Clinical Applications of the Microbiome in Oral Mucositis

Subjects: Oncology | Dentistry, Oral Surgery & Medicine | Infectious Diseases

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Oral mucositis (OM) is a common and impactful toxicity of standard cancer therapy, affecting up to 80% of patients. Its aetiology centres on the initial destruction of epithelial cells and the increase in inflammatory signals. These changes in the oral mucosa create a hostile environment for resident microbes, with oral infections co-occurring with OM, especially at sites of ulceration. However, increasing evidence suggests that oral microbiome changes occur beyond opportunistic infection, with a growing appreciation for the potential role of the microbiome in OM development and severity.

Keywords: microbiota ; stomatitis ; biomarkers

1. Introduction

The oral and gut microbiome are undeniably involved, to some extent, with the development and presentation of OM. However, as it is outlined, dissecting their causal effect has been extremely difficult. Despite this complexity, accumulating data support the idea that the microbiome can be used as a tool to improve OM outcomes in patients with cancer, thus, supporting a clinically meaningful causal role [1]. In addition, it is becoming increasingly clear that the highly individualised nature of both the oral and gut microbiomes (which has been likened to a fingerprint) could be used as a predictive or diagnostic biomarker.

2. Microbial Fingerprints as Biomarkers for Oral Mucositis

The human microbiome, including the oral and gut microbiome, is shaped by various factors such as genetics, lifestyle, and diet, and each person harbours a unique microbial community that reflects the highly unique combination of endogenous and exogenous factors. The temporal dynamics of the oral and gut microbiome differ more significantly between individuals than within individuals, and each individual has a distinct microbial fingerprint [2].

An individual's unique microbial fingerprint is increasingly recognised for its capacity to influence their risk of disease and response to various medications, including cancer treatments. The oral microbiome has been shown to predict the risk of not only of oral diseases (e.g., dental caries, periodontitis and oral cancer) but also distant and systemic conditions such as gastric, pancreatic and colorectal cancers [3][4][5]. A machine-learning model based on the oral microbiome composition was able to predict the risk of developing dental caries in early childhood with an area under the curve (AUC), an indicator of model accuracy, of 0.71 (2 years before caries onset) and 0.89 (immediately before caries diagnosis) [6]. Similarly, another study used an oral microbiome panel to develop a model to identify individuals with oral and oropharyngeal cancer (AUC: 0.98) [7]. Systemically, studies have established oral microbiome-based prediction models to distinguish gastric cancers from non-malignant gastric lesions (AUC: 0.91) [3] and colorectal cancers from healthy controls (AUC: 0.90) [5].

Similarly, oral microbiome-based models are being developed to predict the risk and severity of OM using the baseline/pre-therapy or post-therapy oral microbiome. Despite the theoretical potential of this approach, only a few studies have been conducted to assess the feasibility of using such models in the context of OM. Zhu et al. analysed the oral (mucosal) microbiome of 41 patients with nasopharyngeal carcinoma treated with radiotherapy or chemoradiotherapy. The samples were collected before irradiation and between day 5 and day 35 (at five-day intervals) during irradiation. The results demonstrated that, following treatment initiation, as OM severity increases, the oral microbiome community of patients who developed severe OM (grade ≥ 2) became more distinguished from those who developed less severe OM (grade 0–1) and healthy controls prior to therapy. Interestingly, analysing the microbiome from OM lesions early in their development (Grade I/II) showed that those who progressed to develop more severe OM had lower alpha diversity and a high abundance of Gram-negative rods (*Streptobacillus*, *Actinobacillus* and *Mannheimia*). The authors then used a random forest model to compare the oral microbiome using baseline (non-irradiated) samples, Grade 0 OM samples and

Grade I/II OM samples. While the use of baseline and Grade 0 OM samples yielded low accuracy models (AUC: 0.64 and 0.65 respectively), using samples collected at grade 1–2 OM produced a more accurate predictive model (AUC: 0.89) that can differentiate between those who progressed to severe OM and those who had stable mild OM throughout treatment. This suggests that oral microbiome at the early stages of OM can predict the clinical course of OM and determine whether the patient will develop more severe OM at later stages of the treatment [8].

Another study by Bruno et al. assessed the oral microbiome of mucosal swabs collected from 30 allogeneic SCT recipients before conditioning (preconditioning), at ulcerative OM onset and at ulcerative OM healing time points. The analysis revealed a dynamic change in microbial alpha and beta diversity throughout the course of OM, with the lowest alpha diversity observed at the OM healing time point. Furthermore, the relative abundance of *Porphyromonas* in the preconditioning samples positively correlated with ulcerative OM, while, at ulcerative OM onset, a higher relative abundance of *Lactobacillus* was associated with a shorter duration of ulcerative OM. Additionally, the study established a support vector machine (SVM) model using eight genera from the preconditioning samples which could predict the OM onset with 96.6% accuracy [9].

In addition to OM onset and severity, one study has investigated the impact of the oral microbiome on OM healing months post-treatment completion. Jiang et al. analysed the oral mucosal microbiome of 64 patients with nasopharyngeal carcinoma to assess the association between the oral microbiome and OM healing six months post-treatment. Patients were divided based on the WHO OM scoring system into three groups: normal healing (Grade 0), mild delay in OM healing (Grade I/II) and severe delay in OM healing (Grade III/IV). The results demonstrated that the severe OM healing delay group had a higher abundance of Actinobacteria phylum and Veillonellaceae, Actinomycetaceae families and *Veillonella* genus. The study also found that two genera, *Actinomyces* and *Veillonella*, can be used as predictive markers (AUC of 0.96 and 0.82, respectively) for severe delay in OM healing [10].

Finally, Reyes-Gibby et al. utilised a mixture cure model to generate hazard ratios for OM development based on the oral microbiome community. Buccal mucosa samples of 66 patients with head and neck squamous cell carcinoma were collected at baseline, immediately before any grade OM onset and immediately before severe OM onset. At baseline, a high abundance of *Cardiobacterium* and *Granulicatella* was associated with the risk of early onset of severe OM. Moreover, immediately prior to OM development, a higher abundance of *Streptococcus* was associated with delayed onset of severe OM, while a higher abundance of *Fusobacterium* and *Prevotella* was linked to early severe OM development. Additionally, immediately before severe OM onset, an increased abundance of *Cardiobacterium* and *Megasphaera* correlates to a higher risk of early severe OM onset [11]. These data indicate that oral microbiome-based models have the potential to be used as a biomarker for OM, with the potential to predict people at risk of developing OM. However, it is important to note that most studies have only been able to demonstrate meaningful results using microbial data during OM development, not before cancer therapy has started. Identifying strategies to increase the predictive power of the baseline microbial community is clinically necessary to identify high-risk OM patients. These patients may be offered tailored treatment programs or proactive, supportive care to minimise OM development and impact. It is likely that oral microbiome fingerprints will need to be used in conjunction with other conventional OM risk factors (e.g., genetics, comorbidities, medications) to create an integrated risk model.

Furthermore, given that the oral microbiome is influenced by multiple biological and environmental factors [12][13], several considerations need to be considered when using oral microbiomes as biomarkers. This includes sample collection (time point and method), sampling site and microbiome analysis techniques. The use of standardised protocols for oral microbiome sampling and analysis and the collection of the relevant clinical metadata are essential for establishing oral microbiome as a reproducible and reliable biomarker for OM. In addition to the oral microbiome, it is also relevant to consider the gut microbiome for its clinical use as a biomarker of OM. The gut microbiome has a larger and more stable microbial community than the oral microbiome and, therefore, can influence systemic inflammatory responses (and thus OM) with greater magnitude. Although a strong evidence base exists linking the composition of an individual's gut microbiome with a variety of intestinal and systemic conditions [14][15], there are limited data in the context of OM. Currently, only one study has reported an association between the gut microbiome and the risk of developing severe OM. Al-Qadami et al. analysed the faecal microbiome of 20 patients (only 17 patients of these were included in OM analysis) with head and neck cancer treated with radiotherapy or chemoradiotherapy. They reported no significant difference in alpha and beta diversity between those who developed mild (Grade I/II) and severe OM (Grade III/IV). However, the higher relative abundance of three genera (*Victivallis*, *Eubacterium* and *Ruminococcus*) was associated with the development of Grade III/IV OM [16]. This did not investigate the potential of using gut microbiome-based models to predict OM severity, likely due to the limited sample size. Given the profound heterogeneity in gut microbiome composition, the sample size needed to power these approaches is significant. It, therefore, highlights the need for international collaboration and leadership to deliver meaningful findings that hold relevance on a global scale.

3. Microbial Therapeutics for OM Prevention and Treatment

Given the microbial disturbances observed in the oral cavity during the course of OM, and the difference in composition at pre-treatment/baseline among patients who have severe/ulcerated OM and patients with milder symptoms, microbial-based therapies hold promise in minimising the burden of OM.

One of the most used yet non-specific microbial therapies for OM is chlorhexidine (CHX), a biocidal agent with membrane destruction action on bacteria and fungi [17]. CHX is prescribed in patients at risk of OM to decrease the load and potentially contain the inflammation and degree of bacterial OM [18]. To date, there are no studies that prove the effectiveness of using CHX alone in the clinical course of OM. Its use is also undermined by CHX-related side effects [19]. Huang et al. retrospectively analysed 13,969 patients with head and neck cancer, of whom 482 patients were treated with 5-FU. It was noted that performing the periodontal procedure associated with the use of CHX increased the incidence of OM in patients treated with 5-FU [20]. Importantly, the MASCC/ISOO Clinical Practice Guidelines for OM prevention and management generally advise against the use of antimicrobials, including CHX, to prevent OM citing insufficient evidence of clinical benefits and possible collateral effects in HNC patients, such as intense taste alterations [21][22]. This highlights the fact that these strategies generally induce profound ecologic stress on the microbial environment, depleting commensal (beneficial) microbes as well as pathogens. Commensal microbes are critical in restricting pathogen growth whilst also promoting epithelial health [17][23]. This was shown by Bescos et al. [24], who evaluated the effect of using 0.2% CHX for 1 min twice a day, for seven days, in 36 healthy patients and noted a decrease in salivary buffering capacity, lower nitrate-reducing capacity, lower alpha diversity and increases in *Neisseria*, *Streptococcus* and *Granulicatella*. Correlations between the higher abundance of specific genera with metabolites were reported: *Fusobacterium* and higher glucose concentration; *Actinobacteri*a and lower lactate concentration; and *Proteobacteria* and lower nitrite concentration.

In addition to their limited efficacy, antimicrobial strategies for OM are also unattractive as they contradict global antibiotic stewardship efforts, which aim to reduce the reliance on and use of antimicrobials and associated resistance. As such, efforts to support a “healthy” microbiome have shifted away from directly targeting pathogens to instead promoting commensal populations. Probiotics consist of live bacteria, possibly genetically mutated to produce metabolites, that provide benefits to the host [25]. The use of probiotics for personalised treatment aiming to reduce bacterial-dependent diseases, such as periodontal disease, is constantly improving [26][27], and the combination with other therapeutics, such as ozone and photobiomodulation, may be beneficial for decreasing the bacterial load [28].

Probiotics in people with cancer have generally been approached rather cautiously due to the perceived risk of infection in immunocompromised hosts. Despite this, a growing number of reports exist on their use for OM prevention and/or treatment. For example, in patients with nasopharyngeal carcinoma, Xia et al. [29] evaluated, through a phase II RCT, the use of a probiotic cocktail containing *Lactobacillus plantarum*, *Bifidobacterium animalis*, *Lactobacillus rhamnosus,* and *Lactobacillus acidophilus* with 7-week use, one capsule twice a day. The use of probiotics reduced OM severity and altered intestinal bacterial composition. Similarly, Jiang et al. [30] performed a randomised, double-blind, placebo-controlled trial in 93 patients with nasopharynx submitted to chemoradiotherapy. The intervention group that used the probiotics combination of *Bifidobacterium longum, Lactobacillus lactis*, and *Enterococcus faecium* had lower grades of OM. Similar results were found with the same study design in another cohort, Mirza et al. [31] reported a beneficial effect of the use of a *Bacillus clausii* suspension, prescribed twice a day for 30 days or until the end of RT, in 52 patients with HNC. Patients receiving the suspension had a later onset of OM and an average duration of ulceration shorter than the control group. Positive results were not observed in the other cohorts. De Sanctis et al. evaluated the use of *Lactobacillus brevis* CD2 in 75 patients undergoing HNC treatment. No difference in OM grade III/IV between the groups was reported or in other measurements of quality of life, such as body weight, general pain, and dysphagia [32]. As a result of this sustained research activity investigating the efficacy of probiotics for OM prevention and/or treatment, a recent systemic review and meta-analysis were able to confirm sufficient evidence to support their use during cancer therapy [33].

While these studies again reinforce the clinical utility of the microbiome in OM, it should be noted these studies were designed to influence OM via modulation of the gut microbiome. This highlights the difficulties in directly targeting the oral microbiome, a task that is complicated by the dynamic and hostile environment of the oral cavity that makes colonisation challenging but not impossible. For instance, strains of *Streptococcus dentisani*, an oral microbe that produces bacteriocins against oral pathogens and buffers acidic pH through an arginolytic pathway [34], were able to improve clinical and microbial parameters associated with oral health in healthy volunteers [35]. *Streptococcus salivarius* K12 is also a candidate oral probiotic. It is associated with oral health as it stimulates an anti-inflammatory response, modulates genes associated with adhesion to the epithelial layer and homeostasis and produces bacteriocin-like inhibitory substances [36]. Moreover, it is associated with lower OM in mice [37]. Therefore, investigating oral-directed probiotics, either alone or in conjunction with gut-directed probiotics, may offer a more substantial effect on OM prevention or control. Of interest is that

oral microbiome transplantation (OMT)—the collection and application of a complex microbial ecosystem to the oral cavity—is emerging as a possible therapeutic strategy to support oral health. OMT is considered more advantageous compared with probiotics due to the diversity of species included (i.e., the whole ecosystem, not just selected strains). Although in its infancy, OMT is currently under investigation for the treatment of dental caries and periodontal disease [38]. In progressing with this treatment option, there are many practical considerations that must be defined or at least adequately justified, including the choice of the donor(s) and relevant eligibility considerations, microbial strain selection (if at all), sample collection, processing, dosing and administration.

As an alternative to direct microbial inputs, prebiotics are an alternative strategy to support commensal organisms-balancing and sustaining microbial homeostasis. Defined as a “food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria, and thus improves host health” [39], prebiotics have also been largely applied with the goal of supporting the gut microbiome. Despite this, some prebiotics (e.g., nitrate) have been designed with the goal of improving oral health, helping to stabilise salivary pH, the oral biofilm and microbial eubiosis. Despite emerging evidence outlining the potential benefit of prebiotics for oral health, there have been no studies specifically investigating their ability to alter the development or progression of OM.

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