Gastrointestinal Complications

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12.1 Introduction

Over the past decade, the number of patients with haematological cancer that are being treated for a variety of chemotherapy, radiation therapy or targeted therapy continues to grow. In order to improve patient care and their survival, better

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recognition and proper management of gastrointestinal complications including infections are warranted.

The entire gastrointestinal (GI) tract is susceptible to a range of acute and chronic complications associated with the treatment of haematological diseases especially if treatment includes a haematopoietic stem cell transplantation (HSCT). Rarely is the intestinal tract itself infiltrated by leukaemia. In general, acute complications are mainly the result of toxicities associated with cytotoxic drugs, while graft-versus-host disease (GVHD) is the main driver of late or chronic GI events. Both conditions hamper the barrier function of the GI tract, enabling both local and systemic infections to occur when the patient is already immunocompromised either by neutropenia or dysfunctional cellular immunity. High-dose chemotherapy conditioning regimens, with or without total body irradiation (TBI), cause severe GI side effects including nausea, vomiting, as well as mucositis along the entire GI tract that cause pain, ulcerations, bloating, malabsorption and diarrhoea. These GI-related symptoms and signs can easily be mistaken for infections by opportunistic microorganisms. The clinical presentation of each complication is nonspecific, and diagnostic procedure includes physical examination, microbiological cultures, imaging and endoscopy with biopsies. Patients undergoing intensive cytotoxic therapy report oral mucositis-induced pain as the most debilitating complication but not emesis or diarrhoea. Aside from pain, discomfort, poor appetite and decreased quality of life, these GI side effects, especially gut mucositis, are associated with increased risk of infection, sepsis and death. Neutropenic enterocolitis is one of the most extreme toxicity accompanied by life-threatening complications. It is obvious that GI toxicities significantly contribute towards increased resource utilisation and prolonged hospital stays.

Real progress has been achieved in treating nausea and vomiting with better antiemetics, but unfortunately the treatment of mucositis either caused by the cytotoxic regimen itself or related to acute or chronic GVHD has been a failure. It is also becoming increasingly clear that some patients are genetically predisposed to certain toxicities and warrant tailored supportive management. Close monitoring of GI complications and awareness of related infections are the critical aspects of supportive care management to optimise the use of specific drugs that can significantly improve treatment outcomes. Management of the following GI toxicities also in relation to infections will be discussed below: cytotoxic therapy-induced nausea and vomiting, mucositis (including oesophagitis and neutropenic enterocolitis) and gastrointestinal GVHD.

12.2 Cytotoxic Therapy-Induced Nausea and Vomiting

12.2.1 Background

Cytotoxic therapy-induced nausea and vomiting (CINV) is commonly feared by patients before start of treatment and can lead to serious medical problems such as dehydration, electrolyte disturbances and renal insufficiency. CINV results in a rise

in health care costs, prolonged hospital stay with impairment of quality of life in patients receiving highly and moderately emetogenic therapy [1]. It is obvious that CINV itself is unlikely to ascribe to infection unless the medical history of the preceding days indicates otherwise, for instance, an intercurrent acquired food-borne infection. Nausea, the perception that emesis might occur, can only be judged by the patient, making it difficult to test the efficacy of new drugs in reducing nausea and vomiting. Emesis is basically a defence mechanism based upon different pathways, including the chemoreceptor trigger zone, vestibular nuclei and central nervous system. Emesis has been described as acute (the first 24 h of chemotherapy administration), delayed (from 24 h onwards unto 5 or 7 days after the cytotoxic insult), breakthrough (CINV during antiemetic therapy), anticipatory (before the insult) and refractory (despite antiemetic therapy). The discovery of the importance of the serotonin receptor in the management of CINV was crucial to controlling CINV [2].

12.2.2 Management of CINV

Aprepitant is the first neurokinin-1 receptor antagonist approved for prevention of CINV. NK_1 receptors are the binding sites of the tachykinin substance P and are located in the brainstem emetic centre and in the GI tract. Patients treated with cisplatin or an anthracycline–cyclophosphamide regimen clearly favoured the use of aprepitant in the prevention of acute and delayed emesis [3]. Aprepitant is known to moderately inhibit cytochrome (CYP) P450 3A4 in normal volunteers, and its use is limited in patients receiving high-dose chemotherapy because of concerns about potential drug interactions with some chemotherapeutic and prophylactic agents used for GVHD prevention. CINV is still a significant problem for HSCT recipients as only 20 % completely responded and antiemetic rescue therapy especially for delayed nausea and emesis failed completely [4]. If patients with anticipatory emesis are scheduled to undergo HSCT, anxiolytic drugs such as lorazepam or olanzapine may be useful additions to the antiemetic protocol. The corticosteroids dexamethasone and methylprednisolone are effective as monotherapy or in combination with other drugs for patients treated for cancer. The reader is referred to the recommendations of the American Society of Clinical Oncology Guideline for Antiemetics in Oncology for details [5].

12.3 Mucositis

12.3.1 Pathogenesis

Chemotherapy and radiotherapy damage the entire alimentary mucosa initiating an inflammatory cascade that culminates in mucosal barrier injury (MBI), which manifests itself clinically as mucositis. The alimentary tract undergoes the same embryological development, but mucosal cells at various regions of the alimentary undergo specific differentiation later on in order to evolve site-specific functions. The

pathogenesis of MBI is thought to consist of five phases [6, 7]: (1) the activation of nuclear factor-κB directly by chemo-/radiotherapy and indirectly from ROS formation, DNA and non-DNA damage; (2) production and release of pro-inflammatory cytokines and chemokines (IL-1, IL-6, IL-8, TNFα, IL-23, IFNγ) by macrophages, intestinal epithelial cells and endothelial cells; (3) positive feedback loop of TNFα, epithelial cell apoptosis and increased mucosal permeability; (4) translocation of microbes or their cell wall components such as lipopolysaccharide or peptidoglycan; and finally (5) repair and healing. Although the impact of microbes and their cell wall components on the inflammatory response is secondary, stimulation of pattern recognition receptors (PRRs) by pathogen-associated molecular patterns (PAMPs) translocating across the disrupted mucosal barrier with subsequent bacteraemia and endotoxaemia aggravates inflammation.

12.3.2 Clinical Features

The course of mucositis following conditioning regimens is relatively predictable. Clinical evidence of mucosal injury arises about 5 days of conditioning; it peaks at about 12–14 days and then spontaneously resolves 3 weeks after starting chemotherapy. The average duration of severe mucositis when present is almost a week. The exposure to a specific cytotoxic drug or radiation dose is the most prominent factor determining the character, onset and progression of GI mucositis [8]. Symptoms such as diarrhoea or constipation are the net result of clinical mucositis of the entire GI system. The incidence rate of GI mucositis varies from 10 % in patients with advanced disease to around 40 % of patients receiving standard dose chemotherapy. Symptoms of diarrhoea and abdominal complaints affect almost every patient immediately following high-dose chemotherapy and HSCT. These data are retrieved from toxicity scores not specifically designed in documenting the course of specific symptoms [9].

The importance of this observation is highlighted by the incidence of 44 % of severe oral mucositis [World Health Organization (WHO) grade ≥3] found among patients receiving high-dose melphalan or BEAM (carmustine, etoposide, cytarabine and melphalan) before autologous HSCT in a prospective audit [10]. Ulcerative mucositis (WHO Grade ≥2), the major driver of symptoms and infection risk, was noted in 64 %. Because ulceration is, important as major driver of patient related symptoms and risk factors of infection.

12.3.3 Mucositis and Infectious Complications

ASCT recipients with severe oral mucositis (OM) had a significantly higher incidence of fever (68 % versus 47 % of patients), microbiologically defined infection (27 % versus 12 %) and a longer duration of fever (4.2 versus 3.0 days) [11]. Whereas OM is relatively easy to recognise, detection of gut mucositis is more demanding. It was shown that citrulline appeared to be particularly useful to detect

gut mucosal damage since blood concentrations of this amino acid directly reflect functioning small intestinal cell mass [12]. Plasma concentrations of citrulline corresponded to the severity and extent of gut injury after intensive myeloablative therapy. Recent exploratory studies in more than 90 HSCT recipients validated a citrulline-based assessment score making it a suitable first choice for measuring and monitoring intestinal MBI [13]. Impaired integrity of the mucosal barrier is thought to promote translocation of microorganisms from the lumen of the digestive tract to the blood stream resulting in bacteraemia. Plasma concentrations of citrulline reached a nadir within 12 days after initiating HDM in 29 patients. Patients with bacteraemia had significantly lower citrulline concentrations on the first day of fever than did those without bacteraemia [14]. Twenty patients (69 %) developed fever that was accompanied by bacteraemia in ten cases, due to oral viridans streptococci (OVS) with or without coagulase-negative staphylococci (CoNS). The lowest citrulline concentrations coincided with the onset of bacteraemia, but not with neutropenia. Low citrulline rather than the duration of neutropenia is associated with bacteraemia indicating the importance of an intact mucosal barrier in neutropenic patients. This suggests that the severity of gut MBI determines whether bacteraemia occurs or not rather than neutropenia per se. This was confirmed in a larger cohort of 67 ASCT patients after HDM where the onset of bacteraemia due to Gram-positive cocci only occurred after a low citrulline level been reached irrespective of duration of neutropenia [15]. A similar association between the presence of gastrointestinal toxicity and the development of OVS bacteraemia was seen in children treated for AML [16].

In out-patients treated with multiple cycles of chemotherapy for lymphoma, myeloma and solid tumours, severe GI mucositis defined and characterised as oesophagitis, gastritis, colitis and typhlitis by NCI common toxicity criteria resulted in significantly more infections than with OM and was associated with prolonged use of antibiotic therapy [17]. The mean duration of hospitalisation of patients receiving myelosuppressive chemotherapy was extended by 2 days during cycles accompanied with only OM, but when gut mucosal damage was also present the length of stay was increased by an average of 8 days [17]. The risk of infection was significantly higher during chemotherapy cycles complicated by any GI mucositis despite the fact that there was no difference in the depth or duration of neutropenia. The risk of infection was almost 100 % during cycles associated with grades 3 and 4 GI mucositis. CoNS are the most frequent isolates, and though CoNS bacteraemia is assumed to be related to the use of central venous catheters, mucosal sites may be as important as source of these bacteria [18]. Indeed, molecular analysis of CoNS isolated from blood cultures indicated that the mucosa was the origin in most of the cases [19]. Bacteraemia due to OVS mainly *Streptococcus mitis* and *Streptococcus oralis* is related to MBI and can be associated with more serious complications such as sepsis and adult respiratory distress syndrome which carries a high mortality (80 %), though MBI is not the sole predictor of the viridans streptococcal shock syndrome [20].

Severe disruption of the mucosal barrier is clearly not the only risk factor for developing bacteraemia, which affected only a third of our patients with low citrulline concentrations. To identify those patients at risk for bacteraemia, citrulline

measurements need to be combined with other tests. For instance, the Multinational Association of Supportive Care of Cancer (MASCC) developed a risk score to predict at the onset of fever during neutropenia which patients are at high risk for development of serious medical complications [21].

12.3.4 Mucositis and Fever During Neutropenia

Neutropenia (granulocytes $<0.5 \times 10^9$/l) has been used for more than 40 years to recognise those patients who are at imminent risk of developing infectious complications following intensive chemotherapy [22]. This formed the foundation for developing a successful strategy for managing these patients, namely, administering broad-spectrum antimicrobial therapy promptly as soon as fever occurs during neutropenia. Indeed, empirical antibacterial therapy is still the backbone of the supportive care given to these patients [23]. However, many studies also reported that a substantial number of patients remained febrile without an infection ever being documented [24]. Hence, such episodes of fever were designated 'unexplained fever'.

Patients with severe OM have not only an increased risk of infections, but the incidence of fever and number of days with fever during neutropenia are also higher [25]. Although, the magnitude of the inflammatory response can be aggravated by infections fever as symptom of a systemic inflammatory response is predominantly driven by the course of MBI in HSCT recipients [26]. Data show a clear pattern of an inflammatory response measured by C-reactive protein or IL8, irrespective of the presence or absence of infection, coinciding with the course of mucositis. Consequently, the term 'febrile mucositis' might be suitable in these cases [15].

12.4 Oesophagitis

Oesophagitis causes burning retrosternal chest pain. The differential diagnosis includes cytotoxic therapy-induced oesophagitis and viral or candida infections. Herpes simplex virus (HSV) reactivates commonly in HSV-positive patients after cytoreductive therapy especially in the presence of mucositis after HSCT. Therefore, anti-HSV prophylaxis is routinely given after HSCT. CMV oesophagitis is actually only seen after allogeneic HSCT with active GVHD.

Candida species are part of the commensal flora of the skin and mucosal surfaces, and in many adults they may become the prevalent opportunistic pathogen under the pressures of antimicrobial agents and changes in adherence sites. Under normal circumstances, the intact epithelial surface repel invasion of yeast cells. However, cytoreductive agents and irradiation inflict serious damage to the mucosal barrier, and colonising microorganisms such as *Candida* can gain easy access to the submucosal tissue and subsequently to the bloodstream. The clinical relevance of culturing *Candida albicans* from saliva or stool is a matter of controversy with respect to the diagnosis of *Candida* oesophagitis. It might help in directing initial

antifungal therapy in case of suspected candida oesophagitis. Blood cultures mostly remain negative, and results of endoscopy may be delayed. Fluconazole can still be started if the *Candida* species known from the surveillance cultures was shown to be sensitive. Otherwise, echinocandins or lipid formulations of amphotericin B or voriconazole are alternatives.

Oesophagitis was seen in more than 50 % of the upper GI endoscopy procedures performed after intensive chemotherapy (median of 22 days) in 94 patients with leukaemia. The other complications were gastritis, gastric erosions and hiatus hernia and duodenitis. The most therapeutic consequences were the addition of antacid therapy [27]. There is level I evidence that H_2 receptor blockers and proton pump inhibitors can reduce the pain and haemorrhage from standard dose chemotherapy oesophagitis, but there is a link with OVS sepsis [28].

12.5 Neutropenic Enterocolitis

Typhlitis or neutropenic enterocolitis (NE) is used to describe an inflammatory process involving the colon, mainly caecum with or without involving adjacent areas of the small intestine in the context of chemotherapy-induced neutropenia. NE can potentially result in life-threatening complications such as ischemia, necrosis, haemorrhage, bacteraemia and perforation. Mortality rates vary between 5 and 100 % [29]. A prospective survey reported an overall incidence of abdominal infections of 17.7 % and incidence of NE of 6.5 % among adults treated for acute leukaemia [30]. The common clinical manifestations of NE are fever, abdominal pain and diarrhoea. These symptoms are neither specific nor pathognomonic for NE and must be differentiated from other potential causes of abdominal complications such as appendicitis, pseudomembranous colitis, ischemic colitis, obstruction and intussusceptions, and both viral (CMV, adenovirus or rotavirus) and fungal (candidiasis, *Aspergillus* and *Mucorales*) infection can supervene especially after allogeneic HSCT. Typically, NE occurs between 10 and 30 days after starting cytotoxic treatment.

Ultrasound sonography (US) or computer tomography (CT) appears more valuable in the diagnosis and monitoring of suspected NE. Most reports concerning NE adopt the principle that a bowel wall thickness >3 mm is abnormal, and either matches or supports a diagnosis of NE [31]. CT is able to differentiate NE from other intestinal complications in neutropenic patients. For instance, the highest mean BWT (12 mm) was seen in *Clostridium difficile*-related colitis in an analysis of 76 neutropenic patients with various gastrointestinal disorders. Although, US showing BWT >10 mm was associated with a significantly higher mortality rate (60 %) than a BWT ≤10 mm (4.2 %) [32].

Bacteraemia due to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Clostridium* species, and *Candida* species are clearly associated with neutropenic enterocolitis [33]. Indeed bacteraemia due to certain species of *Clostridium*, for example, *Clostridium tertium* and *Clostridium septicum*, is considered pathognomonic in the setting of NE. Presumably, prolonged exposure to antibiotics results in

a marked shift in the gut microflora towards toxin-producing bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Clostridium septicum*. Mucosal or transmural necrosis and haemorrhage of the mucosal surface of the ileocecal region probably provide a favourable environment for the spores of *Clostridium* species to germinate and may be their portal of entry into the bloodstream. The pathogenesis of NE seems to require various elements to be present simultaneously, namely, cytotoxic therapy-induced mucosal damage, a perturbed resident microflora and profound neutropenia. The recovery of neutrophils usually resolves the clinical problem of NE but might be deleterious since tissue infiltration of neutrophils in an inflamed bowel wall containing microorganisms could result in perforation.

Treatment with broad-spectrum antibiotics targeting Gram-negative and anaerobic bacteria is mandatory and antifungals to target *Candida* spp. is beneficial. If the patient is a carrier, plus supportive care measures consisting of bowel rest, nasogastric suction, total parenteral nutrition [34]. Surgery should be avoided unless there is perforation or massive bleeding. Pneumatosis intestinalis due to NE is very worrisome as it suggests imminent bowel perforation. The use of G-CSF to hasten neutrophil count or function is still under debate.

12.6 Management of Mucositis and Infections

Despite its frequency and consequences, the prevention and treatment options for mucositis are sparse. Pain control is a major goal of mucositis management. Palifermin, keratinocyte growth factor-1, has been approved for use in the prevention of OM associated with TBI-containing conditioning regimens for autologous HSCT for the treatment of hematologic malignancies. Data demonstrated that palifermin effectively reduces incidence, severity and duration of severe mucositis. There was a striking reduction of febrile neutropenia episodes in the pivotal study of Spielberger et al., and there were fewer episodes of bacteraemia among HSCT recipients given palifermin, albeit not statistically significant (15 vs. 25 %) [35]. A small study showed that treatment with recombinant human IL-11 resulted in less bacteraemia and improved gut permeability [36]. Hence, agents such as recombinant human IL-11 and palifermin which are designed to protect the mucosa may prove helpful in reducing bacterial infection in neutropenic patients. Clinical trials have demonstrated the role of several antimicrobial prophylactic strategies after intensive chemotherapy or HSCT. Patients who are *herpes simplex* seropositive before the transplant procedure have a 70 % change of reactivation within 8–10 days after transplantation. This can be prevented by prophylaxis with acyclovir or valacyclovir. Fluoroquinolones are effective in not only reducing *Gram-negative* bacterial infections but also related mortality and improved overall survival [37]. Fluconazole is effective in reducing *Candida* infections, including fungaemia. In general, broad-spectrum antimicrobial therapy promptly as soon as fever occurs during neutropenia, and subsequent complementary antimicrobial therapy based upon clinical and laboratory results remains the cornerstone of management.

12.7 Gastrointestinal Graft-Versus-Host Disease

12.7.1 Pathogenesis

Acute GVHD results from the complex interaction of donor T cells and host tissues that involves recognition of major and minor histocompatibility antigens in an inflammatory milieu. The pathophysiology of acute GVHD involves both the innate and adaptive immune systems and is thought to follow a reproducible pattern of (1) tissue damage from the conditioning regimen, for example, gastrointestinal mucositis, (2) donor T-cell activation and (3) an inflammatory effector phase. In the first phase, cytotoxic therapy-induced MBI enables translocation of bacteria and microbial wall products, like LPS and peptidoglycan into the bloodstream, with activation of pro-inflammatory cytokines as described earlier. In the second phase activated host antigen presenting cells (APCs), and less important donor APCs, present host antigens to alloreactive T-lymphocytes. Subsequent activation and proliferation of T-lymphocytes, predominantly Th1-lymphocytes and probably Th17, ensues. The last phase concerns trafficking of alloreactive T- and natural killer (NK) cells to inflamed tissues and the occurrence of damage to these target tissues. Subsequently, translocation of bacterial products in intestinal GVHD leads to amplification of inflammation.

12.7.2 Clinical Features

Acute GVHD is a syndrome mostly involving the skin, liver and intestinal tract. The median time to diagnosis of acute GVHD varies with conditioning, with recipients of high-dose therapy and transplantation being diagnosed at a median of 17 days post-HSCT, as compared with recipients of reduced-intensity conditioning and transplantation being diagnosed at a median of 3 months post-HSCT where it is commonly associated with tapering of immunosuppressive agents. Similar to OM, conditioning regimen-induced lower GI toxicity can persist until the development of acute GVHD thereby complicating the diagnosis. The symptoms of gastrointestinal GVHD are similar as those associated with chemotherapy consisting of nausea, vomiting, anorexia, malabsorption, malnutrition, abdominal complaints and diarrhoea. Even when typical erythematous skin lesions erupt, biopsy is still necessary for definitive diagnosis. Infectious diarrhoea also needs to be considered. However, despite all this, infectious diarrhoea is not that common early post-HSCT, except maybe for *Clostridium difficile*-related pseudomembranous enterocolitis. The intestinal tract is a prevalent site for post-HSCT thrombotic microangiopathy. Although rare the clinical picture mimics gut GVHD, but laboratory findings of intravascular hemolysis are discriminatory.

Chronic GVHD is a multisystem immune-mediated disorder characterised by immunosuppression and immune dysregulation, resulting in increased risk of infection, impaired organ function, and reduced quality of life. Incidence of chronic GVHD is increasing, likely because of increasing age of patients undergoing HSCT, decreased early post-transplant mortality, use of peripheral blood cells as the stem cell source and increased utilisation of unrelated donors.

12.7.3 Management of GVHD and Infections

The recommended initial dose of corticosteroids for moderate to severe acute GVHD is 2 mg/kg/day of methylprednisolone or its equivalent. The response rate to single-agent corticosteroid therapy is approximately 50 %; however, complete durable responses are noted in fewer patients. Patients with steroid-refractory GVHD (either acute or chronic) have a poor survival, and second-line therapy, such as polyclonal (ATG) or monoclonal antibodies (daclizumab, inolimomab, basiliximab, alemtuzumab, rituximab) or TNF-α blockade (infliximab or etanercept) only further diminishes the activity of remaining innate and adoptive immunity. GVHD itself is an immunosuppressive condition, but therapy is extremely immunosuppressive making the patient prone to systemic infections especially viral and fungal diseases. Intestinal GVHD after nonmyeloablative HSCT significantly increased the risk of invasive aspergillosis over time [38]. Sometimes, symptoms of severe abdominal pain and nausea or diarrhoea due to visceral involvement of *varicella zoster*, CMV or H1N1 infection are misdiagnosed as GVHD. *Varicella zoster* is revealed only after eruption of skin vesicles. Intestinal adenovirus infections are associated with significant morbidity and potentially life-threatening primary in paediatric transplant recipients. The intestinal tract maybe the primary site of adenovirus reactivation [39]. Endoscopy with biopsies, CT scanning and extensive microbial culturing are mandatory in these clinically difficult patients to establish the cause(s) of their misery. Often patients with severe GI tract GVHD need intravenous hyperalimentation for prolonged periods exposing them to additional risks of infections related to the use of a central venous catheter.

Many patients with steroid-refractory GVHD will succumb to systemic infections. Therefore, standard infection prophylaxis to prevent *Pneumocystis jiroveci* pneumonia, herpesvirus reactivation and prophylaxis against invasive fungal diseases with an azole antifungal agent is recommended. In case of CMV reactivation prophylactic ganciclovir or valganciclovir is required. Patients with chronic GVHD are at risk for infection particularly by encapsulated organisms. Rare intestinal opportunistic infections with *non-tuberculous Mycobacteria*, *Mucorales species* or *Cryptosporidium species* can occur demanding meticulous diagnostic procedures if the clinical condition of the patient deteriorates.

12.8 Future Options of Management

The role of innate immunity in cancer patients has been brought to attention by the impact of single nucleotide polymorphisms (SNP) of innate immune genes (Toll-like receptors (TLRs), the Nod-like receptors (NLRs) and C-type lectin receptors (CLRs)), which result in enhanced or attenuated expression and/or function, on treatment-related complications including infections. Polymorphisms in PRRs of importance in intestinal host–microbe interactions like NOD2, originally described in Crohn's disease, and TLRs have been implicated in the occurrence of GvHD and infections.

Dectin-1, a C-type lectin that recognises 1,3-b-glucans from fungal pathogens, including *Candida species*, is involved in the initiation of the immune response against fungi. The Y238X polymorphism demonstrated a loss of function in functional assays by decreased cytokine production. Patients undergoing an allogeneic HSCT bearing this polymorphism *DECTIN-1* Y238X polymorphism had an increased oral and gastrointestinal colonisation with *Candida species* necessitating more frequent use of fluconazole in the prevention of systemic *Candida* infection [40]. Furthermore, patients from patient–donor pairs bearing the wild-type allele who where colonised with *Candida species* had a significant increased incidence of acute GVHD compared to non-colonised patients (OR = 2.6, $P = 0.04$), but this was not the case in patients from pairs with the Y238X polymorphism (OR = 1.2, ns) [41]. This might suggest that *Candida* could have a role in the pathogenesis of acute GvHD. There are also several reports indicating the role of NOD2 polymorphisms on GVHD and infections [42]. Intriguing is the fact that the impact of NOD2 polymorphisms on GVHD disappears with the use of comprehensive antimicrobial prophylaxis suggesting a role of intestinal sensing of a microbial product in such a way that the balance of immunity is influenced.

Conclusions

All these preliminary findings point out that selection of high-risk patients with the use of SNP of innate immune genes in the future might offer another tool in optimising supportive care in an attempt to prevent life-threatening gastrointestinal complications and related infections (Table 12.1).

Table 12.1 Gastrointestinal complications of haematological therapy

	Early onset <28 days	**Management**
GI mucositis	Chemotherapy/irradiation complicated by OVS or CoNS bacteraemia	Pain killers (morphine) and antibiotics
Oesophagitis	Chemotherapy	Antacids
	Herpes simplex	Antiviral prophylaxis
	Candida spp.	Antifungal therapy
Gastritis	Chemotherapy/irradiation	Antacids
Neutropenic enterocolitis	Multifactorial origin	Conservative approach
	High risk of candidaemia and bacteraemia with *Clostridia* spp. and *Staph. aureus*	Broad antimicrobial coverage
	late onset >28 days	**Management**
GI mucositis	GVHD high risk of invasive fungal diseases	Start corticosteroids antifungal therapy
Colitis	*Clostridium difficile*	Metronidazole
	CMV, *adenovirus*, *H1N1*	Antiviral treatment
	Other opportunistic pathogens:	Targeted therapy
	Cryptosporidium spp.	
	Mucorales spp.	
	Non-tuberculous mycobacteriae spp.	

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