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Oxidative Stress, Microbiome Dysbiosis, and Oral Mucositis After Radiotherapy: Cause, Consequence, or Vicious Cycle?

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ABSTRACT

Radiation-induced oral mucositis is a common complication of radiotherapy in patients with head and neck cancer, resulting from complex interactions between cellular damage, oxidative stress, inflammation, and oral microbiome alterations. This narrative review examines the interplay between radiation-induced oxidative stress and oral microbiome dysbiosis in EBRT-induced oral mucositis. Radiation generates reactive oxygen species (ROS) that cause cellular and DNA damage and activate inflammatory pathways, while radiation-induced changes in saliva, pH, and mucosal immunity promote microbiome dysbiosis. Conversely, dysbiosis may further increase oxidative stress and inflammation, suggesting a bidirectional interaction that forms a vicious cycle and contributes to progressive mucosal injury and ulceration. Emerging strategies, including oxidative stress modulation, probiotics, predictive biomarkers, and local drug delivery systems, show potential but remain supported by limited and variable clinical evidence. Understanding this interaction may support the development of personalized multi target strategies for the prevention and treatment of radiation-induced oral mucositis.

Keywords: oral mucositis; oxidative stress; oral microbiome dysbiosis; radiotherapy; host-microbe interaction

INTRODUCTION

Oral mucositis is one of the most common acute adverse effects in patients with head and neck cancer undergoing radiotherapy, with a reported prevalence of more than 65% among patients receiving active treatment. This condition can cause pain, impaired nutritional intake, and reduced quality of life. In severe cases, mucositis may compromise treatment adherence and necessitate treatment modification or temporary interruption [1].

Historically, radiation-induced oral mucositis was primarily understood as a consequence of direct damage to mucosal tissues caused by ionising radiation [2]. However, current understanding indicates that its pathogenesis involves a complex interplay of cellular damage, reactive oxygen species (ROS) generation, inflammatory signalling, and alterations in the oral microbial environment [1,2]. Oxidative stress contributes to the initiation and amplification of these biological responses, while radiotherapy-induced changes in the oral environment may also influence the composition and function of the oral microbiome [1–3].

Furthermore, oral microbiome alterations have been associated with clinical conditions and disease outcomes in patients with head and neck cancer [3,4].

Although the relationship between oxidative stress, oral microbiome alterations, and oral mucositis has increasingly been investigated, the directionality and causal interactions among these factors remain incompletely understood. Specifically, it remains unclear whether radiation-induced oxidative stress acts as an initial trigger of microbiome dysbiosis, whether dysbiosis primarily develops as a consequence of tissue damage and changes in the oral environment, or whether these processes interact bidirectionally to form a vicious cycle that amplifies inflammation and mucosal injury [1–3]. Therefore, this narrative review aims to synthesise current evidence on the interplay between oxidative stress and the oral microbiome in the pathogenesis of EBRT-induced oral mucositis, examine the potential directionality of these interactions, and identify clinical implications and potential therapeutic targets arising from this understanding [1,2,5].

RADIATION INDUCED OXIDATIVE STRESS AS THE INITIAL INSULT

Radiation exposure broadly induces ROS accumulation and activates oxidative stress pathways across different modalities, including non-ionising radiation [6]. In ionising radiation specifically, this occurs primarily through water radiolysis, considering that approximately 70% of cellular composition consists of water. This process generates ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, which can damage lipids, proteins, and DNA. In addition, radiation can impair mitochondrial function, thereby increasing ROS production and prolonging oxidative stress after radiation exposure has ceased. The accumulation of ROS subsequently causes DNA damage, including single- and double-strand breaks, alterations in proteins and lipid membranes, as well as disruption of mitochondrial DNA and metabolic function [7,8]. Radiation-induced damage to mitochondrial membranes can reduce mitochondrial membrane potential, further increasing ROS production and creating a sustained cycle of oxidative damage [9].

Post-radiation oxidative stress also activates cellular signalling pathways, particularly the transcription factors NF-κB and AP-1, which increase the expression of proinflammatory cytokines such as TNF-α, IL-6, and TGF-β [7]. The recruitment of inflammatory cells to the site of injury further exacerbates mucosal damage by increasing ROS production and causing additional epithelial injury [8]. Therefore, ROS not only cause direct structural damage but also contribute to the maintenance of the inflammatory cascade that aggravates tissue injury.

Although the relationship between oxidative stress, microbiome alterations, and oral mucositis has increasingly been investigated, the causal interactions among these factors remain incompletely understood. Specifically, it remains unclear whether radiation-induced oxidative stress serves as an initial trigger of microbiome dysbiosis, whether dysbiosis is a consequence of tissue damage and changes in the oral environment, or whether both processes form a vicious cycle that mutually amplifies inflammation and mucosal injury [1,2,4]. Therefore, this narrative review aims to synthesise current evidence on the interplay between oxidative stress and the oral microbiome in the pathogenesis of EBRT-induced oral mucositis, examine the potential direction of causality between these factors, and identify clinical implications and potential therapeutic targets arising from this understanding [1,2,3].

The available evidence supports the role of oxidative stress as an initial trigger or initiator and as a factor that sustains the pathobiological processes of oral mucositis, rather than merely being a consequence of radiation-induced tissue damage. Conceptually, the initial sequence begins with radiation exposure, followed by ROS generation, DNA, lipid, and mitochondrial damage, activation of NF κB and proinflammatory cytokines, and progressive epithelial injury. This framework places oxidative stress as a cause that precedes alterations in the oral microbiome, which may subsequently contribute to further mucosal damage and will be discussed in the following section [2,10]. Clinical evidence corroborates this mechanistic framework: in a cohort of head and neck cancer patients undergoing radiotherapy, salivary levels of malondialdehyde and lactate dehydrogenase increased alongside oral mucositis severity, while antioxidant markers glutathione and superoxide dismutase declined, supporting a direct correlation between salivary oxidative stress and RIOM severity [11].

ORAL MICROBIOME SHIFTS FOLLOWING RADIOTHERAPY

Beyond disease-associated dysbiosis, the oral microbiome is inherently dynamic and responsive to shifts in the local host environment [12]. Head and neck radiotherapy consistently alters the composition of the oral microbiota compared with both pretreatment conditions and healthy individuals [4,3]. In patients with head and neck cancer, these changes are characterised by a reduction in generally commensal Firmicutes and Streptococcus, along with an increase in Bacteroidetes even before treatment. During radiotherapy, dysbiosis becomes more pronounced, including increases in Fusobacterium and Porphyromonas, which have been associated with poorer clinical outcomes [3]. In patients with nasopharyngeal carcinoma, increased Actinobacteria and Veillonella have also been observed in patients with delayed mucositis healing, indicating an association between microbiome alterations and the severity of oral complications [13].

Microbiome changes also appear to follow the clinical course of mucositis. A longitudinal study of patients with head and neck squamous cell carcinoma showed that changes in the abundance of specific microorganisms were associated with patterns of mucositis severity over time [14]. In patients with nasopharyngeal carcinoma, several periodontopathogenic bacterial genera exhibited dynamic changes in abundance during radiotherapy, with certain increases coinciding with the development of severe mucositis [4,14]. Microbiome alterations also occur alongside declining salivary gland function, particularly as xerostomia develops during the later stages of radiotherapy [4].

These findings support the possibility that oral microbiome dysbiosis not only contributes to the initiation of mucositis but may also result from radiation-induced tissue damage and changes in the oral environment [15]. Tissue injury, alterations in saliva, pH, and local immunity may create conditions that promote microbial shifts and the colonisation of opportunistic microorganisms such as Candida [15,16]. Candida colonisation has also been reported as a consistent predisposing factor for severe mucositis with early onset, with 77% of patients with grade 2 to 4 mucositis exhibiting pseudomembranous candidiasis [16]. Thus, current evidence suggests that dysbiosis may at least partly emerge as a consequence.

of tissue damage that occurs earlier, although its potential contribution to the worsening of mucositis should also be considered.

THE CRITICAL QUESTION OF DIRECTIONALITY IN THE OXIDATIVE STRESS AND DYBIOSIS RELATIONSHIP

Most of the literature on post-radiotherapy oral mucositis discusses oxidative stress and oral microbiome dysbiosis as parallel pathogenic pathways without explicitly addressing the direction of the causal relationship between them [1,2]. However, understanding whether one factor precedes the other or whether they mutually influence each other is important for determining appropriate therapeutic targets and intervention timing. Radiation generates ROS through water radiolysis and mitochondrial dysfunction, which subsequently cause tissue damage and alterations in the oral environment, including reduced salivary flow, changes in pH, and impaired mucosal immunity such as salivary IgA secretion [7,10,16]. These conditions may create selective pressure on oral microorganisms and potentially promote dysbiosis. Evidence from periodontal disease also indicates that oxidative stress can reshape the microbial ecosystem by selecting microorganisms that are more tolerant of oxidative conditions, although direct evidence in the context of oral radiotherapy remains limited [17].

Conversely, dysbiosis may also exacerbate oxidative stress and preexisting tissue damage. Bacterial products such as lipopolysaccharide can activate Toll-like receptors on epithelial and immune cells, thereby increasing ROS production by neutrophils and macrophages. Some opportunistic pathogenic microorganisms may also manipulate host immune responses, disrupt antioxidant defences, and create a prooxidative environment that supports their persistence [17]. Furthermore, exposure of oral fibroblasts to lipopolysaccharide has been shown to increase ROS accumulation and induce double-strand DNA damage, suggesting that bacterial products may represent an additional source of oxidative stress beyond the direct effects of radiation [18]. These findings indicate that the relationship between oxidative stress and dysbiosis is unlikely to be unidirectional.

Therefore, the model that best fits the current evidence is likely a bidirectional relationship that forms a vicious cycle in which both processes mutually reinforce each other. In the context of post-radiotherapy oral mucositis, radiation may trigger initial oxidative stress that alters the oral environment and promotes dysbiosis. The subsequent expansion of opportunistic microorganisms may generate bacterial products and virulence factors that increase ROS production and inflammation, thereby exacerbating tissue damage and further promoting dysbiosis. This cycle may persist and progressively amplify mucosal injury, ultimately contributing to ulceration in severe oral mucositis [17,19].

DOWNSTREAM CONSEQUENCES FROM MOLECULAR CROSSTALK TO MUCOSAL ULCERATION

The feedback cycle between oxidative stress and microbiome dysbiosis ultimately leads to progressive structural damage of the oral mucosal epithelium. Radiation-induced DNA damage, particularly double-strand breaks, increases ROS generation, which subsequently activates NF-κB and the release of proinflammatory cytokines such as TNF-α. These cytokines further amplify tissue damage through feedback mechanisms, while disruption of tight junctions increases epithelial permeability, allowing bacterial products or pathogen-associated molecular patterns to further enhance inflammation [20]. When epithelial regeneration is inadequate, mucosal atrophy and ulceration develop, accompanied by loss of barrier integrity that allows bacterial translocation into deeper tissues. This condition makes the ulcerative phase the most painful stage because nerve endings in the lamina propria become exposed and increases the risk of secondary bacterial and fungal infections, which can further exacerbate inflammation and tissue damage [8].

Sonis's five-phase model, introduced in 2004, remains a key framework for understanding the progression of oral mucositis and consists of initiation, primary damage response, signal amplification, ulceration, and healing. Radiation induces epithelial cell damage and ROS generation, which subsequently activate inflammatory responses and amplify tissue injury until mucosal ulceration occurs, followed by healing through epithelial proliferation [21]. However, the original model did not position the microbiome as a major component. The updated framework from MASCC and ISOO subsequently highlights the potential role of the oral and gastrointestinal microbiota in mucositis development, although the causal contribution of microbiota and their metabolites to each phase remains incompletely understood [22].

Integrating evidence on oxidative stress and dysbiosis into the updated Sonis model suggests that these processes do not act independently or within a single phase but interact throughout the pathobiological course of mucositis. Oxidative stress primarily contributes to the initiation of radiation-induced injury, whereas subsequent changes in the oral environment and microbiome dysbiosis may further amplify inflammation, epithelial damage, and microbial translocation during the ulcerative phase [20,21]. This integrative framework provides a basis for developing mechanism-guided therapeutic strategies that target not only individual pathways but also the points of interaction between oxidative stress and microbiome dysbiosis.

CLINICAL IMPLICATIONS OF THE CAUSALITY DEBATE

The direction of causality between oxidative stress and oral microbiome dysbiosis carries direct implications for the target and timing of therapeutic intervention. If oxidative stress acts as the initial trigger, antioxidant or cytoprotective agents would

ideally be administered from the very start of radiotherapy, consistent with the rationale underlying the use of avasopasem manganese [9,23]. Conversely, if dysbiosis develops mainly as a result of radiation-induced changes in saliva, pH, and local immunity, microbiome modulation such as probiotics may be more appropriately administered in the mid to late course of radiotherapy [1,15]. However, if oxidative stress and dysbiosis form a bidirectional relationship constituting a vicious cycle, a single intervention at one stage alone is unlikely to be sufficient, making a combined approach that targets both pathways throughout the course of radiotherapy necessary [16,24].

Current management of oral mucositis remains largely reactive, focusing on oral hygiene, pain control, and nutritional support after symptoms have already emerged, while therapies that directly target the underlying molecular mechanisms remain limited [1]. Although antioxidants, probiotics, and targeted therapies have shown potential, their implementation in routine clinical practice is still limited [9]. Avasopasem manganese further illustrates that mechanistic success and promising clinical outcomes do not always translate into regulatory approval [23]. Therefore, a clearer understanding of the causal relationship between oxidative stress and dysbiosis is needed to develop preventive, mechanism-guided, and personalized therapeutic strategies in line with the MASCC and ISOO framework [21].

EMERGING THERAPEUTIC TARGETS BASED ON THE PROPOSED MODEL

If oxidative stress acts as an initial trigger, targeting superoxide represents a rational therapeutic approach. Avasopasem manganese or GC4419 is a selective superoxide dismutase mimetic that converts radiation-generated superoxide into hydrogen peroxide, potentially protecting normal tissues without reducing the effectiveness of radiation against cancer cells [23]. A phase IIb clinical trial showed that avasopasem reduced the duration, incidence, and severity of severe oral mucositis in patients with head and neck cancer receiving radiotherapy with cisplatin, without negatively affecting tumour control at one- and two years follow up [25]. Similar findings were reported in the phase III ROMAN trial, which demonstrated a significant reduction in the incidence of severe oral mucositis among patients receiving IMRT. However, in 2023, the FDA stated that the available evidence was insufficient to establish the efficacy and safety of avasopasem, indicating that additional clinical trials were needed before regulatory approval could be granted.

If microbiome dysbiosis also contributes to mucositis development, microbiota modulation through probiotics represents a relevant therapeutic approach. Systematic reviews and meta-analyses indicate that probiotics may reduce the incidence of severe oral mucositis in patients with head and neck cancer, although their effects on oral mucositis of all grades remain limited and variable across studies [26,24]. A phase II clinical trial in patients with nasopharyngeal carcinoma undergoing concurrent chemoradiotherapy also demonstrated that probiotics could reduce mucositis severity and better preserve CD3+, CD4+, and CD8+ T cell counts [27]. In addition to probiotics, immunonutrition involving fatty acids and polyphenols may support commensal bacterial diversity and reduce ulcerative mucositis [1]. Given the potential bidirectional relationship between oxidative stress and dysbiosis, a combination approach targeting both pathways simultaneously may be more effective than targeting either pathway alone. Such a strategy could combine antioxidant or cytoprotective agents during the early phase with microbiome modulation during subsequent phases, consistent with the MASCC and ISOO framework recognising the role of the microbiome throughout the course of mucositis [22].

The effectiveness of these strategies may also be enhanced through local drug delivery systems, as salivary flow, mechanical stress, and uneven drug distribution can reduce drug retention on the mucosa [28]. Nanotechnology-based systems, including nanoparticles with mucoadhesive coatings, may improve bioavailability, regulate drug release, and prolong drug retention in mucositis-affected tissues [29]. Clinical evidence involving a mucoadhesive gel with antioxidant activity has also demonstrated potential for promoting wound healing through antioxidant activity and enhanced collagen synthesis [30]. Such local delivery approaches may be particularly relevant for patients with OSCC undergoing EBRT, as changes in salivary flow, epithelial turnover, and the presence of prosthetic surfaces may affect drug contact time and overall therapeutic efficacy.

FUTURE PERSPECTIVES

The failure of avasopasem manganese to obtain regulatory approval despite its mechanistic ability to reduce superoxide and promising results in early-phase trials highlights the persistent gap between molecular understanding and successful clinical translation in oral mucositis [25]. Predictive blood-based biomarkers, such as circulating miR-18b-3p, have emerged as potential tools for predicting chemoradiotherapy-induced oral mucositis in patients with head and neck cancer and may enable risk stratification before clinical symptoms become evident [31]. Future approaches could further integrate salivary microbiome features into broader predictive models to identify patients at high risk of severe mucosal injury and support individualised prevention and treatment strategies [16].

Given the potential feedback cycle between oxidative stress and microbiome dysbiosis, future management should move beyond single-target interventions toward integrated multi-target strategies. Topical calcitriol gel has shown potential to accelerate traumatic oral ulcer healing, suggesting that local regenerative approaches may support mucosal repair, although its applicability to radiation-induced oral mucositis requires further investigation [32].

These approaches may complement current strategies involving antioxidants, probiotics, mucosal protective and healing agents, targeted therapies, immunomodulatory approaches, photobiomodulation, and other emerging technologies [22,33].

Consistent with the updated MASCC and ISOO framework, simultaneously targeting oxidative stress, microbiome dysbiosis, and inflammatory pathways may provide greater therapeutic benefit than isolated interventions. Plant-derived natural products and nanomaterials have been explored as potential adjunctive strategies in oral cancer management through modulation of the tumour microenvironment, although their specific roles in preventing or alleviating radiation-induced oral mucositis remain to be established [34]. Systematic evaluation remains necessary, particularly through controlled clinical trials designed to assess combinations of interventions across these interconnected pathways and advance personalised, microbiome-informed prevention and management of oral mucositis [16,22].

Beyond local drug delivery systems, cell-free regenerative therapies may provide another potential avenue for managing radiation-related tissue injury. MSC-derived secretomes containing bioactive mediators such as SDF-1, IL-10, and VEGF may represent a promising cell-free regenerative approach for radiation-induced salivary gland dysfunction and xerostomia. However, further preclinical and clinical studies are needed to determine their therapeutic efficacy, safety, and potential integration with existing strategies for managing radiation-related oral complications [35].

CONCLUSION

Oxidative stress plays an important initial role in the pathogenesis of EBRT induced oral mucositis through ROS generation, cellular damage, and activation of inflammatory responses. However, available evidence indicates that oral microbiome alterations are not only a consequence of tissue damage and changes in the oral environment but may also exacerbate oxidative stress, inflammation, and mucosal injury. Thus, the interaction between these processes may form a vicious cycle that contributes to the progression and severity of mucositis, ultimately leading to the ulcerative phase.

This understanding supports therapeutic approaches that target not only oxidative stress or the microbiome independently but also their interaction through multi-target strategies, predictive biomarkers, and local drug delivery systems. Although approaches such as avasopasem and probiotics have shown potential, clinical evidence remains limited and variable. Future research should validate these causal relationships through controlled clinical studies and develop more personalised and microbiome-based strategies for the prevention and treatment of oral mucositis.

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