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CURRENT OPINION

Gastrointestinal mucositis: a sign of a (systemic) inflammatory response

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Purpose of review
Gastrointestinal mucositis (GIM) is a significant complication of cancer therapy. Whilst inflammation is a central feature of GIM, studies attempting to mitigate mucosal damage via this mechanism are scarce. This review describes the relation between GIM, local and systemic inflammation, and the microbiome and its metabolites, and explores recent research on therapeutics that target this relationship.

Recent findings
Recent literature underscores the pivotal role of inflammation in GIM, elucidating its bidirectional relation with disturbance of the gut microbiota composition and intestinal permeability. These events cause a heightened risk of bloodstream infections and lead to systemic inflammation. While studies investigating risk prediction models or therapeutics targeting GIM-related inflammation remain scarce, results have shown promise in finding biomarkers and alleviating GIM and its accompanying clinical symptoms.

Summary
The findings underscore the important role of inflammation and the microbiome in GIM. Understanding the inflammatory pathways driving GIM is crucial for developing effective treatments. Further research is needed using genomics, epigenomics, and microbiomics to explore better risk prediction models or therapeutic strategies aimed at mitigating GIM-related inflammation.

Keywords
inflammation, intervention, microbiome, mucositis

INTRODUCTION

Mucositis is defined by the National Library of Medicine as inflammation of the mucosa caused by radiotherapy and chemotherapy. Mucosa as such is not specified or restricted to any region of the human body although the alimentary tract, covering the oropharyngeal, intestinal, and rectal segments is mostly focus of past investigations. This review focuses on gastrointestinal mucositis (GIM) as sign of a local and systemic inflammatory response (SIR) induced by chemotherapy and radiation, in relation to the gut innate immune defense, gut microbiome and its metabolites and explores possible therapeutic interventions. Patients suffer from GIM with symptoms of abdominal pain, bloating, nausea, vomiting, anorexia and diarrhea and GIM can often be a dose-limiting complication, induce cessation of treatment and could be life threatening. The incidence of GIM is extremely high for a wide array of chemotherapeutic and radiation regimens especially in high-dose chemotherapy preparing for hematopoietic stem cell transplant affecting 60–100% of patients [1]. Because interventions to inspect or sample the gastrointestinal tract of patients with GIM is not feasible, results of (human) studies in oral mucositis will sometimes be used to exemplify current thinking or insights related to GIM given the inherent similarities in pathophysiology.

GASTROINTESTINAL MUCOSITIS AS SIGN OF LOCAL INFLAMMATION

Sonis *et al.* already proposed a well-defined pathobiological model of oral mucositis in 2004 [2] which has been proven to apply to GIM too, albeit with region-

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KEY POINTS

- Gastrointestinal mucositis (GIM), a common complication of cancer therapy, is characterized by inflammation but attempts to target this mechanism have been sparsely studied.
- Rapidly dividing enterocytes are vulnerable to apoptosis and pyroptosis induced by cytotoxic drugs and irradiation, which, combined with ROS, upregulation of numerous proinflammatory cytokines, and microbiome disturbances, leads to excessive local inflammation and destruction of intestinal mucosa.
- Changes in gut microbiota composition and increased permeability contribute to systemic inflammation and an increased risk of bloodstream infections, but predicting these infections using inflammatory markers remains challenging.
- Therapeutic interventions targeting inflammatory pathways, microbiome modulation, and mucosal repair show promise in mitigating mucosal damage and systemic inflammation associated with GIM.
- Understanding the complex interplay between genetic, epigenetic, and microbiomic factors will aid in developing effective risk prediction models and novel treatments for GIM.

specific features [3▪]. Inflammation is a hallmark of this complication of cancer therapy with key mediators that include generation of reactive oxygen species (ROS); DNA damage responses, including apoptosis; upregulation of transcription factors, such as nuclear factor-kappa B (NF-κB); induction and self-perpetuating inflammatory cytokine cascades; submucosal signals that alter matrix deposition and mesenchymal structures; and epithelial and vascular restitution signaling. This local process is then superimposed by the impact of microbial-derived signals, including metabolites, alterations in redox status, and mucus components, merely because of colonization or infiltration at sites of breaches in the epithelial layer that increases the risk further of local and systemic infection and can result in a higher mortality during profound neutropenia [4▪].

Vulnerability of the gut to local inflammation after cytotoxic therapy

The gastrointestinal epithelium is rich in rapidly dividing cells and hence is a prime target for cytotoxic drugs and irradiation. Sender and Milo [5] performed an integrated study of ubiquity, mass, and lifespan of all major cell types to achieve a comprehensive quantitative description of cellular turnover on the human body. The lifespan of gut epithelia is 3–5 days. They found that the total turnover rate of the human body is $0.33 \pm 0.02 \times 10^{12}$ (330 ± 20 billion) cells/d (equal to about 4 million cells/s). About 14% of these cells are gut cells. This process of cellular turnover is tightly regulated by several modes of cell death [6].

Cell death and inflammatory response

Intestinal epithelial cells undergo programmed cell death through various modes including anoikis, apoptosis, necroptosis, and pyroptosis. In general, pyroptosis and necroptosis are pro-inflammatory, leading to the spread of inflammation, whereas anoikis (a form of regulated extrusion of cells from the epithelial monolayer causing cell death) and apoptosis restrict the spread of inflammation. Apoptosis is programmed cell death triggered by cellular challenges that activate either receptor-driven (extrinsic) or mitochondria-driven (intrinsic) pathways, culminating in the activation of the executioner proteases, caspase 3 and caspase 7, via the initiator caspase 8 or caspase 9 during extrinsic and intrinsic modes. Chemicals and radiation are sensed by BH3-only proteins leading to the release of mitochondrial cytochrome c and activation of effector caspases downstream. Pyroptosis is triggered by pathogen-induced activation of the inflammasome, which consists of pattern recognition receptors (PRRs) interacting with inflammatory caspases. Necroptosis is another lytic, proinflammatory mode of cell death, in which cellular contents are released into the surrounding tissues.

Cancer-therapy induced enterocyte cell death and local inflammation

Chemotherapy acts by interrupting DNA synthesis, leading to apoptotic cell death via activation of tumor suppressor gene and transcription factor p53 and subsequent creation of the proteins p53-upregulated modulator of apoptosis (PUMA) and p21, which in turn signal cells to begin apoptosis [7]. Enterocytes of the small intestines are far more sensitive to apoptosis than colonocytes. This process alone would result in non-inflammatory crypt loss, villus atrophy, loss of renewal capacity, and impairment of the gut absorptive and barrier function. But at the same time reactive oxygen species (ROS) and activation of NF-κB result in an upregulation of around 200 second messengers, most notably proinflammatory cytokines such as tumor-necrosis factor-α (TNFα), interleukin-6 (IL-6), and IL-1β, as well as cyclooxygenase-2 (COX2) [8▪]. And, despite the characteristic neutropenia and lymphocytopenia that follows chemotherapy, both resident innate immune cells (macrophages) and circulating neutrophils are attracted and activated

by those released proinflammatory cytokines and chemokines [TNFα, monocyte chemoattractant protein 1 (MCP1), IL-1α, IL-6, and CXCL8] [9] and exaggerate local inflammation by forming NETs and further release of alarmins, such as S100A8/9, proinflammatory cytokines, and ROS [10,11]. Production of ROS mediates activation of the inflammasome during GIM [12▪] by increased cleavage of caspase-1 and subsequently IL-1β and IL-18 release.Caspase-1 activated by the NLRP3 inflammasome can cleave and activate gasdermin D protein, a direct-acting molecule of inflammation-induced pyroptosis [13▪]. Animal studies involving manipulation of IL-1β, IL-18, or caspase-1 provide further support for a role of the inflammasome in mediating tissue injury during chemotherapy treatment [9]. Also, fibronectin is degraded by matrix metalloproteases (MMPs), a class of zinc-dependent endopeptidases with breakdown of extracellular matrix, further compromising the intestinal barrier. MMPs downstream mediators of NF-κB activation have been previously shown to be altered in radiation- and chemotherapy-induced gut toxicity [14].

Innate immune response to enterocyte cell damage

A recent review by Bowen nicely highlighted the role of innate immune responses in the pathogenesis of oral mucositis that is also relevant and applicable to the pathogenesis in the gut [15▪]. PRRs constitute a continuous surveillance system for the presence of endogenous-damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) and are expressed on both the external and internal cellular compartments of immune and epithelial cells [16]. DAMPs, such as heat shock proteins and high-mobility group box 1 (HMGB-1), are able to activate TLRs on IEC and innate immune cells. Alarmins, such as IL-1α and HMGB1, but also mtDNA and ATP, are necroptotic DAMPS. HMGB1 blockade, using NecroX-7(tetrahydropyran-4-yl)-[2-phenyl-5-(1,1-dioxo-thiomorpholin-4-yl)methyl-1H-indole-7-yl]amin), ameliorated basal layer epithelial cell death and ulcer size in oral mucositis, inhibited HMGB1 release and subsequent release of TNFα, IL-1β, and MIP-1β, decreased mitochondrial oxidative stress and expression of PUMA and downregulated factors involved in the excessive inflammatory microenvironment, including nuclear NF-kB [17]. By blocking TLR9/caspase3/GSDME (gasdermin E) in IEC-6 cells, 4-hydroxycyclophosphamide (CyC)-induced pyroptosis could be prevented [18▪]. Furthermore, deficiency of *Gsdme* or *TLR9* in mice, or pretreatment with hydroxychloroquine effectively attenuated intestinal damage in that CYC-induced GIM model. Dalby *et al.* were able to visualize GIM in mice treated with doxorubicin using 2-deoxy-2-[(18)F] fluoro-D-glucose positron emission tomography combined with computed tomography (2-[(18)F]FDG-PET/CT) [19▪]. Abdominal standard uptake value of 2-[(18)F] FDG corrected for body weight was significantly increased on day 1 ($P < 0.0001$), day 3 ($P < 0.0001$), and day 6 ($P < 0.05$) in the doxorubicin-treated mice compared with controls. Abdominal SUV (BW) returned to baseline levels on day 10. Villus lengths were decreased by 23–28% on days 1 and 3 in the small intestine ($P < 0.05$), and jejunal levels of TNF and IL1β were significantly increased on day 3 ($P < 0.05$). In conclusion, the rapid destruction of the intestinal mucosa has been shown to induce a debilitating local proinflammatory 'cytokine storm' as depicted in Fig. 1.

Changes in microbial tolerance and microbiome contributing to local inflammation after cytotoxic therapy

As mentioned earlier PRRs, such as TLRs and nucleotide-binding oligomerization (NOD)-like receptors (NLRs) amongst many others, also sense microorganisms through PAMPs like lipopolysaccharide (LPS), lipoproteins, peptidoglycan, and lipoteichoic acid (LTA) to control homeostatic tolerance to commensal microbes and host responses to potential microbial threats [16]. Recognition of LTA and LPS from various gram-positive and gram-negative microbes activates TLRs and drives GIM-related inflammation after formation and activation of the NLRP3 inflammasome and pyroptotic cell death [20▪]. Activation of NF-κB by TLR signaling through MyD88-dependent and -independent pathways is another important mechanism of inflammation. Knock-out of specific TLRs [2,4▪, 9] in animal studies demonstrated their contribution to pathogenesis of GIM [21▪]. TLR-2 seems to have a mucosal protective role by downregulating the excessive activation of inflammatory cells and promoting the expression of the anti-inflammatory cytokine IL-10. Wei *et al.* [22▪] recently evaluated the effect of different chemotherapeutics on the varying expression of TLRs related to different types of drugs, dosages, species and routes of administration across animal models. In general, chemotherapy can shape intestinal microbiota, which, in turn, can aggravate the mucositis through TLR signaling pathways, leading to an increased expression of inflammatory mediators and elevated epithelial cell apoptosis and decreased epithelial cell differentiation and mucosal regeneration. The gut microbiome is known to be altered by chemotherapy and radiotherapy, contributing to the severity of mucosal injury, and may be a predictive factor for risk of GIM development [23▪]. A retrospective study in 1188 allogeneic-HCT recipients

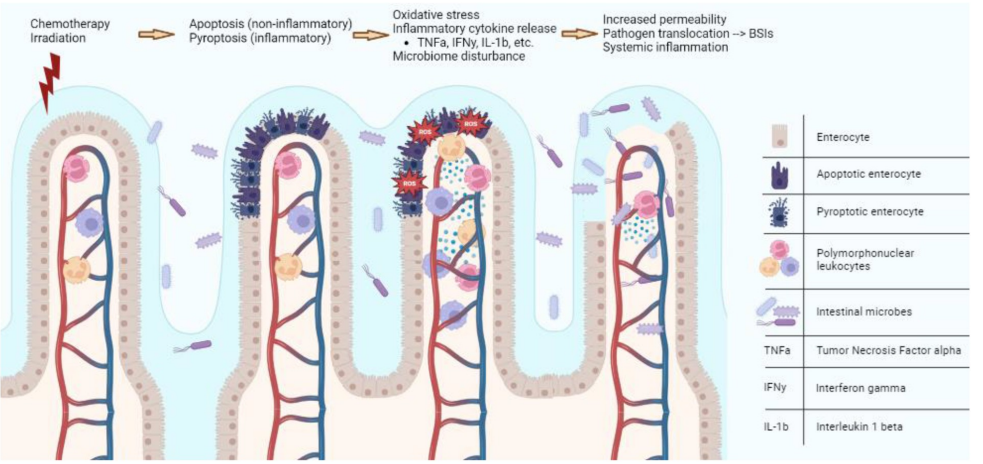

FIGURE 1. Key players in mucositis-induced intestinal inflammation, changes in microbial tolerance and microbiome contributing to local inflammation after cytotoxic therapy. Created in BioRender.com.

evaluated the relationship between conditioning regimens exposure and microbial injury [24▪]. The extent of conditioning regimen intensity was clearly related to vast changes in microbial diversity. The mechanisms by which the microbiome exerts this influence and how it responds to major stressors are still difficult to establish. Furthermore, anatomical and functional secretory changes, such as loss of integrity, Paneth [25], and goblet cell deficiencies, result in alterations of production of mucus and defensins. These secretory changes are influenced by inflammatory processes, underpinning the role of the gut microbiome in GIM development [26▪]. Typically a compositional shift occurs with loss of commensals and increased abundance of more pathobiont-dominated enterotypes. This shift directly increases bacterial and fungal colonization causing unbalanced PAMP and DAMP release that triggers PRR-mediated inflammasome activation [8▪]. It also indirectly causes dysfunctional host–microbial signaling due to network communication by immunological regulators, such as gut microbial metabolites (short-chain fatty acids, bile acids, and polyamines), defensins, CXCL2, and GAS6 [27,28].

GASTROINTESTINAL MUCOSITIS AS SIGN OF SYSTEMIC INFLAMMATION

Interplay between host and microbial metabolites

Interestingly up to 60% of patients with neutropenic fever (NF) after intensive chemotherapy present with fever of unknown origin (FUO) defined by the absence of clinical or microbial infection despite extensive investigations [29▪]. Rashidi *et al*. documented that gut microbiota of patients on the day before FUO occurrence had a lower abundance of *Blautia* spp. than their matched controls without NF on the same day after transplantation, suggesting a protective role for *Blautia* spp. associated with the group of *Lachnoclostridium*, obligate anaerobic commensals [30]. Furthermore, a metabolomic shift after fever during neutropenia contained 13 (such as citrulline and indole derivatives) out of 18 metabolites that were markers of intestinal epithelial health and bacterial metabolites of dietary tryptophan with known anti-inflammatory and gut-protective effects [31▪]. These markers were found to decrease after NF. Greater *Blautia* abundances predicted higher levels of citrulline a biomarker of total functional enterocytes mass. In another cohort of patients treated with intensive chemotherapy increases in *Akkermansia* abundance, a mucolytic genus, occurred 5–7 days before the increase of NF incidence, suggesting that *Akkermansia* increases the risk of NF likely by consuming the protective mucus layer [32▪]. Systemic cytotoxic therapy increases the relative abundance of mucin-degrading intestinal bacteria in mice that have been associated with the development of NF in humans [33▪]. Luminal acidity and SCFAs like propionate inhibit mucin utilization by *Akkermansia in vitro*. SCFAs, especially butyrate, have anti-inflammatory and barrier-protective capacities. Butyrate, propionate and acetate reduced inflammatory cytokine-induced IEC activation and, in particular, butyrate was capable of fully protecting against cytokine-induced epithelial permeability for a prolonged period in a Caco-2/PBMC co-culture model [34▪]. So, the decreased plasma levels of some metabolites after fever, in parallel with biologically consistent changes in the abundance of mucolytic and butyrogenic bacteria may indicate a disturbed luminal host-microbial metabolite network that interferes with the inflammatory processes involving the intestinal epithelium.

Role of increased permeability and microbial translocation

Tight junctions are the main determinant of epithelial barrier function and are made up of transmembrane and intracellular proteins of the claudin, occludin, zonula occludens, and junctional adhesion molecule groups. Loss of tight junction proteins has been shown following both radio- and chemotherapy and is considered important in mucositis development [35▪]. The inflammatory cytokines, TNFα and IFNγ, directly induce intestinal epithelial barrier dysfunction and alter the tight junctional morphology and rate of cellular turnover in bovine intestinal epithelial cells [36▪]. These effects occur very quickly, even within 24 h after radiation. Administration of human alpha-defensin 5 (normally produced by Paneth cells) in the diet 24 h before irradiation significantly blocked radiation-induced gut microbiota dysbiosis, disruption of intestinal epithelial tight junction and adherens junction, mucosal barrier dysfunction, and mucosal and SIRs [37▪]. Intestinal permeability measured by a modified lactulose: rhamnose (LR) assay was assessed before allogeneic transplant, and at days +7 and +30 to 80 pediatric and young adult patients. Metagenomic shotgun sequencing of stool for microbiome analyses and enzyme-linked immunosorbent assay analyses of plasma LPS binding protein (LBP), ST2 (suppression of tumorgenicity-2 protein), REG3-alpha (regenerating islet-derived-protein 3-alpha, an intestinal antimicrobial peptide), claudin1, occludin, and intestinal alkaline phosphatase were performed at the same timepoints. L:R correlated with LBP levels (r^2 = 0.208; P = 0.0014). High L:R ratios were associated with lower microbiome diversity (P = 0.035), loss of anaerobic organisms (P = 0.020), and higher plasma LBP (P = 0.0014) [38▪▪]. Different routes of permeation are normally strictly controlled but during development of GIM, control over permeability is lost, causing charge and size selectivity of tight-junction-dependency to be lost and permeability evolves to the unrestrictive tight-junction independent, high-capacity and non-selective pathway of paracellular passage or translocation in case of microbes or PAMPs [39▪, 40]. Pathogens that colonization the gut such as gram-negative bacteria in intensively chemotherapy treated patients will have more opportunity to translocate merely because of the compositional microbial change and increased gut permeability [35▪,41▪]. Claudin-2 upregulation and increased pore pathway permeability are key intermediates that contribute to development of dysbiosis, intestinal damage, inflammation, ineffective pathogen control, and increased mortality in sepsis [42▪]. It is evident and will not be discussed further that bloodstream infections (BSIs) especially during neutropenia can induce sepsis, a form of severe SIR. De Mooij *et al*. were able to classify cytotoxic regimens and their risk of gut mucositis-related bloodstream infections during NF according to the extent of intestinal mucosal damage measured by citrulline [43▪]. Several researchers have tried to document SIR measured by CRP or other cytokines in an attempt to decipher whether inflammation is related to GIM and BSIs [29▪]. Weischendorff *et al*. prospectively evaluated intestinal mucositis severity in 85 children with acute leukemia, representing 242 febrile episodes (122 with concurrent neutropenia) by measuring plasma levels of citrulline (REG3-alpha, an intestinal antimicrobial peptide) and CCL20 (a mucosal immune regulatory chemokine) along with the general neutrophil chemo-attractants CXCL1 and CXCL8 at fever onset. Decreasing citrulline levels and increasing REG3-alpha and CCL20 levels were independently associated with increased odds of BSI (OR = 1.6, 1.5, and 1.7 per halving/doubling, all $P < 0.05$). Additionally, higher CXCL1 and CXCL8 levels increased the odds of BSI (OR = 1.8 and 1.7 per doubling, all $P < 0.0001$). All three chemokines showed improved diagnostic accuracy compared with C-reactive protein and procalcitonin [44▪▪]. The jury is still out how to use inflammatory markers to predict BSIs. Their limited accuracy in various populations of interest probably limits the application of those biomarkers to situations in which there is a non-infectious condition apparent as is the case in cytotoxic-induced GIM. The use of these inflammatory markers could be improved by aiming at a high negative predictive value instead of trying to reach a high positive predictive value.

GASTROINTESTINAL MUCOSITIS AS TARGET FOR PREVENTING INFLAMMATION

Given the critical role of IL-1 in neutrophil recruitment and other consequences of GIM, the inflammasome presents a compelling target for further research. Anakinra is a recombinant human IL-1 receptor antagonist (IL-1RA), which has been shown to alleviate intestinal mucositis in various preclinical models. Kullenberg *et al*. concluded that dexamethasone reduced apoptosis in the jejunal crypts, both alone and in combination with anakinra, IL-1RA in a rat model and Wardill *et al*. could document that inhibition of the hyperactive IL-1b/CXCL1/neutrophil signaling with anakinra after high-dose melphalan in rats minimized the duration and intensity of GIM and accompanying clinical symptoms, including diarrhea, weight loss, and fever in rats. 16S analysis of fecal microbiome

demonstrated a more stable composition in rats receiving anakinra, with reduced pathogen expansion [45▪]. Clinical Phase IIA trial of anakinra has also established safety in HCT recipients and a Phase IIB trial is currently under review [46▪]. More upstream in the initiation process of GIM, anti-IL12-p40 neutralizing antibody inhibits inflammation and rescues the defects including a reduction in the number of activated T cells, TNFα concentration, number of apoptotic cells, and intestinal stem cell damage, in intestinal epithelial regeneration post-irradiation in p53-deficient mice. This indicates that p53 inhibits the expression of inflammatory cytokine IL12-p40, which in turn suppresses the expression of MHC class II on intestinal epithelial cells to suppress T cell activation and inflammation post-irradiation that causes intestinal stem cell damage [47]. Dioscin, a steroidal saponin significantly inhibited cisplatin-induced intestinal mucosal damage and activated the Nrf2/HO-1 pathway in a rat intestinal injury model to increase the level of antioxidant enzymes, reduce the levels of MDA and H(2)O(2), reduce ileum epithelial NLRP3 inflammasome formation and decreased the levels of inflammatory factors [48▪▪]. In 5-FU-injected mice, high molecular weight hyaluronic acid supplementation significantly reduced serum levels of IL-6 and the chemokine CXCL1/KC, while the serum antioxidant activity of superoxide dismutase was elevated [49▪▪]. More directed at the role of microbiota or microbial–host metabolites, research on the novel TLR4 antagonist, IAXO-102, indicated that it attenuated gastrointestinal inflammation [50▪], and offered options for interfering with metabolite crosstalk [51▪] and use of probiotics. *Lactobacillus rhamnosus*-treated mice had significantly attenuated proinflammatory cytokine levels (IL-1beta, IL-6, and TNFα), mitigated damaged tight junction integrity via upregulation of the levels of claudin, occludin, ZO-1, and mucin-2 protein (MUC-2) and enhanced growth of beneficial bacteria that is *Firmicutes* and *Lachnospiraceae*, while the relative abundance of the opportunistic bacteria *Bacteroides* and *Proteobacteria* was decreased. *Bacillus coagulans* MZY531 ameliorated CYP-induced intestinal mucosal injury and inflammation by upregulating the ZO-1 pathway and downregulating the expression of the TLR4/MyD88/NF-κB pathway [52]. Unfortunately third-party fecal microbiota transplantation in hematology patients was safe but did not decrease infections in this randomized double-blind phase II trial [53▪]. Diet components such as vitamin D are promising as prebiotics often in combination, and result in downregulation of inflammation and harnessing integrity [54]. New drugs have also shown promising results. Firstly CPX-351, a liposomal combination of cytarabine plus daunorubicin simultaneously exploits antileukemia potency, promotes production of immunomodulatory metabolites by commensal anaerobes and prevents mucosal damage via the aryl hydrocarbon receptor-IL-22-IL10 pathway [55▪]. Secondly, Uproleselan (GMI-1271) a novel E-selectin antagonist added to chemotherapy in AML patients was associated with lower rates of mucositis probably by blocking attraction and extravasation of PMNs [56▪]. Finally, Sargramostim (glycosylated yeast-derived recombinant GM-CSF) prevented immune-related GI toxicity of immune checkpoint inhibitors. Sargramostim has been in practice for over 30 years and might deserve a revival in attention [57▪]. Supporting or modulating intestinal stem cells either for preventing apoptosis or boosting repair is to be explored [58].

CONCLUSION: FUTURE PERSPECTIVES

A change of perspective based on cellular, animal, and clinical studies proposes that mucosal damage is largely the consequence of cumulative chemo/radiotherapy-induced biological mucosal changes overwhelming physiologic self-protective mechanisms [59▪]. Furthermore, an individual's ability to mount and maintain a protective response is dependent on interacting pathways which are primarily determined by a multiplex consisting of genomics, epigenomics, and microbiomics [60]. Exploitation of these vast data sets seems promising either to develop a better risk prediction model and to detect promising targets for development of new drugs to prevent or treat the mucosal and systemic inflammation related to GIM as depicted in Fig. 1 [61▪].

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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This study reported an increased risk of NF after *Akkermansia* expansion, and therefore identified novel aspects of NF pathogenesis and targets for therapeutic strategies.

33. ■ Schwabkey ZI, Wiesnoski DH, Chang CC, *et al*. Diet-derived metabolites and mucus link the gut microbiome to fever after cytotoxic cancer treatment. Sci Transl Med 2022; 14:eabo3445.

This clinical trial indicates an important role of the microbiome in neutropenic fever and highlights therapeutic potential of diet and other microbiome-based preventive strategies.

34. ■ Korsten S, Vromans H, Garssen J, Willemsen LEM. Butyrate protects barrier integrity and suppresses immune activation in a Caco-2/PBMC co-culture model while HDAC inhibition mimics butyrate in restoring cytokine-induced barrier disruption. Nutrients 2023; 15:2760.

This study reported a beneficial effect of SCFAs butyrate, propionate, and acetate on inflammatory parameters in intestinal epithelial cells, showing the importance of SCFAs and the microbiome in intestinal homeostasis.

35. ■ Dahlgren D, Lennernas H. Review on the effect of chemotherapy on the intestinal barrier: epithelial permeability, mucus and bacterial translocation. Biomed Pharmacother 2023; 162:114644.

This review emphasizes that chemotherapy renders the mucosal barrier more permeable and increases bacterial translocation, but stresses that a more thorough characterization is needed to outline a clear temporal model of the different gastrointestinal events. This could enhance our understanding of the pathogenesis of GIM.

36. ■ Crawford CK, Lopez Cervantes V, Quilici ML, *et al*. Inflammatory cytokines directly disrupt the bovine intestinal epithelial barrier. Sci Rep 2022; 12:14578.

This study showed that the pro-inflammatory cytokines TNFα and IFNγ directly induce intestinal epithelial barrier dysfunction and alter tight junctional morphology and rate of cellular turnover in bovine intestinal organoids, indicating a role of local inflammation in mucosal damage.

37. ■ Shukla PK, Rao RG, Meena AS, *et al*. Paneth cell dysfunction in radiation injury and radio-mitigation by human alpha-defensin 5. Front Immunol 2023; 14: 1174140.

This study shows the beneficial effects of HD5 administration on radiation-induced intestinal mucsal injury, endotoxemia, and systemic inflammation. HD5 helps maintain homeostasis of intestinal microbiota, again indicating the role of the microbiota in GIM.

38. Wang YM, Abdullah S, Luebbering N, *et al*. Intestinal permeability in patients ■■ undergoing stem cell transplantation correlates with systemic acute phase responses and dysbiosis. Blood Adv 2023; 7:5137–5151.

This study validated a new method to assess intestinal permeability. In addition, this study showed that this intestinal permeability was correlated to several adverse outcomes, including lower microbiome diversity, loss of anaerobic organisms, systemic acute phase responses, etc. Therefore, this study indicates that loss of permeability increases risk of systemic inflammation, and it has significant implications for risk prediction modeling in patients with GIM.

39. Haroun E, Kumar PA, Saba L, *et al*. Intestinal barrier functions in hematologic ■ and oncologic diseases. J Transl Med 2023; 21:233.

This review explores the role of mucosal barrier disruption in hematologic and oncologic diseases, providing therapeutic strategies.

40. Horowitz A, Chanez-Paredes SD, Haest X, Turner JR. Paracellular permeability and tight junction regulation in gut health and disease. Nat Rev Gastroenterol Hepatol 2023; 20:417–432.

41. Stoma I, Littmann ER, Peled JU, *et al*. Compositional flux within the intestinal ■ microbiota and risk for bloodstream infection with gram-negative bacteria. Clin Infect Dis 2021; 73:e4627–e35.

This study showed that gram-negative intestinal colonization is highly predictive of BSI in the setting of allo-HCT, which has important implications for antibacterial treatments.

42. Oami T, Abtahi S, Shimazui T, *et al*. Claudin-2 upregulation enhances intest- ■ inal permeability, immune activation, dysbiosis, and mortality in sepsis. Proc Natl Acad Sci U S A 2024; 121:e2217877121.

This study shows that claudin-2 and increased pore pathway permeability are involved in dysbiosis, intestinal damage and inflammation, ineffective pathogen control, and increased mortality in sepsis, indicating that mucositis could be a cause of systemic inflammation and sepsis.

43. de Mooij CEM, van der Velden W, de Haan AFJ, *et al*. Grading bloodstream ■ infection risk using citrulline as a biomarker of intestinal mucositis in patients receiving intensive therapy. Bone Marrow Transplant 2022; 57:1373–1381.

This study describes a non-invasive, easy method, that is citrulline plasma concentration, to grade BSI risk for several commonly used intensive treatment regiments, potentially enabling clinicians to better distinguish between patients that should receive antibiotics from those who do not.

44. Weischendorff S, Rathe M, Petersen MJ, *et al*. Markers of intestinal mucositis ■■ to predict blood stream infections at the onset of fever during treatment for childhood acute leukemia. Leukemia 2024; 38:14–20.

This study reported that citrulline, REG3-alpha, CCL20, CXCL1, and CXCL8 levels were correlated with BSI risk. Not only does this indicate that intestinal mucositis can cause BSIs and systemic inflammation, it also provides new markers for predictive risk modeling.

45. Wardill HR, de Mooij CEM, Ferreira ARD, *et al*. Supporting the gastrointest- ■ inal microenvironment during high-dose chemotherapy and stem cell transplantation by inhibiting IL-1 signaling with anakinra. Sci Rep 2022; 12:13.

This study showed that inhibition of hyperactive IL-1b/CXCL1/neutrophil signaling with anakinra minimized the duration and intensity of mucosal barrier injury and accompanying clinical symptoms in rats. In addition, administration of anakinra was safe in humans. This study provides a new exciting therapeutic to alleviate GIM.

46. Wang J, Chang CY, Yang X, *et al*. p53 suppresses MHC class II presentation ■ by intestinal epithelium to protect against radiation-induced gastrointestinal syndrome. Nat Commun 2024; 15:137.

This study indicates that IL12-p40/MHC class II is involved in the protective effects of p53 in radiation-induced gastrointestinal toxicity, providing a new potential therapeutic strategy.

47. de Mooij CEM, van Groningen LFJ, de Haan AFJ, *et al*. Anakinra: efficacy in the management of fever during neutropenia and mucositis in autologous stem cell transplantation (AFFECT-2)-study protocol for a multicenter randomized double-blind placebo-controlled trial. Trials 2020; 21:16.

48. Jin S, Zhu T, Deng S, *et al*. Dioscin ameliorates cisplatin-induced intestinal ■■ toxicity by mitigating oxidative stress and inflammation. Int Immunopharmacol 2022; 111:109111.

This study showed that dioscin could reduce oxidative stress and inflammation in a rat model of intestinal injury, thereby ameliorating cisplatin-induced intestinal toxicity. This indicates that dioscin, or other therapies targeting oxidative stress and inflammation, could potentially alleviate mucositis in patients treated with intensive cytotoxic therapies or irradiation.

49. Mohammed AI, Celentano A, Paolini R, *et al*. High molecular weight hyaluro- ■■ nic acid drastically reduces chemotherapy-induced mucositis and apoptotic cell death. Cell Death Dis 2023; 14:453.

In this study, hyaluronic acid was shown to attenuate 5-FU-induced mucositis, at least partly by impeding apoptosis, inhibiting oxidative stress, and suppressing inflammatory cytokines, highlighting the therapeutic potential of hyaluronic acid and other therapeutics targeting apoptosis, oxidative stress, or inflammation.

50. Tam JSY, Crame EE, Elz AS, *et al*. Effects of a novel toll-like receptor 4 ■ antagonist IAXO-102 in a murine model of chemotherapy-induced gastrointestinal toxicity. Cancer Chemother Pharmacol 2022; 90:267–278.

This study showed that TLR4 inhibition attenuated symptomatic parameters of GIM and tissue injury in the colon, showing, at least, a partial role of TLR4 activation in GIM development.

51. Zhao Z, Sun M, Cui X, *et al*. *Bacillus coagulans* MZY531 alleviates intestinal ■ mucosal injury in immunosuppressive mice via modulating intestinal barrier, inflammatory response, and gut microbiota. Sci Rep 2023; 13:11181.

This study found that *B. coagulans* MZY531 ameliorated CYP-induced intestinal mucosal injury and inflammation by modulating the ZO-1 and TLR4/MyD88/NF-κB pathways, providing new targets for therapeutic intervention.

52. Ornelas A, Dowdell AS, Lee JS, Colgan SP. Microbial metabolite regulation of epithelial cell–cell interactions and barrier function. Cells 2022; 11:944.

53. Munem F, Thianhlun PCK, Anderson PH, Stringer AM. Vitamin D is a potential ■ treatment for the management of gastrointestinal mucositis. Curr Opin Support Palliat Care 2023; 17:247–252.

This review highlights the therapeutic potential of vitamin D, which has been reported to reduce intestinal inflammation by reducing NF-κB activation, indicating a central role for NF-κB in intestinal inflammation.

54. Rashidi A, Ebadi M, Rehman TU, *et al*. Randomized double-blind phase II trial of fecal microbiota transplantation versus placebo in allogeneic hematopoietic cell transplantation and AML. J Clin Oncol 2023; 41:5306–5319.

55. Renga G, Nunzi E, Stincardini C, *et al*. CPX-351 exploits the gut microbiota ■ to promote mucosal barrier function, colonization resistance and immune homeostasis. Blood 2024;

This study showed that CPX-351 protected from gut dysbyiosis, mucosal damage, and gut morbidity, while increasing antifungal resistance, through pathways involving the host and intestinal microbiota. These results indicate an important role of the microbiota in the pathophysiology of GIM.

56. DeAngelo DJ, Jonas BA, Liesveld JL, *et al*. Phase 1/2 study of uproleselan ■ added to chemotherapy in patients with relapsed or refractory acute myeloid leukemia. Blood 2022; 139:1135–1146.

This study showed that uproleselan, an E-selectin antagonist, was associated with low rates of mucositis, indicating the potential involvement of PMNs in the pathogenesis of GIM.

57. Dougan M, Nguyen LH, Buchbinder EI, Lazarus HM. Sargramostim for pro- ■ phylactic management of gastrointestinal immune-related adverse events of immune checkpoint inhibitor therapy for cancer. Cancers (Basel) 2024; 16:501.

This review describes the benefits of sargramostim as treatment for mucositis through differentation/maturation of monocytes, macrophages, and neutrophils, and induction of anti-inflammatory T cell responses, providing a new therapeutic strategy.

58. Wang Z, Qu YJ, Cui M. Modulation of stem cell fate in intestinal homeostasis, injury and repair. World J Stem Cells 2023; 15:354–368.

59. Wardill HR, Sonis ST, Blijlevens NMA. Using real world data to advance the ■ provision of supportive cancer care: mucositis as a case study. Curr Opin Support Palliat Care 2022; 16:161–167.

This review provides advice for improvement of data collection and governance, which would ultimately lead to better development of treatments.

60. Sonis ST. A hypothesis for the pathogenesis of radiation-induced oral mucositis: when biological challenges exceed physiologic protective mechanisms. Implications for pharmacological prevention and treatment. Support Care Cancer 2021; 29:4939–4947.

61. Hertz DL, Lustberg MB, Sonis S. Evolution of predictive risk factor analysis ■ for chemotherapy-related toxicity. Support Care Cancer 2023; 31:601.

This review describes the evolution of cancer toxicity biomarker discovery and proposes methods that can aid in development of new biomarkers and risk prediction models.