68198, United States. kailash.mosalpuria@unmc.edu
Telephone: +1-402-5595388
Fax: +1-402-5596520

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Abstract

Diarrhea is a common complication of allogeneic hematopoietic stem cell transplant (HSCT), with an average incidence of approximately 40%-50%. A wide variety of etiologies can contribute to diarrhea in HSCT patients, including medication-induced mucosal inflammation, infections, graft-*vs*-host disease and cord colitis syndrome in umbilical cord blood transplant. Clinical manifestations can vary from isolated diarrheal episodes, to other organ involvement including pneumonia or myocarditis, and rarely multiorgan failure. The approach for diagnosis of diarrheal disorders in HSCT patients depends on the most likely cause. Given the risk of life-threatening conditions, the development of clinically significant diarrhea requires prompt evaluation, supportive care and specific therapy, as indicated. Serious metabolic and nutritional disturbances can happen in HSCT patients, and may even lead to mortality. In this review, we aim to provide a practical approach to diagnosis and management of diarrhea in the post-transplant period.

Key words: Diarrhea; Medication-induced diarrhea; Allogeneic hematopoietic stem cell transplant; Enteric infection; Graft-*vs*-host disease

Core tip: Diarrhea is a common complication following allogeneic hematopoietic stem cell transplant. However, there is no recent review dedicated to guiding clinicians about the different causes and their management. Our objective is to conduct a thorough review of literature to provide a working schema for the busy clinician on

evaluation and management of diarrhea in this special population.

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INTRODUCTION

Hematopoietic stem cell transplant (HSCT) is increasingly used to treat a variety of hematologic disorders. Worldwide, more than 50000 HSCTs are performed every year; approximately 40% of these HSCTs are allogeneic HSCT[1]. Given the increased volume of HSCT procedures, the number of HSCT-associated toxicities is expected to increase. Gastrointestinal complications are common in HSCT recipients and significantly contribute to HSCT-related morbidity and mortality. A wide variety of gastrointestinal complications are reported including nausea, vomiting, oropharyngeal mucositis, dysphagia, diarrhea, gastrointestinal bleeding and graft-*vs*-host disease (GVHD) of the gastrointestinal tract. These manifestations are seen in more than two-third of patients undergoing HSCT[2].

Diarrhea is a common complication of HSCT, with an average incidence of approximately 40%-50%, with a higher occurrence within the first several weeks post-transplant[3,4]. High-dose chemotherapy and radiotherapy used for myeloablation, without any other identifiable etiology, can alone cause diarrhea in up to 50% of patients[2]. Here, we will review a practical approach to diagnosis and management of diarrhea in the post-transplant period.

ETIOPATHOGENESIS

A wide variety of etiologies can contribute to diarrhea in HSCT patients, including mucosal inflammation caused by medications used for myeloablation or immunosuppression, infections, GVHD or other causes seen in non-transplant patients (Tables 1 and 2)[2-7]. Apart from conditioning regimen and immunosuppressant (*e.g.,* mycophenolate mofetil or tacrolimus), antibiotics, proton pump inhibitors, promotility agents (*e.g.,* metoclopramide), and magnesium salts are common causes of medication-induced diarrhea. Infection accounts for 5%-10% of diarrhea in adults HSCT patients[2-7]. Among different infectious etiologies, viruses are the most common pathogens and include cytomegalovirus (CMV), herpes simplex virus (HSV), Ebstein-Barr virus, adenovirus, norovirus and enteric viruses such as rotavirus, coxsackie, and echo virus. Clinical manifestations can vary from isolated diarrheal episodes, to other organ involvement including pneumonia or myocarditis, and rarely multiorgan failure. Clostridium difficile remains to be an important cause of antibiotic-associated diarrhea[3]. Its occurrence is related to the exposure to multiple antibiotics, antineoplastic agents, prolonged hospitalizations, and extended period of reduced host immunity that can lead to disruption of normal intestinal epithelium. Clostridium difficile may possibly contribute to an increased risk of gastrointestinal GVHD as well by providing the antigenic substrate and adding to the mucosal damage by activated donor T cells that release pro-inflammatory cytokines that drives the immune response towards GVHD[8]. Neutropenic enterocolitis, characterized by cecal involvement and occasionally ascending colon, can result from polymicrobial infection following a combination of mucosal cytotoxic injury, impaired host defense and profound neutropenia. The interaction of pro-inflammatory mediators present in the lumen with innate immune system in the intestinal submucosa leads to the release of pro-inflammatory cytokines resulting in epithelial cell apoptosis and increased mucosal permeability culminating into the syndrome of neutropenic enterocolitis. Microscopically there is a minimal inflammatory exudate along with submucosal edema and hemorrhagic necrosis. Thus, without the presence of any inflammatory response, different bacterial and/or fungal organisms including gram-negative bacilli, gram-positive cocci, anaerobes (*e.g., Clostridium septicum*) and *Candida* species can readily translocate through the bowel wall causing bloodstream infection[9].

Acute GVHD, neutropenic enterocolitis/typhlitis or cytomegalovirus-colitis are among the serious causes of diarrhea and can cause significant morbidity, prolonged hospitalization and increased non-relapse mortality[9-11]. Any moderate to severe diarrhea, regardless of its cause, particularly when associated with vomiting, can contribute to fluid and electrolyte losses, malnutrition, requirement for parenteral nutrition, deconditioning and slow recovery from the effects of conditioning regimen and HSCT.

CLINICAL FEATURES

Medication-induced diarrheal disorders are watery and usually not associated with bloody stool or significant abdominal pain[12]; however, nausea, vomiting, anorexia and mild abdominal cramps are not uncommon in HSCT recipients. Clinical manifestations in viral infections can vary from isolated diarrheal episodes, to other organ involvement including pneumonia or myocarditis, and rarely multiorgan failure[10]. *Clostridium difficile* (*C. difficile*) infection causes multiple episodes of watery diarrhea, associated with abdominal cramp, nausea, low-grade fever and leukocytosis[8]; however, it can also cause severe disease with mortality rate reaching up to 20%, particularly in patients who were previously treated with linezolid[13]. Neutropenic enterocolitis presents with abdominal pain, fever, bloody or watery diarrhea and occasionally nausea and vomiting. The

Table 1 Common causes of diarrhea in hematopoietic stem cell transplant recipients

Etiology	Time period	Percentage of diarrheal episodes	Tests	Management	Comments
Acute GVHD	Early post engraftment	40%-60%, particularly after engraftment	Colonoscopy and biopsy	High-dose prednisone; if no response, other immunomodulators, and extracorporeal photopheresis	Steroid-refractory gut acute GVHD can be fatal
Conditioning regimen, without other etiology	Within 5-7 d after chemotherapy	50%	No-specific tests, other etiologies need to be ruled out	Supportive care	
Medications	During any time, usually within few weeks after initiation	Variable	No-specific tests, other etiologies need to be ruled out	Supportive care, medication withdrawal if possible	Usually diarrhea stops after cessation of the offending medication
Infections	Pre-engraftment for Clostridium difficile infection and typhlitis; early post-engraftment for enterovirus, adenovirus, CMV colitis	5%-10%	Microbiologic, molecular or pathologic tests; CT, CTE, or MRE; colonoscopy with biopsies	Supportive care if viral, antibiotics if bacterial, antifungal therapy if fungal	Neutropenic enterocolitis and CMV colitis can be life threating in severe cases
Cord colitis	Late post-engraftment	10% of cord transplant	Negative cultures and a colon biopsy demonstrating chronic active colitis	Metronidazole	Only occurs in recipients of umbilical cord blood transplant

Also consider other causes unrelated to transplant such as malabsorption syndrome including pancreatic exocrine insufficiency, adrenal insufficiency, lactose intolerance, or other malabsorption syndromes[2-7]. CMV: Cytomegalovirus; CT: Computerized tomography; CTE: Computerized tomography enterography; GVHD: Graft-*vs*-host disease; MRE: Magnetic resonance enterography.

Table 2 Most common medications and infectious etiologies causing diarrhea in hematopoietic stem cell transplant recipients

Categories	Agents
Medications	Conditioning regimen, antibiotics, mycophenolate mofetil, tacrolimus, proton pump inhibitors, promotility agents, magnesium salts
Viral infection	Cytomegalovirus, herpes simplex virus, Ebstein-barr virus, adenovirus, norovirus and other enteroviruses
Bacterial infection	*Campylobacter*, *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Vibrio cholera*, *Clostridium difficile*, other enteric pathogens
Others	Fungal, *e.g.*, candida, parasitic, *e.g.*, Cryptosporidium and *Mycobacterial* infections
Mixed infection	Neutropenic enterocolitis

abdominal pain can be generalized or localized usually in the right lower quadrant. In severe cases, patients may develop acute abdomen with peritonitis, often indicative of complications such as perforation or abscess formation[9].

Acute GVHD is among the most common cause of diarrhea in HSCT patients, accounting for one-third of cases in some studies, especially if diarrhea persists beyond 3 wk of a HSCT[3,4]. Symptoms vary from watery to bloody diarrhea, usually high volume, associated with abdominal pain or cramping. The bleeding can be serious to require blood transfusion. If upper gastrointestinal tract is involved, patients may develop nausea, vomiting and anorexia. Other features of GVHD such as skin rash may also be present[11].

Cord colitis syndrome occurs only in recipients of umbilical cord blood transplant, with an occurrence rate of 10% in such patients. It manifests as watery diarrhea, presenting at about 4 mo after the transplant, and persisting for more than a week. Fever and weight loss are not uncommon, and the majority of patients require hospitalization. Colonoscopy usually reveals erythematous mucosa with or without ulcerations, with occasional granuloma formation[6]. It responds to metronidazole[6] despite negative viral and bacterial cultures, and is felt to be related to infection with bradyrhizobium enteric[14].

EVALUATION AND DIAGNOSIS

The approach for diagnosis of diarrheal disorders in HSCT patients depends on the most likely cause. Given the risk of life-threatening conditions, the development of clinically significant diarrhea requires prompt evaluation, supportive care and specific therapy, as indicated. A thorough history and review of medications may provide information regarding possible medication-induced diarrhea. Stool analysis including viral culture and *C. difficile* toxin assay or polymerase chain reaction (PCR) should be performed. Monitoring of renal function, electrolyte and nutritional status are important. Timing of onset of diarrhea may provide an idea about potential causes.

Pre-engraftment period

Medications including conditioning regimen, calcineurin inhibitors, oral magnesium and prophylactic antimicrobials are frequently used in HSCT recipients, hence

important causes of diarrhea[12]. *C. difficile* is another common cause during this phase and is seen in up to 10%-20% of the patients[8,13,15]. Detection of *C. difficile* toxin or the toxigenic *C. difficile* organism in the stool can be achieved with PCR, enzyme immunoassay for *C. difficile* toxins A/B or *C. difficile* glutamate dehydrogenase[16]. Although non-diagnostic, the classic computed tomography (CT) findings include pancolitis with marked colonic wall thickening (11-15 mm) and wall nodularity, most frequently involving sigmoid colon and the rectum[17,18]. Contrast-enhanced CT scan of the abdomen may show a characteristic but non-specific finding of "target sign" or "double halo sign" due to submucosal edema and mucosal enhancement. Colonic edema may also result in "accordion sign" due to thickening of the haustral folds[19]. Other non-specific imaging features include pericolic fat stranding and ascites. Colonoscopy, performed to rule out other diagnosis, may demonstrate pseudomembrane formation, apoptosis and nonspecific ulceration. However, the absence of pseudomembrane does not rule out the *C. difficile* infection in HSCT patients[20,21].

Neutropenic enterocolitis is a common cause of diarrhea during this phase[9]. Initial workup for suspected typhlitis includes *C. difficile* toxin assays, stool and blood cultures. All patients with suspected neutropenic enterocolitis should have CT scan of the abdomen with intravenous and oral contrast in the absence of any contraindication for contrast use. CT scan of the abdomen has a lower false-negative rate (15%) than ultrasound (23%) or plain radiographs of the abdomen (48%)[22]. CT findings are usually less severe than that seen in pseudomembranous colitis and include bowel wall thickening (7 mm on average, range 4-15 mm), especially in the ileocecal area[23]. Pneumatosis intestinalis, seen in up to 20% of cases[23], is usually not seen in other non-vascular causes of colitis or GVHD[17]. Other non-specific findings include mesenteric stranding (51%), bowel dilatation (38%), and mucosal enhancement (28%)[23]. Plain films of the abdomen are nonspecific but may show fluid-filled, distended cecum with dilated adjacent small bowel loops, thumb-printing or localized pneumatosis intestinalis[24].

Early post-engraftment period

Medications and *C. difficile* infection are common causes of diarrhea during this period as well. Additionally, viral infection (*e.g.,* enteric virus, adenovirus and CMV virus) and acute GVHD of gut are important etiologies. Enteric virus infections (*e.g.,* coxsackie A, rotavirus or norovirus) can cause prolonged gastroenteritis among HSCT recipients. Nevertheless, isolation of virus in a stool specimen, even in cases of diarrhea, may be the result of viral shedding and not be related to intestinal infection[4]. The specific diagnosis of adenovirus infection is also challenging and may require the use of multiple diagnostic tests. Viral culture, direct antigen assays, or PCR of upper nasopharyngeal, throat, urine, stool or rectal samples may detect viral shedding. Results should be correlated with the clinical picture. Quantitative PCR of blood may be helpful to establish the diagnosis, evaluate the risk of dissemination, monitor response to antiviral therapy and determine prognosis[25-28].

CMV colitis is an important differential of diarrheal disorder in HSCT patients. The diagnosis is challenging and may be complicated by the presence of concomitant gastrointestinal GVHD. The final diagnosis of CMV is based on the presence of any positive microbiological, molecular or pathological tests identifying CMV, and a response to treatment. Diagnostic tests for active CMV disease include CMV phosphoprotein 65 antigenemia assay and quantitative nucleic acid testing, which may be used to establish diagnosis, determine a need to initiate pre-emptive therapy, and monitor response to therapy[29,30]. Viral culture of blood, urine or tissue specimens can be slow and expensive, and is also less sensitive and specific than molecular diagnostic assays. Culture of gastrointestinal tissue for the diagnosis of tissue-invasive disease can be an option when both antigenemia and PCR testing on blood are negative[31]. Sigmoidoscopy with biopsy appears to have equivalent diagnostic yield for CMV colitis, compared to colonoscopy[32]. Typical histopathology finding includes the presence of viral nuclear inclusions but the presence of gastrointestinal gland apoptosis without viral inclusions does not rule out CMV involvement[33]. If a CT scan is done, findings usually include ascending colon wall thickening with an average thickness of 15 mm[34]. The most characteristic feature is mural edema with deep ulcerations, likely due to occlusive vasculitic process, with or without small bowel involvement, surrounding fat stranding and ascites[35].

Acute GVHD of gut is the most frequent cause of diarrhea during the early post-engraftment period, and most commonly occurs within the first few months after HSCT or following a reduction in immunosuppression. The presence of a maculopapular skin rash or otherwise unexplained elevated serum bilirubin or alkaline phosphatase within the first 100 d of HSCT may support the diagnosis. Most but not all cases of acute GVHD of lower gastrointestinal tract can be diagnosed by rectal biopsy[36,37]. Hence, a negative rectal biopsy in patients with a clinical suspicion of acute GVHD requires evaluation with colonoscopy. Additionally, multiple colonic biopsies and pathologic evaluation of tissue are necessary for the diagnosis even when mucosal lining of colon appears normal[37]. Epithelial cell apoptosis, particularly involving cryptic cells, is the characteristic histological feature observed in patients with acute gastrointestinal GVHD[38]. A study has indicated that the presence of 6 or less apoptotic bodies per 10 contiguous crypts may not be predictive of gastrointestinal GVHD[39]. The presence of concurrent GVHD in another organ greatly increases the specificity of isolated crypt apoptosis as a diagnostic feature of gastrointestinal GVHD[21]. Epithelial cell apoptosis can be seen after the use of conditioning regimen but the changes are noted within the first 20 d, whereas acute GVHD is only seen

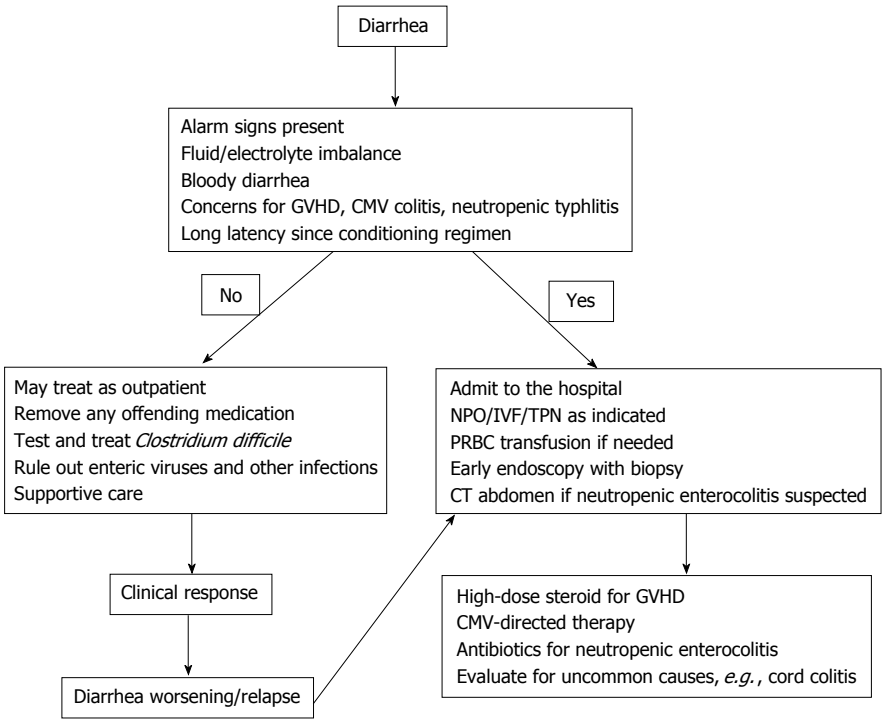

Figure 1 Algorithm for management of diarrhea in transplant recipients. CMV: Cytomegalovirus; CT: Computerized tomography; GVHD: Graft-*vs*-host disease; IVF: Intravenous fluids; NPO: Nil per os; PRBC: Packed red blood cells; TPN: Total parental nutrition.

after engraftment, which occurs after the second or third week following the transplant[40]. Other differentials that can cause gland epithelial apoptosis include drugs such as mycophenolate mofetil and proton pump inhibitors, and viruses such as adenovirus and CMV infection[38]. Radiologic findings are not diagnostic of GVHD. The most consistent CT finding is abnormal mucosal enhancement of the entire gastrointestinal tract, mostly affecting the small bowel. Other frequent features include dilated, fluid-filled bowel loops, submucosal edema with "target sign"[34]. However, a wall thickness of greater than 7 mm can help exclude GVHD[23].

Late post-engraftment period

Diarrhea is more likely to be related to aforementioned infections, but less commonly could be a manifestation of chronic GVHD, particularly if other features of chronic GVHD are also present. The chances of drug-induced diarrhea from mycophenolate, tacrolimus or prophylactic antimicrobial may be relatively less, unless the medications have been changed recently. Other causes of diarrhea, as observed in general population, including pancreatic insufficiency should also be considered. Adrenal insufficiency, possible because of steroid exposure for treatment of GVHD, may also result in gastrointestinal symptoms including diarrhea. If etiologies are not established, a colonoscopy and biopsy may be needed for diagnosis. No histological changes involving the colon are specific for chronic GVHD, but common features may include apoptotic epithelial cells and crypt drop out. These features, however, are also seen in patients with inflammatory bowel disease[38,41]. Cord colitis syndrome, exclusively seen in cord blood transplant recipients, may mimic chronic GVHD[42]. It is distinguished from other causes of diarrhea by negative viral and bacterial cultures, and a colon biopsy that demonstrates chronic active colitis, frequently with associated granulomas. A response to antibacterial treatment can be both diagnostic and therapeutic[6,14].

MANAGEMENT

Diarrhea in HSCT recipients can induce serious metabolic and nutritional disturbances and may even lead to mortality. Therefore, many HSCT patients with diarrhea may require inpatient admission for volume and electrolytes replacement. However, some patients may be treated as an outpatient with close follow up if they do not have alarming signs such as bloody diarrhea, significant abdominal pain, fever, inability to tolerate oral intake, hypovolemia, tachycardia or hypotension (Figure 1).

Supportive care

If infectious causes of diarrhea are ruled out, loperamide can be used at an initial dose of 4 mg orally, followed by 2 mg with each bowel movement as needed up to a total of 16 mg in 24 h. If diarrhea persists, atropine, diphenoxylate, bismuth subsalisylate, or tincture of opium may be added to the scheduled loperamide. Octreotide may be useful in select cases, particularly when it is started early on in GVHD[43,44]. Other supportive measures that may be used in moderate to severe cases include the use of cholestyramine, bowel rest,

hydration, electrolyte replacement and parenteral nutrition.

GVHD

High-dose steroid remains the preferred frontline therapy for both acute GVHD (1-2 mg/kg per day of prednisone) and chronic GVHD (1 mg/kg per day of prednisone) of gut. High-dose steroid is continued for 1-2 wk or until response, than it is tapered over next several weeks[11,45]. Patients with acute GVHD, who respond to high dose prednisone within the fifth day of therapy, have significantly improved outcomes, compared to non-responders[46]. Non-absorbable steroids such as budesonide can improve response, reduce steroid doses and prevent relapse of gastrointestinal GVHD following the tapering of prednisone[47]. Addition of any other agent to prednisone as a frontline therapy has not been shown to improve outcomes. For steroid-refractory patients, outcomes are poor but several therapy agents have been used including extracorporeal photopheresis, calcineurin inhibitors, sirolimus, etanercept, pentostatin, among others[11,45].

Infections

Identifying the offending organism is crucial in decisions about further treatment of infectious enterocolitis. Culture and susceptibility may guide therapy selection. *C. difficile* infection needs a prompt treatment, and clinicians should treat empirically in suspicious cases because of a high mortality rate. Treatment options include metronidazole, and vancomycin for complicated cases. Fidaxomicin has been recently approved by Food and Drug Administration, and can be considered in refractory cases. Fecal transplant is yet another treatment modality in recurrent/refractory cases[48]. Certain viral diarrhea with enteric viruses may be self-limited but require cautious monitoring; however, where specific agents are available, therapy should be instituted. Ganciclovir or valacyclovir is the therapy of choice for CMV, whereas HSV infection may be treated with acyclovir or valacyclovir for 2-3 wk. Foscarnet is the second-line therapy in both cases[49]. Although data regarding bacterial gastroenteritis are lacking in HSCT patients, empirical antibiotics are not usually indicated in the absence of clinically significant fevers, bloody stools, and evidence of invasive disease based on significant white blood cell or red blood cells in the stool. Trimethoprim/sulfamethoxazole has a good coverage for most of the enteric bacteria and may be used as the first line therapy. Quinolones also provide a good coverage for the enteric bacteria, but the concerns exist regarding an increased resistance to quinolones. Erythromycin is a good therapy option for campylobacter-related diarrhea[50].

Neutropenic enterocolitis

Treatment of neutropenic enterocolitis requires high level of care, as it is potentially life threatening. All patients should be treated as an inpatient with intravenous fluids, nasogastric tube placement for gastric decompression, and bowel rest. Anti-diarrheal should be avoided as it may aggravate the ileus and worsen the symptoms. Broad-spectrum antibiotics with good coverage against anaerobes and gram-negative rods including pseudomonas are recommended. Suggested empiric regimens include tazobactam-piperacillin, cefepime plus metronidazole, or carbapenem plus metronidazole. The therapy should be adjusted based on the culture results. A lack of response to broad-spectrum antibiotics within 72 h should raise the suspicion for fungal etiology. In such context, addition of antifungal therapy may have to be considered. Intravenous antibiotics can be switched to oral after 48 h of being afebrile and recovery of absolute neutrophil count to above 500/μL. However, antibiotics should be continued for additional 14 d[9,51,52]. Surgical exploration is largely avoided in patients with neutropenic enterocolitis, but may have to be considered in severe cases with suspected perforation or bowel necrosis. Other potential indications for surgical intervention may include clinical deterioration despite the appropriate treatment, or persistent bleeding[9,53].

Cord colitis syndrome

Antibiotic therapy with metronidazole alone or with quinolones for a total of 14 d is the mainstay of the treatment[6].

CONCLUSION

Diarrhea is common in HSCT recipients and accounts for significant morbidity and possibly mortality in these patients. The increasing use of HSCT procedures worldwide indicates that the diarrheal disorder in this patient population is likely to rise. Mediations, infections and GVHD are common causes of diarrhea in post-transplant period[2-7]. Medication history, stool analysis, culture, and *C. difficile* PCR should be routinely performed to establish the underlying cause. CT scan and colonoscopy with biopsies may be performed if the other tests are unrevealing and may help diagnose conditions such as neutropenic enterocolitis and GVHD[23,38,54]. In addition to supportive care such as hydration, monitoring and correction of electrolytes and acid-base balance, timely initiation of appropriate specific treatment is important to improve outcomes. Management often requires a specialized multidisciplinary transplant team with experienced transplant physicians, gastroenterologists, infection disease experts and nursing staff. Many HSCT recipients leave the transplant centers after initial hospitalization and follow-up with community oncologists, hence training of community oncologists and patient education in post-transplant issues are important. Frequent communication between community oncologists, patient/caregivers and transplant physicians can help expedite diagnosis and initiate early management. Certain diagnoses such as neutropenic enterocolitis, steroid-refractory acute GVHD and CMV

colitis are difficult to treat with current therapeutic modalities, hence further research to optimize therapy is needed.

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