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Exploration of key targets and mechanisms in radiotherapy-induced gastrointestinal mucositis: A systematic literature review

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► ***Review article***

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ABSTRACT

This review article explores the key targets and mechanisms of radiotherapy (RT)-induced gastrointestinal mucositis (RIGIM) development and progression. RIGIM is a frequent and potentially disabling side effect of radiation therapy, impacting the mucosal lining of the gastrointestinal tract. The pathophysiology of RIGIM is complex, involving oxidative stress, inflammatory pathways, DNA damage, changes in the gut microbiota, and disruption of the mucosal barrier's integrity. The clinical presentation of RIGIM varies, ranging from mild inflammation to severe ulceration, significantly impacting patients' quality of life, nutrition, and treatment adherence. This article discusses the risk factors, symptoms, and clinical manifestations of RIGIM, as well as current and potential therapeutic strategies. These strategies include pharmacological interventions, microbiome modulation, and supportive care, aimed at preventing, mitigating, or treating RIGIM and ultimately improving the lives of cancer patients undergoing RT.

INTRODUCTION

Radiotherapy (RT) is a cornerstone of modern oncology, contributing to cure or durable tumour control in roughly half of all cancer patients treated worldwide [1]. Yet this benefit is tempered by collateral injury to healthy, rapidly proliferating tissues, nowhere more clinically consequential than along the gastrointestinal (GI) tract, where radiotherapy-induced gastrointestinal mucositis (RIGIM) has emerged as one of the most frequent, dose-limiting, and cost-intensive toxicities of cancer care [2].

RIGIM encompasses a spectrum of inflammatory and ulcerative lesions from oral mucositis through oesophagitis, enteritis, and radiation proctitis. Patients may endure odynophagia, abdominal cramping, intractable diarrhoea [3], rectal bleeding [4], nausea and vomiting [5]; severe cases trigger dehydration, malnutrition, sepsis, and opioid-level pain control, often necessitating hospitalisation, parenteral nutrition, or stoma formation [2]. These complications drive up direct medical costs, increase unplanned admissions, and amplify indirect societal costs due to loss of productivity and caregiver burden. Treatment interruptions or dose reductions forced by grade ≥3 mucositis reduces tumour-control probability and are independently associated with poorer survival [6].

The incidence of RIGIM remains alarmingly high despite technological advances in RT planning. Up to 80 % of head-and-neck cancer patients develop mucositis, with ~56 % progressing to grade 3–4 disease, and altered-fractionation schedules can push incidence to nearly 100 % [7]. In pelvic or abdominal RT, clinically significant diarrhoea still affects about one in two patients [8]. Risk is modulated by radiation dose, fractionation, irradiated volume, concurrent chemotherapy, and host factors such as age, nutritional status, diabetes, inflammatory bowel disease or polymorphisms in DNA-repair and cytokine genes, as discussed later [9].

Biologically, RIGIM is initiated by radiation-induced DNA damage and oxidative stress, followed by a tightly interwoven cascade of cytokine signalling [10], immune dysregulation, microbiota disruption, and extracellular-matrix degradation that culminates in barrier breakdown and microbial translocation [11, 12]. The complexity and multistage nature of this pathophysiology explain why singular interventions have achieved only modest success and underscore the urgent need for integrated, mechanism-based

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solutions.

Although expert bodies such as MASCC/ISOO and the NCCN publish guideline recommendations, current prophylactic and therapeutic options remain inadequate, and no agent is universally accepted as a standard of care for GI mucositis [13, 14]. Moreover, recent promising agents, for example, the superoxide -dismutase mimetic avasopasem manganese, have encountered regulatory setbacks, highlighting persistent translational gaps [15].

Therefore, we undertook a systematic literature review to summarize the most up-to-date clinical and pre-clinical evidence on the molecular drivers, risk modifiers, and therapeutic targets of RIGIM. By integrating mechanistic insights with trial data, we aim to: delineate the key cellular and molecular pathways underpinning RIGIM; map current and emerging preventative or mitigating strategies against these pathways; and identify knowledge gaps that must be bridged to deliver effective, patient-centred care.

Through this comprehensive approach, we intend to provide researchers, clinicians, and guideline panels with a consolidated evidence base to accelerate the development of multifaceted prophylactic and therapeutic strategies that will ultimately improve patients' quality of life, safeguard treatment adherence, and reduce the economic burden of cancer therapy.

SEARCH CRITERIA

The search strategy employed a combination of relevant MeSH terms and keywords to identify studies related to RIGIM. The following terms, including variations and truncations (*), were used with appropriate Boolean operators (AND, OR): "radiotherapy", "radiation therapy", "irradiation", "gastrointestinal mucositis", "oral mucositis", "esophagitis", "enteritis", "colitis", "proctitis", "intestinal mucositis", "GI mucositis", "mucositis", "gastrointestinal toxicity", "GI toxicity", "radiation enteropathy", "radiation proctopathy", "oxidative stress", "inflammation", "inflammatory pathways", "NF-κB", "cytokines", "DNA damage", "gut microbiota", "microbiome", "mucosal barrier", "intestinal permeability", "prevention", "treatment", "management", "mechanism", "pathophysiology", "target".

The search timeline was from database inception to April 2025. The following databases were systematically searched: PubMed, EMBASE, and Web of Science.

The inclusion criteria encompassed original research articles (both preclinical and clinical), systematic reviews, meta-analyses, and relevant clinical practice guidelines focusing on the mechanisms, targets, prevention, and management of RIGIM. Studies investigating the pathophysiology of RIGIM, including the role of oxidative stress, inflammatory pathways, DNA damage, gut microbiota alterations, and mucosal barrier disruption, were prioritized. Articles exploring potential therapeutic and preventative targets and strategies were also included.

Studies were initially screened based on their titles and abstracts for relevance to RIGIM. Full-text articles of potentially relevant studies were retrieved and assessed against the inclusion criteria. The reference lists of the included articles and reviews were manually searched to identify any additional relevant publications.

CLINICAL LANDSCAPE OF RIGIM

Risk factors for GIM

Several interconnected factors determine the severity and likelihood of GIM development; however, the radiation dose and fractionation schedule are well-established factors. Radiotherapy targeting the pelvic or abdominal regions carries a ~50% risk of RIGIM, a risk that rises further when chemotherapy is delivered concurrently. Higher total radiation doses (generally exceeding 45 Gy) are notably associated with increased mucosal damage [4]. Fractionated doses, delivered over several weeks, allow for some degree of mucosal repair between each session; however, the cumulative effect of radiation exposure remains a major risk factor [16]. In addition to direct DNA damage, the gastrointestinal tract is highly susceptible to radiation-induced oxidative stress, and prolonged exposure promotes epithelial apoptosis, further compromising mucosal integrity. The extent of the irradiated area is also crucial; a larger portion of the gastrointestinal tract exposed to radiation increases the chances of developing GIM [17].

The simultaneous application of chemoradiotherapy greatly increases the risk. Chemotherapy drugs, especially those known for their mucotoxic properties like 5-FU, capecitabine, and irinotecan, work in conjunction with radiation to amplify the harm to epithelial cells that are dividing rapidly in the gastrointestinal mucosa [18]. It is important to differentiate these modalities: chemotherapy generally causes acute, systemic injury, whereas conventionally fractionated radiotherapy inflicts a more gradual, cumulative insult; when the two are combined, particularly with monoclonal antibodies, their toxicities are synergistic, markedly heightening gastrointestinal morbidity. Although more recently developed RT techniques, such as intensity-modulated RT (IMRT), as well as novel methods for calculating doses such for pencil beam scanning proton therapy [19] are designed to accurately target tumors while minimizing damage to nearby healthy tissues, patients who undergo total body irradiation as part of hematopoietic stem cell transplantation (HSCT) still face high incidences of GIM due to the extensive

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exposure of the mucosa [20]. Radiation-dose rate also modifies risk: high-dose-rate monotherapy and the use of a high-dose-rate boost are both associated with lower acute toxicity compared with low-dose-rate, multi-session regimens; conversely, low-fraction schedules intensify acute mucosal reactions but do not appear to increase late-onset injury [18].

Beyond treatment-related factors, certain pre-existing conditions may affect the risk of an individual developing GIM. Individuals suffering from inflammatory bowel disease (IBD), which includes diseases such as ulcerative colitis and Crohn's disease, experience existing mucositis and impaired barrier function, which significantly increases their vulnerability to damage caused by radiation [21]. Diabetes mellitus, through its associated microvascular complications, can impair oral mucosal healing and increase vulnerability to radiation damage, and this may also be a concern with GIM. Malnutrition, a common issue in cancer patients, further weakens the body's ability to repair damaged tissues and maintain immune function, exacerbating mucosal injury and delaying recovery [22]. Finally, research suggests that genetic factors, specifically polymorphisms in genes involved in DNA repair (for example, *XRCC1*, *ERCC1*) and inflammatory responses (for example, *TNF-α*, *IL-6*), may influence susceptibility to GIM [23].

Symptoms and clinical manifestations

The clinical presentation of RIGIM varies, reflecting complex pathophysiological processes triggered by radiation exposure to the GI tract. Symptoms can vary from minor discomfort to serious, potentially life-threatening issues.

Diarrhea, a very common symptom, affects up to 80% of patients undergoing pelvic RT. Radiation causes villous atrophy, crypt cell depletion, and impaired absorptive function, leading to increased fluid and electrolyte loss into the intestinal lumen. Additionally, radiation increases colonic permeability and disrupts intercellular adhesion, further exacerbating fluid and electrolyte loss. Diarrhea severity varies from mild to severe and may require hospitalization for intravenous fluid and electrolyte replacement [3].

Abdominal pain and cramping are frequent complaints arising from mucosal inflammation, ulceration, and submucosal edema. Inflammatory mediators contribute to visceral hypersensitivity, making the gut more sensitive to stimuli. The pain may resemble IBS or exacerbate pre-existing gastrointestinal conditions [3].

Nausea and vomiting were more frequently observed if the radiation treatment area, when treated with orthovoltage RT, included the upper gastrointestinal tract [24]. Radiation-induced damage to the gastric mucosa and enterochromaffin cells stimulates vagal nerve afferents, triggering the Medulla oblongata. Concurrent use of emetogenic chemotherapeutic agents amplifies these symptoms [25].

Mucosal ulceration and bleeding represent a more severe manifestation of GIM. In mice, radiation induces apoptosis of crypt stem cells and damages endothelial cells, leading to mucosal breakdown and ulcer formation. Ulceration exposes submucosal blood vessels, resulting in gastrointestinal bleeding, which may manifest as hematochezia or melena. Microvascular injury and radiation-induced coagulation abnormalities increase bleeding risk [26].

Bacterial translocation and sepsis are potentially life-threatening complications of severe GIM. Loss of mucosal barrier integrity allows gut bacteria and endotoxins to enter systemic circulation. Immunocompromised patients, especially those undergoing HSCT, are at higher risk for bacteremia and sepsis. Gram-negative and anaerobic bacteria are commonly implicated in these infections [27].

Grading and evaluation systems

Accurate assessment of GIM severity is crucial for guiding treatment decisions, monitoring interventions, and comparing clinical trial outcomes. Several standardized grading systems are used, each with strengths and limitations.

The Common Terminology Criteria for Adverse Events (CTCAE), developed by the National Cancer Institute, grades adverse events in cancer trials, including GIM, based on parameters such as diarrhea frequency, daily activity impact, hospitalization need, and life-threatening consequences, ranging from Grade 1 (mild) to Grade 5 (death) [28].

The World Health Organization (WHO) Mucositis Scale assesses mucosal injury severity based on symptoms and eating ability, ranging from Grade 0 (no symptoms) to Grade 4 (ulcers preventing oral intake) [28].

The Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) Radiation Morbidity Scoring Schema grades radiation-induced toxicity from 0 (no change) to 4 (severe ulceration or necrosis requiring surgery) [28].

While these grading systems provide a standardized language for describing GIM severity, they have limitations. Interobserver variability and subjective symptom reporting can introduce inconsistencies. Research is ongoing to identify objective biomarkers that can more accurately reflect mucosal injury.

Potential biomarkers include lower citrulline levels in the plasma, indicating functional enterocyte mass [29]. Fecal calprotectin, an indicator of intestinal inflammation, might also act as a potential biomarker since increased levels are associated with mucosal damage in various other gastrointestinal disorders [30]. Cytokine profiling, measuring pro-inflammatory

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cytokines, may indicate mucosal injury. Researchers are investigating advanced imaging techniques, like PET scans and diffusion-weighted MRI, for the non-invasive evaluation of mucosal integrity and inflammation [31].

The effect of RIGIM on cancer treatment and a patient's QoL

The consequences of GIM significantly impact cancer treatment efficacy and patient well-being. Challenges include treatment interruptions, chronic radiation enteropathy, nutritional complications, microbiota dysbiosis, psychosocial impact, and economic burdens (Table 1).

Table 1. Challenges and impacts of RIGIM.

Category	Impact
Treatment interruptions and modifications	Severe mucositis leads to RT interruptions, dose reductions, or treatment cessation, reducing tumor control probability and affecting survival rates.
Chronic Radiation enteropathy	Long-term effects include fibrosis, strictures, fistula formation, and chronic malabsorption due to endothelial cell damage and fibroblast activation. Can cause intestinal obstruction, requiring surgical intervention.
Nutritional complications	Mucosal damage impairs nutrient absorption, leading to malnutrition, weight loss, weakened immune function, and delayed tissue repair.
Microbiota dysbiosis	Radiation alters gut microbiome, reducing beneficial bacteria (e.g., *Lactobacillus*, *Bifidobacterium*), promoting mucosal inflammation, and systemic effects.
Psychosocial impact	Chronic diarrhea, abdominal pain, and fatigue lead to anxiety, depression, social withdrawal, and reduced adherence to treatment.
Economic burden	Increased healthcare costs due to hospitalizations, supportive care (parenteral nutrition, pain management), and loss of productivity for patients and caregivers.

Addressing these impacts requires a comprehensive management approach. Prophylactic interventions, such as radioprotective agents like amifostine (limited by side effects and cost), aim to reduce mucosal toxicity by scavenging free radicals. Pharmacological therapies, including anti-inflammatory agents (corticosteroids, COX-2 inhibitors), growth factors (keratinocyte growth factor), and antioxidants, are being investigated to protect the mucosa and promote healing. Microbiome modulation, using probiotics and prebiotics, aims to restore gut microbial balance and enhance mucosal integrity. Advanced RT techniques, like proton therapy and image-guided RT, offer more precise tumor targeting with reduced exposure to healthy tissues, potentially lowering GIM incidence. Supportive care, including nutritional support, pain management, antidiarrheal medications (loperamide, octreotide), and psychological counseling, is integral to patient care.

PATHOPHYSIOLOGY OF RIGIM

This section offers a comprehensive overview of the various stages involved in the development of RIGIM. It includes findings from a range of studies, including *in vitro* experiments, animal models, and clinical investigations, to provide a holistic understanding of the underlying mechanisms.

Initial cellular damage and oxidative stress

The development of RIGIM starts with the immediate impact of ionizing radiation on the cells of the intestinal tract, particularly targeting the rapidly dividing epithelial cells. The initiating event is water molecule radiolysis within the cellular environment, generating highly reactive ROS and RNS. These include hydroxyl radicals (•OH), superoxide anions (O_2^-•), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$), leading to oxidative stress [11].

ROS and reactive nitrogen species (RNS) can damage essential cellular macromolecules, with DNA being particularly vulnerable. Exposure to ionizing radiation results in both single-stranded DNA breaks and double-stranded DNA breaks, in-turn activating the DNA damage response (DDR) pathways. Central to DDR are proteins such as ATM kinase and p53. When p53 is activated, it can either halt the cell cycle, giving the cell an opportunity to repair the DNA, or, if repair is not possible given the extent of damage, initiate apoptosis [32].

Apoptosis of intestinal epithelial cells, particularly the crypt stem cells, diminishes the mucosa's ability to regenerate, leading to villus shrinkage and a weakened epithelial barrier. This weakened barrier is less capable of absorbing nutrients and blocking the entry of harmful substances [12].

Oxidative stress also damages proteins and lipids, disrupting cellular homeostasis and impairing membrane receptors, transporters, and signaling pathways.

Ionizing radiation activates intracellular signaling cascades, notably NF-κB and MAPK pathways. These regulate gene expression, leading to the transcription of genes that are central to apoptosis (p53), cell survival (Bcl-2 family), and inflammation (ZEB1). The initial cellular damage amplifies through a cascade of events [32].

Figure 1 provides an overview of the initial pathophysiological mechanism by which radiation leads to RIGIM.

The balance between antioxidant defense mechanisms and the production of oxidants is crucial. An imbalance favoring oxidants exacerbates oxidative stress and drives mucosal injury progression.

Inflammatory cascade and immune dysregulation

The initial cellular damage caused by radiation triggers a complex inflammatory cascade. Damaged epithelial cells release damage-associated molecular patterns, which are identified by pattern recognition receptors (PRRs) located on immune cells like macrophages and dendritic cells within the lamina propria [33].

This recognition activates intracellular signaling

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pathways, primarily activator protein 1 and NF-κB, within immune cells. This leads to the release of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [34].

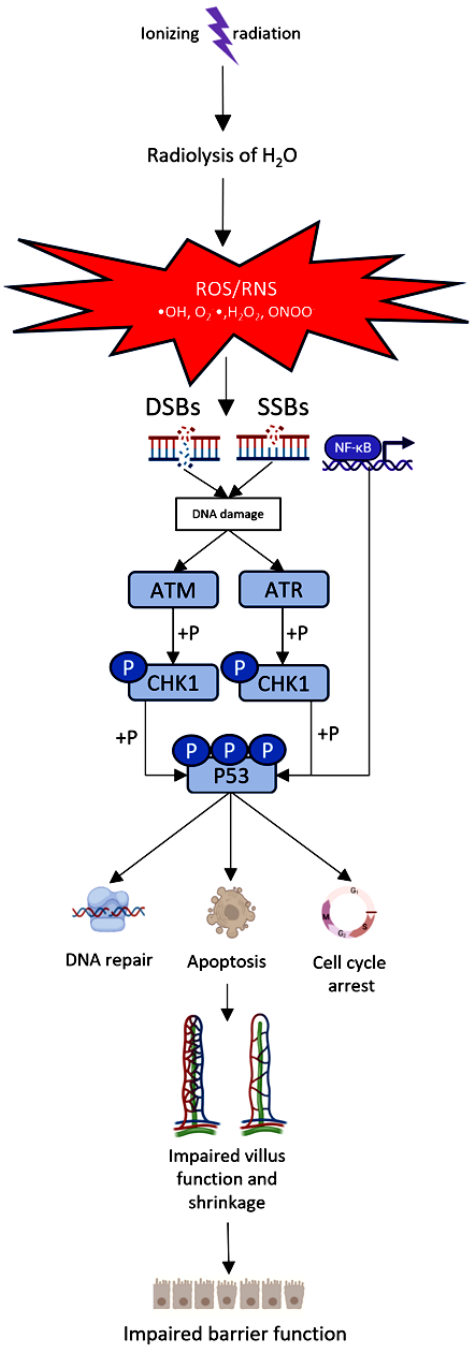

Figure 1. RIGIM pathogenesis: Ionizing radiation generates ROS/RNS, causing DNA damage and activating p53-dependent apoptosis.

TNF-α amplifies the inflammatory response by increasing vascular permeability, promoting leukocyte adhesion and migration, and inducing epithelial cell apoptosis. IL-6 and IL-1β promote neutrophil recruitment and activation, sustaining inflammation [35].

Radiation disrupts the gut-associated lymphoid tissue balance, causing immune dysregulation [36]. There is a shift towards T-helper 1 and T-helper 17 responses (pro-inflammatory), with decreased regulatory T-cell activity. This imbalance leads to unchecked inflammation and tissue damage [37].

The gut microbiota is crucial in the development of GIM. Exposure to radiation changes its makeup, leading to dysbiosis, which is marked by a decrease in beneficial bacteria and an increase in harmful bacteria. These pathogens stimulate inflammatory responses through interactions with PRRs, particularly Toll-like receptors (TLRs), intensifying immune dysregulation [38].

Breakdown of the mucosal barrier and microbial invasion

The combined effects of epithelial cell apoptosis, oxidative stress, and pro-inflammatory cytokine production ultimately lead to mucosal barrier breakdown, a critical component of gut health.

MMPs, enzymes that break down extracellular matrix components, are upregulated in response to cytokines like IL-1β and TNF-α. MMP-2 and MMP-9 are particularly important in GIM. These MMPs not only break down the extracellular matrix, which serves as the tissue's structural framework, but also degrade tight junction proteins like claudins and occludin. These proteins are crucial for preserving cell-cell adhesion and epithelial barrier integrity [39].

Disruption of tight junctions results in an increase in the permeability of the intestines, also known as leaky gut, which allows luminal antigens, bacteria, and bacterial products, such as lipopolysaccharide (LPS), to translocate across the epithelium and into the lamina propria. The presence of LPS and other microbial components in the lamina propria and, subsequently, in the systemic circulation, further stimulates immune activation through TLR4 signaling on immune cells [40]. This can result in the establishment of a positive feedback loop, perpetuating the inflammatory cycle.

Microbial invasion exacerbates mucosal damage and can lead to secondary infections. Opportunistic pathogens exploit the compromised barrier, leading to localized infections within the intestinal wall. In severe cases, this can progress to systemic dissemination of bacteria, resulting in bacteremia and sepsis [40,41]. Immunocompromised patients, such as those undergoing cancer treatment, are particularly susceptible to these serious complications. The translocation of bacteria and their endotoxins further fuels the inflammatory process, potentially contributing to sustained mucosal injury.

Recovery and wound healing mechanisms

Despite the extensive damage inflicted by radiation, the gastrointestinal mucosa possesses a remarkable capacity for regeneration, provided that appropriate wound-healing mechanisms are activated. Recovery involves a coordinated series of events, including cellular proliferation, differentiation, migration, and extracellular matrix

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remodeling [42].

Epithelial regeneration is primarily driven by the proliferation of surviving crypt stem cells. The Wnt/β-catenin signaling pathway sustains the stem cell population and growth. Notch signaling also contributes by regulating cell fate decisions, ensuring the proper balance between absorptive enterocytes and secretory cells during epithelial regeneration [43].

Extracellular matrix remodeling is vital for wound healing. This process is controlled by the equilibrium between MMPs and tissue inhibitors of metalloproteinases (TIMPs), their endogenous inhibitors. As healing progresses, the activity of TIMPs rises, which reduces MMP activity and facilitates the reconstruction of the extracellular matrix framework, crucial for cell movement and the restoration of tissue integrity [44].

Growth factors play essential roles in mucosal repair. Epidermal growth factor stimulates migration and epithelial cell proliferation. TGF-β can suppress inflammation in early healing stages, but excessive signaling can promote fibrosis. Fibroblast growth factors support angiogenesis and tissue repair by promoting endothelial cell proliferation and migration, enhancing nutrient and oxygen delivery to regenerating mucosa [45].

Self-healing success in mucosal tissue is influenced by several factors. Persistent inflammation impairs healing by promoting tissue damage and epithelial cell apoptosis. Nutritional status is crucial, as adequate nutrition is essential for DNA synthesis and cell proliferation. The gut microbiota composition exerts a notable influence, with a balanced microbiome supporting epithelial healing through short-chain fatty acid production. Adequate tissue oxygenation is indispensable for effective healing; hypoxia hinders healing by limiting ATP production and cellular functions necessary for regeneration [46].

If wound healing mechanisms are insufficient, chronic mucositis can develop. Fibrosis may occur due to excessive extracellular matrix deposition, driven by overactive TGF-β signaling and fibroblast proliferation. This may result in long-term issues, such as narrowing and decreased flexibility of the mucosa [47].

Understanding these pathophysiological processes provides a foundation for identifying potential therapeutic targets. Antioxidant agents could attenuate initial oxidative damage. Anti-inflammatory drugs might mitigate cytokine-mediated injury. Modulating the gut microbiota could restore microbial balance and enhance barrier function. Therapies that deliver growth factors or promote stem cell survival and proliferation are promising avenues for enhancing mucosal repair.

THERAPEUTIC STRATEGIES AND DRUG TARGETS

RIGIM is the principal dose-limiting toxicity for abdominal and pelvic RT. Its pathogenesis can include epithelial DNA damage, increases in ROS levels, cytokine amplification, microbiome disruption, and barrier breakdown. These processes are complex and multifactorial; thus, a single disease-modifying "silver bullet" remains elusive. Consequently, many of the drugs currently deployed (or trialed) in this setting target peripheral or parallel pathways that modulate the manifestations of injury rather than the molecular pathogenesis of RIGIM itself: antidiarrheals and motility agents aim to reduce fluid loss; opioids and neuromodulators inhibit nociceptive signaling; cytoprotective coatings such as sucralfate shield denuded mucosa; probiotics re-seed dysbiotic flora; and late-phase anti-fibrotics attempt to remodel scarring. These symptomatic strategies can alleviate suffering, preserve quality of life, and keep patients on schedule for curative RT, yet they leave the upstream epithelial-immune-microbiome axis largely unchallenged. Recognizing this gap underscores the need for multifaceted regimens that combine true pathophysiology-targeted interventions with supportive symptom control to achieve durable prevention and mitigation of RIGIM.

Pharmacological approaches

Pharmacological interventions for GIM can be broadly divided into radioprotective agents, anti-inflammatory drugs, and growth factors/cytokine modulators.

Amifostine acts as a cytoprotective agent following its conversion into an active free thiol metabolite within normal tissues. This metabolite shields cells from harm by neutralizing free radicals produced by ionizing radiation and chemotherapy, safeguarding DNA, and speeding up DNA repair processes. The selective protection of healthy tissues is a significant benefit, as it lessens the frequency and intensity of gastrointestinal toxicity without notably diminishing the antitumor effects of RT. Amifostine is metabolized into the active form, known as WR-1065, which is preferentially absorbed by healthy tissues. WR-1065 defends cells by neutralizing free radicals, providing hydrogen atoms for DNA repair, and possibly triggering apoptosis in cancer cells. These actions enable amifostine to reduce damage to normal tissues during chemotherapy and radiation treatments [48]. Amifostine is primarily indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer and to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation therapy for HNC [49]. The common side effects are nausea, hypotension, and vomiting. It is contraindicated in individuals who are hypersensitive to aminothiol-based compounds [50].

Metformin, which is prescribed for managing type 2 diabetes, also possesses properties that protect

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against radiation and reduce inflammation. It activates AMPK, which reduces oxidative stress and inhibits the mTOR pathway, leading to enhanced DNA repair and decreased cell death in the gut lining. Preclinical studies in mice suggest metformin may have a role in preventing GIM, but clinical trials are needed [51].

Sucralfate, a medication commonly prescribed for peptic ulcers, creates a protective layer over the ulcers, preventing further harm from stomach acid and digestive enzymes [52]. It also stimulates prostaglandin E2 production, which promotes mucosal defense and healing. Sucralfate is recommended for patients with active duodenal ulcers and to prevent the recurrence of healed duodenal ulcers [53]. While it may reduce symptoms like pain and diarrhea in radiation-induced mucositis [54], its efficacy in preventing GIM is less established. The most common side effect is constipation. Sucralfate has minimal systemic absorption and is generally considered safe during pregnancy. However, in patients with kidney impairments, caution is advised as there is a risk of aluminum accumulation and toxicity [55].

Histamine H2-receptor antagonists, including cimetidine [56], ranitidine, and famotidine [57], reduce gastric acid secretion by competitively blocking H2 receptors on gastric parietal cells. This inhibition prevents adenylate-cyclase activation, lowers intracellular cyclic-AMP, and consequently reduces protein-kinase A activity. The downstream effect is suppression of the H^+/K^+-ATPase proton pump, which can alleviate upper-gastrointestinal symptoms and promote mucosal healing in radiation-induced gastritis and esophagitis [56, 57]. Beyond their antisecretory action, clinical data also point to a direct radioprotective benefit: in a phase I/II randomized, placebo-controlled trial of 36 men receiving external-beam RT for prostate cancer, famotidine 40 mg orally twice daily (given 3–4 h before each fraction) significantly reduced both the incidence and duration of grade ≥2 acute rectal toxicity and completely prevented treatment-related rectal bleeding compared with placebo [57].

Glucagon-like peptide-2 (GLP-2), a hormone that promotes gut growth and function, stimulates cell proliferation, inhibits cell death, and enhances nutrient absorption in the intestines. It also improves blood flow and strengthens the gut barrier [58]. GLP-2 analogs, such as teduglutide, have shown promise in preclinical studies for reducing mucosal damage and improving recovery after radiation exposure [59]. Teduglutide functions by binding to GLP-2 receptors and triggering internal pathways, which include those associated with keratinocyte growth factor, insulin-like growth factors, ErbB ligands, IGF-1 receptor, vasoactive intestinal polypeptide, and nitric oxide. These pathways play a role in teduglutide's impact on the proliferation of cells, cell survival, and intestinal healing [60]. Teduglutide is approved for managing short bowel syndrome. Although research on its use for RIGIM is sparse, preclinical findings indicate it might shield the intestinal lining from radiation harm and aid in recovery. This potential is attributed to teduglutide's ability to enhance the growth of the intestinal lining, boost blood circulation, and decrease inflammation. Nonetheless, further investigation, especially human clinical trials, is necessary to verify its effectiveness and safety in this context. Typical side effects of GLP-2 analogs include abdominal discomfort, nausea, vomiting, and reactions at the injection site [61].

Other drugs used to manage RIGIM

Beyond these categories, other drugs are commonly used to manage the symptoms of radiation -induced RIGIM. Loperamide, an opioid, slows gut motility, reducing the frequency of bowel movements and helping to control diarrhea. It is often used to manage diarrhea as a result of RT to the abdomen/ pelvis. Constipation, dizziness, and nausea are common side effects. Loperamide should not be used by individuals with stomach or intestinal issues like ulcerative colitis [62].

Fluoroquinolone antibiotics inhibit bacterial DNA synthesis, preventing bacterial growth. These antibiotics are known for their broad-spectrum capabilities, making them effective against a diverse array of bacteria, and they are utilized to address a variety of infections, including those that may arise in the gut due to damage from radiation therapy. Side effects include gastrointestinal upsets, nausea, and diarrhea. More serious, though rare, side effects include tendonitis, tendon rupture, and peripheral neuropathy [63].

Octreotide is a synthetic analog of somatostatin that inhibits hormone and neurotransmitter release. It is used to treat conditions like acromegaly and carcinoid tumors. In RIGIM, it is primarily used to manage severe diarrhea in patients who do not respond to other treatments like loperamide. Side effects can include gastrointestinal problems, bradycardia, and changes in blood sugar levels. Octreotide should be used cautiously in patients with gallbladder disease, diabetes, and kidney or liver disease [64].

Vitamin D has been shown to exert immunomodulatory effects. Its mechanism of action in this context involves increasing anti-inflammatory cytokine production, such as IL-10, and inhibiting pro -inflammatory mediators, such as NF-κB. This helps to reduce inflammation and protect the gut lining from damage. Vitamin D also enhances epithelial barrier function by upregulating junctional proteins (which hold cells together) and promoting cell differentiation. This strengthens the gut barrier and prevents harmful substances from leaking into the body. Additionally, vitamin D protects intestinal stem

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cells from radiation-induced apoptosis, which is crucial for maintaining the integrity of the gut lining and promoting regeneration. Adequate vitamin D levels may, therefore, reduce susceptibility to mucosal injury. Supplementation with vitamin D could potentially mitigate the severity of GIM, although clinical trials are needed to establish its therapeutic efficacy; however, at present, studies are limited to mice, and its efficacy in humans has not been tested [65].

Zinc-L-carnosine is a chelated compound combining zinc and the dipeptide L-carnosine. It has demonstrated mucosal protective effects. The mechanism of action involves reinforcing the mucosal barrier, enhancing mucus secretion, and encouraging the growth of epithelial cells. It also possesses antioxidant properties, reducing oxidative DNA damage and scavenging reactive oxygen species generated by radiation. Zinc-L-carnosine also exhibits anti-inflammatory effects and promotes wound healing in the gastrointestinal tract [66]. Clinical studies have shown the benefits of zinc-L-carnosine in the repair of the gastric mucosa and protection against injury induced by non-steroidal anti-inflammatory drugs. Its application in GIM is supported by preclinical data showing reduced mucosal damage and enhanced healing after radiation exposure [67].

Palifermin, a recombinant human keratinocyte growth factor (KGF), helps protect against RT-induced damage to the lining of the gastrointestinal tract. Palifermin and amifostine are the only approved radioprotective agents for patients undergoing radiation therapy [68]. It binds to KGF receptors on cells in the gut lining, stimulating them to grow and repair. This helps maintain gut barrier integrity and reduce mucositis severity, which is characterized by inflammation and ulcers in the digestive tract. Palifermin also enhances the natural defenses of these cells, making them more resistant to damage. Although primarily used to prevent oral mucositis, its mechanism of action suggests it could also be beneficial in protecting the entire gastrointestinal tract from radiation-induced damage [69].

Probiotics represent a promising strategy for alleviating GIM [70]. *Lactobacillus* and *Bacillus* species reinforce the intestinal barrier by enhancing tight junction integrity and stimulating mucin production (which is the main component of mucus). They also modulate the immune system, shifting the balance towards anti-inflammatory pathways, and compete with pathogenic bacteria for resources and adhesion sites, preventing dysbiosis. Randomized controlled trials provide clinical evidence that taking probiotics can lessen both the frequency and intensity of diarrhea and enteritis caused by radiation [71].

Hyperbaric oxygen therapy (HBOT) entails inhaling pure oxygen within a chamber under increased pressure. This process works by markedly increasing the oxygen levels in the blood and tissues, which in turn speeds up healing. HBOT encourages the growth of new blood vessels, the proliferation of fibroblasts, and the formation of epithelial tissue. In clinical settings, HBOT has been shown to be effective in managing chronic injuries resulting from radiation, including conditions like RT-induced proctitis and cystitis. Although its effectiveness in acute [6].

In conclusion, the development of effective therapeutic strategies for RIGIM requires a comprehensive approach that addresses the multiple facets of its pathogenesis. From pharmacological interventions targeting oxidative stress, inflammation, and cellular repair, to mechanisms that bolster mucosal defenses, and innovative strategies for microbiome modulation and physical protection, a range of options are being explored. While many of these approaches show promise in preclinical studies and early clinical trials, further research is crucial to optimize their efficacy, safety, and integration into standard cancer care protocols. Table 2 provides an overview of the current status of therapeutic strategies and drug targets in the research phase, clinical testing, and those that have been approved.

KEY CLINICAL TRIALS

RTOG 9801 examined the effects of incorporating amifostine, a cytoprotective agent, into concurrent chemoradiation for locally advanced NSCLC. The 243 participants were randomized to receive standard therapy ± amifostine. Beginning on study day 43, all patients underwent hyper-fractionated RT: 1.2 Gy delivered twice daily, at least 5 hours apart, five days per week, to a total dose of 69.6 Gy. The initial 42 fractions (50.4 Gy) covered the primary tumor and mediastinum, followed by a boost of 19.2 Gy in 16 fractions to the primary tumor and involved nodes. Amifostine did not significantly decrease the incidence of acute esophagitis, nor did it improve overall or disease-free survival. The investigators concluded that, while amifostine was not harmful, it offered no meaningful benefit in this setting. Limitations included the open-label design and modest sample size [72]. Future research could explore the effects of amifostine in combination with different treatment regimens or in preventing other radiation-induced side effects.

The ROMAN Phase IIB trial assessed GC4419 for reducing SOM in patients receiving concurrent chemoradiation for head-and-neck cancer. A total of 223 patients were randomized 1:1:1 to GC4419 30 mg, GC4419 90 mg, or placebo. IMRT was delivered Monday–Friday in daily 2.0–2.2 Gy fractions to a cumulative dose of 60–72 Gy. Each study infusion (250 mL normal saline over 60 min) finished ≤ 60 min before each radiation fraction. The 90 mg arm significantly reduced SOM duration (median 1.5 days vs 19 days, P = 0.024), incidence (43 % vs 65 %, P =

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0.009), and grade 4 frequency (16 % vs 30 %, P = 0.045) compared with placebo. No GC4419-specific toxicity or increase in known IMRT + cisplatin toxicities was observed. Limitations include potential incomplete follow-up and the subjective nature of the WHO OM scoring [73].

In a continuation, the ROMAN Phase III clinical trial assessed GC4419 in mitigating SOM in patients with HNC being treated with chemoradiation. This study included 431 patients who received either GC4419 or a placebo and used the same RT regimen as the previous trial. The findings indicated that GC4419 notably decreased the duration and occurrence of SOM and postponed its onset. Furthermore, GC4419 exhibited a safety profile comparable to that of the placebo. These results corroborate the positive outcomes seen in the Phase IIb trial and imply that GC4419 could be a safe and effective option for preventing SOM in patients undergoing chemoradiation therapy for HNC [1]. Unfortunately, the FDA rejected Avasopasem for RT-induced SOM, stating the trials were not substantial enough to show its efficacy and safety in reducing SOM.

Table 3 summarizes the clinical trials assessing treatments to manage RIGIM.

Table 2. Summary of the therapeutic strategies and drug targets for RIGIM.

Category	Agent / intervention	Key mechanism(s) of action	Evidence / clinical status*	Principal adverse effects or caveats
Radioprotective free-thiol	Amifostine	Scavenges ROS/RNS; donates hydrogen for DNA repair; selective uptake by normal tissues	FDA-approved for cisplatin nephro-protection & RT-xerostomia; Phase II–III data in RIGIM show mixed benefit	Nausea, vomiting, hypotension; IV administration logistics
Metabolic modulator	Metformin	Activates AMPK → decrease mTOR, decrease oxidative stress, enhanced DNA repair	Promising murine & in-vitro data; no human trials yet	GI discomfort; hypoglycaemia risk in frail patients
Mucosal protectant	Sucralfate	Forms adherent coating; increase prostaglandin E_2 production	Used symptomatically for radiation gastritis/proctitis; limited prophylactic data	Constipation, aluminium accumulation in renal impairment
Acid-suppressive therapy	Histamine-2 receptor antagonists (e.g. ranitidine, famotidine)	Block parietal-cell H_2-R → decrease gastric acid	Supportive care for upper-GI mucositis	Generally well-tolerated; tachyphylaxis with prolonged use
Growth-factor analogue	Teduglutide (GLP-2 analogue)	Stimulates epithelial proliferation, inhibits apoptosis, and improves mucosal blood flow	Licensed for short-bowel syndrome; pre-clinical radioprotection data; clinical trials awaited	Abdominal pain, nausea, injection-site reactions, high-cost
Antidiarrheal	Loperamide	μ-opioid agonist, decreases intestinal motility	First-line for RT-induced diarrhoea	Constipation, abdominal cramps; avoid in colitis
Antibiotics	Fluoroquinolones	Inhibit bacterial DNA gyrase/ topoisomerase → broad-spectrum antibacterial cover	Used when mucosal breakdown → infection risk	Tendinopathy, QT prolongation, C. difficile colitis
Antisecretory peptide	Octreotide	Somatostatin analogue, decreases GI hormone & fluid secretion	Rescue therapy for refractory severe diarrhoea	Gallstones, glucose dysregulation, and bradycardia
Nutrient / immunomodulator	Vitamin D	Up-regulates tight-junction proteins; anti-inflammatory (increase IL-10, decrease NF-κB)	Efficacy demonstrated only in animal models	Hypercalcaemia with excessive dosing; human data lacking
Antioxidant chelate	Zinc-L-carnosine	Reinforces the mucus layer, scavenges ROS, and promotes epithelial repair	Clinical use in peptic injury; pre-clinical benefit in RT models	Metallic taste, mild GI upset; limited RIGIM trials
Recombinant growth factor	Palifermin (KGF)	Binds FGFR2b → stimulates epithelial proliferation and cytoprotection	FDA-approved for oral mucositis in HSCT; the mechanism supports GI protection	Oedema, rash, taste alteration, high cost
Microbiome modulation	Probiotics (e.g. *Lactobacillus*, *Bacillus*)	Restore microbial balance; increase mucin and tight-junction integrity; anti-inflammatory immune shift	Multiple RCTs report reduced radiation diarrhoea	Strain-specific efficacy; caution in immunocompromised
Physical therapy	HBOT	Increase tissue pO_2 → angiogenesis, fibroblast & epithelial proliferation	Established for chronic radiation proctitis & cystitis; limited acute RIGIM data	Barotrauma, transient myopia; limited chamber A1:E14+A4:E14 availability

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Table 3. Key clinical trials evaluating treatments for RIGIM: Study designs, outcomes, and safety profiles.

Trial name	Phase	Treatment (dose)	Cohort (sample Size)	Control	Key outcomes	Side effects
RTOG 9801	II	Amifostine (200 mg/m²)	HNC (315)	Placebo	- 63% vs. 57% grade ≥2 mucositis (not significant) - Reduced xerostomia	- Nausea (35% vs. 6%) - Hypotension (15% vs. 2%)
ROMAN (GT-210)	IIB	Avasopasem (30/90 mg)	LA-HNC (223)	Placebo	- 90 mg reduced SOM duration (from 18 to 8 days, P=0.024) - 27% reduction in grade 4 SOM	- Hypotension (mild) - Nausea (comparable to placebo)
ROMAN	III	Avasopasem (90 mg)	LA-HNC (455)	Placebo (3:2)	- 56% reduction in SOM duration (from 18 to 8 days, P=0.002) - Primary endpoint not met	- Consistent with prior ROMAN study - No new safety signals
RTOG 1012	II	Manuka Honey (20 ml TID)	Thoracic cancers (163)	Standard care	- No reduction in esophagitis incidence - Reduction in grade 3+ esophagitis (30% vs. 34%, not significant)	- Dermatitis (15% vs. 11%) - Pain (comparable)

CONCLUSIONS

RIGIM remains a significant and often debilitating complication of cancer RT, impacting not only a patient's QoL but also potentially compromising the efficacy of their treatment. This review has highlighted the complex interplay of factors contributing to RIGIM, from the initial cellular damage caused by ionizing radiation and oxidative stress, through the ensuing inflammatory cascade and immune dysregulation, to the ultimate breakdown of the mucosal barrier and the potential for microbial invasion. The inherent regenerative capacity of the GI mucosa, while remarkable, is often overwhelmed by the severity of the radiation insult, particularly in the context of concurrent chemotherapy or pre-existing conditions.

The management of RIGIM, therefore, necessitates an integrative and multi-pronged approach. This includes combining pharmacological agents that target key pathways in mucosal damage and repair, nutritional interventions that support mucosal integrity and healing, strategies to modulate the gut microbiome and restore a healthy balance, and innovative physical and technological interventions designed to minimize radiation exposure to healthy tissues. Pharmacological strategies aim to reduce oxidative stress, modulate the inflammatory response, and enhance epithelial regeneration.

Given the multifaceted nature of RIGIM, exploring the synergistic effects of combined therapies is likely to be more effective than single-agent approaches. For example, combining a radioprotective agent with an anti-inflammatory drug and a probiotic could potentially offer superior mucosal protection. Integrating genomic, proteomic, and microbiomics data will be crucial for developing tailored treatments based on an individual patient's risk profile. Identifying biomarkers that predict susceptibility to RIGIM will allow for proactive and personalized interventions. Further research is also needed to understand and manage the long-term consequences of radiation-induced damage to the GI tract, including chronic radiation enteropathy and its associated complications. Finally, ongoing work to discover and elucidate any further unknown factors in the development of RIGIM is of utmost importance.

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