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Research Article

Oral Toxicities Following CAR T-Cell Therapy: An Overlooked Clinical Reality

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy is a significant breakthrough in immunotherapy for patients with relapsed or refractory blood cancers, showing high remission rates and longer survival times. While the effectiveness of this treatment is well established, it also has a distinct toxicity profile marked by side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which have been closely examined in both clinical studies and real-world settings. On the other hand, oral toxicities linked to CAR T-cell therapy are less reported, raising concerns about how common they are and their clinical importance. New research indicates that oral issues like mucositis, opportunistic infections, dry mouth (xerostomia), taste disturbances (dysgeusia), and bad breath (halitosis) may result from indirect effects such as systemic inflammation, severe immunosuppression, decreased blood cell counts, and possible off-target immune responses affecting oral tissues. These oral side effects can significantly affect nutrition, communication, and overall quality of life, while also increasing the risk of systemic infections in this immunocompromised group. Due to limited research in this area, this review aims to compile the small but growing evidence on oral side effects related to CAR T-cell therapy and explore the possible biological mechanisms connecting immune responses to oral complications.

Keywords: CAR T-Cell Therapy; Oral Toxicity; Mucositis; Xerostomia; CRS; ICANS

Abbreviations

Chimeric antigen receptor (CAR) T-cell therapy is an innovative and advanced form of adoptive cell immunotherapy designed to target and eliminate cancer cells. The process begins with extracting autologous T lymphocytes from the patient's blood, usually through leukapheresis to gather enough immune cells. After extraction, these T cells undergo ex vivo genetic modification, employing viral vectors or other methods to engineer them to express synthetic receptors that specifically recognize and bind to tumor-associated antigens unique to the patient's cancer. These engineered receptors have two main parts: an extracellular antigen-binding domain, typically derived from a monoclonal antibody single-chain variable fragment (scFv), which helps CAR T-cells identify cancer cells, and intracellular signaling domains that activate strong signaling cascades, ultimately triggering potent cytotoxic responses when engaged with the target antigen [1]. After reinfusion into the

patient, the CAR T-cells rapidly expand and effectively migrate to tumor sites throughout the body. Their mechanism involves releasing cytotoxic molecules like perforin and granzymes, which induce apoptosis in tumor cells. Moreover, these activated T-cells secrete various pro-inflammatory cytokines, boosting the immune response and encouraging additional activation and recruitment of other immune cells, thereby enhancing the overall anti-tumor effect [2]. This comprehensive approach aims to achieve lasting remission and improved survival rates for patients with certain hematologic malignancies and solid tumors.

Clinically, CAR T-cell therapy has revolutionized the treatment landscape for relapsed or refractory B-cell malignancies, particularly acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL). These cancers often prove resistant to conventional treatment modalities, including traditional chemotherapy regimens, targeted therapies, and hematopoietic stem cell transplants, leading to poor prognoses in affected patients [3,4]. Key clinical trials that facilitated the approval of CAR T-cell products such as tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) have demonstrated remarkable efficacy, with durable complete remission rates exceeding 50% in heavily pretreated populations that had previously exhausted almost all available treatment options [5,6]. These groundbreaking results have fundamentally altered treatment expectations and introduced new hope for patients who previously faced minimal prospects for recovery. However, the enhanced efficacy of CAR T-cell therapy is accompanied by a distinct and sometimes severe toxicity profile that clinicians must carefully manage. Notably, cytokine release syndrome (CRS) is among the most common and well-characterized adverse effects. This condition results from a massive and rapid release of cytokines into the bloodstream, which can lead to symptoms ranging from fever and fatigue to more severe complications such as hypotension and organ dysfunction. The severity of CRS can vary significantly among patients, necessitating close monitoring and timely intervention [7-9]. Additionally, immune effector cell-associated neurotoxicity syndrome (ICANS) poses another serious risk, manifesting as a spectrum of neurological symptoms that can range from mild cognitive impairment and confusion to life-threatening conditions such as seizures and cerebral edema. Effective mitigation strategies and supportive care approaches are vital in managing these adverse events, ensuring both the safety and well-being of patients treated with CAR T-cell therapy. Overall, the transformative potential of this innovative therapy is tempered by the need for vigilant oversight and comprehensive care protocols.

While the systemic and neurologic adverse events associated with CAR T-cell therapy are now well-documented and incorporated into standardized grading and management guidelines [10], the oral toxicities linked to this treatment remain inadequately understood. This lack of clarity is particularly notable given the significant role of the oral cavity as both a site of toxicity and an early warning indicator of treatment-related complications in other forms of cancer therapy. For instance, conventional modalities such as chemotherapy, radiotherapy, and hematopoietic stem cell transplantation frequently lead to oral complications, including mucositis, xerostomia, opportunistic infections due to compromised oral flora, and alterations in taste perception [11,12]. These oral side effects rank among the most prevalent and severe complications experienced by patients undergoing cancer treatment. The occurrence of such complications can have profound implications for patient care. For example, mucositis can severely hinder oral intake, limiting nutritional support and hydration, while xerostomia can exacerbate difficulties in swallowing and speaking. Additionally, these oral toxicities can interfere with adherence to the prescribed systemic therapies, leading to interruptions or dose modifications that jeopardize treatment efficacy. Patients may also face an increased risk of systemic infections as a result of oral mucosal breakdown and opportunistic pathogens taking hold. Ultimately, these complications can significantly detract from a patient's overall quality of life, contributing to psychological distress and a decreased sense of well-being during an already challenging time in their cancer journey.

The oral cavity is particularly susceptible to toxic events during cancer treatment due to its rapidly renewing epithelial tissues, diverse microbiota, ongoing mechanical and microbial challenges, and salivary gland function to maintain mucosal health [13,14]. Disruption of these protective mechanisms-whether resulting from systemic inflammation, cytopenia-induced immunosuppression, direct immune-mediated tissue damage, or microbiome imbalance-can have a significant impact on both oral and overall health. Given that CAR T-cell therapy provokes strong immune activation

followed by varying degrees of immune suppression, it is biologically plausible that this treatment may lead to oral complications through both direct and indirect pathways.

Despite the plausible connection between CAR T-cell therapy and oral adverse events, there remains a significant lack of strong epidemiologic data detailing the incidence, severity, and spectrum of these oral complications in patients receiving this treatment. This existing knowledge gap poses substantial challenges for the early detection and effective management of oral toxicities, which, in turn, hinders the integration of dental professionals into the comprehensive care pathways for CAR T-cell recipients. Recognizing and appropriately managing these oral toxicities is critical not only for enhancing patient comfort but also for playing a vital role in infection prevention, ensuring adequate nutritional support, and promoting overall survivorship care within this rapidly expanding patient population. Since oral complications can lead to severe consequences, including increased risk of systemic infections, difficulties in maintaining proper nutrition due to pain or discomfort, which ultimately may impact the effectiveness of the CAR T-cell therapy itself, addressing these issues proactively is essential for optimizing patient outcomes and quality of life throughout the treatment journey [15].

Acknowledging the limited body of literature specifically focusing on the oral toxicities associated with CAR T-cell therapy, this review article aims to synthesize current evidence from the available studies specific to CAR T-cell therapy. Additionally, it will delve into mechanistic insights regarding the associated oral toxicities and their underlying biological processes, thereby providing a clearer understanding of the implications of CAR T-cell therapy on oral health (Table 1).

Mechanism	Potential Oral Manifestations	Supporting Evidence
Cytokine storm (CRS)	Mucosal barrier breakdown, ulceration	Elevated IL-6 in CRS impairs epithelial repair
Immunosuppression and cytopenia	Candida, herpetic lesions, bacterial infections	Similar patterns observed in HSCT and chemotherapy
Off-target antigen recognition	Sialadenitis, xerostomia	Hypothetical in CAR constructs with antigen overlap
Microbiome dysbiosis	Periodontitis, halitosis	Immunotherapy-linked oral microbiome shifts described in checkpoint inhibitor studies

Table 1: Pathophysiological Mechanisms of Oral Toxicity in CAR T-Cell Recipients.

Established Adverse Events of CAR T-Cell Therapy

CAR T-cell therapy exhibits a distinctive toxicity profile that arises primarily from its underlying mechanism of action, which involves robust immune activation and the widespread proliferation of genetically modified T-cells upon their interaction with specific target antigens. While the toxicities associated with this innovative treatment are predominantly characterized by systemic effects, such as fever, fatigue, and hematologic abnormalities, as well as neurologic symptoms that can include confusion, seizures, and encephalopathy, it is crucial to recognize that many of these toxicities can also lead to secondary repercussions on oral health as will be discussed later in this review (Table 2, Figure 1).

Cytokine release syndrome (CRS)

CRS is the most commonly observed acute toxicity associated with CAR T-cell therapy, affecting 40–90% of patients depending on factors such as disease type, tumor burden, CAR construct, and lymphodepletion regimen [16]. This syndrome typically manifests within 1 to 7 days post-infusion, coinciding with the peak expansion of CAR T-cells. The condition is characterized by significant immune activation and systemic release of pro-inflammatory cytokines, including interleukin-6 (IL-6), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) [17]. Clinically, CRS presents a biphasic pattern: an initial febrile phase marked by fever, chills, and malaise, followed by a progression to hemodynamic instability, including hypotension and tachycardia, as well as

Toxicity	Incidence	Pathophysiology	Potential Oral Implications
Cytokine Release Syndrome (CRS)	40–90%	Massive immune activation with release of IL-6, IFN-γ, TNF-α, IL-1; endothelial activation; vascular leakage	Mucosal barrier breakdown; edema; ulceration; delayed healing; increased susceptibility to opportunistic infections
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	30–64%	Endothelial activation, blood–brain barrier disruption, neuroinflammation	Impaired oral hygiene due to motor and cognitive deficits; dysphagia; traumatic oral lesions during seizures
Prolonged cytopenias	Up to 40% at ≥30 days post-infusion	Bone marrow suppression from lymphodepletion, CAR T activity, and inflammatory milieu	Oral mucosal ulcerations; gingival bleeding; delayed wound healing; infection risk
Hypogammaglobulinemia	>80% in anti-CD19 CAR T recipients	On-target B-cell aplasia leading to low immunoglobulin levels	Recurrent oral bacterial and fungal infections; delayed clearance of oral pathogens
Opportunistic infections	Variable; often during neutropenia or B-cell aplasia	Immunosuppression from cytopenias, corticosteroids, and tocilizumab	Oral candidiasis, herpetic stomatitis, and bacterial periodontitis
Metabolic derangements	Common during acute toxicity phases	Tumor lysis syndrome, systemic inflammation, poor nutritional intake	Impaired oral healing; mucosal dryness and discomfort

Table 2: Established systemic toxicities of CAR T-cell therapy and their potential oral implications.

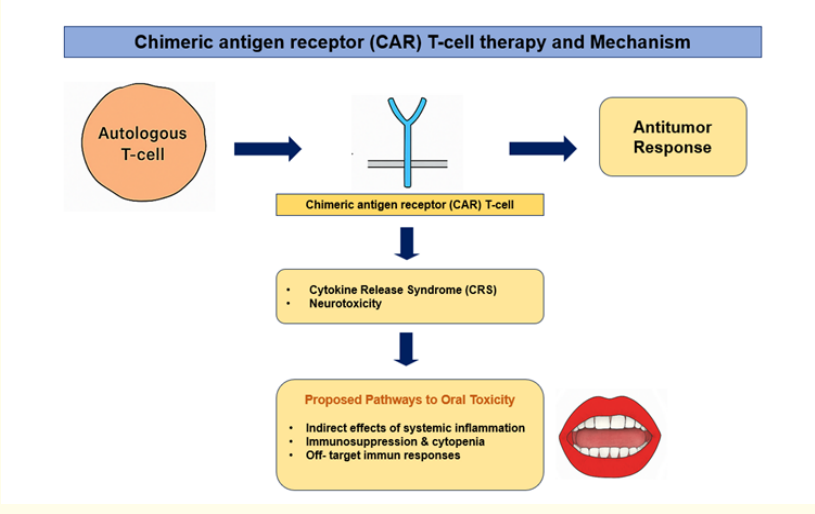

Figure 1

hypoxia and multi-organ dysfunction in severe cases. Laboratory assessments may indicate elevated levels of C-reactive protein, ferritin, and transaminases, accompanied by coagulopathy.

From an oral health standpoint, the hyperinflammatory environment associated with CRS can significantly compromise the integrity of the mucosal barrier. This disruption occurs as inflammatory mediators interfere with epithelial junctions, which are crucial for maintaining barrier function. As a result, the normal processes of wound healing are impaired, leading to increased vulnerability of the oral mucosa to various stressors and pathogens. Moreover, alterations in the composition and flow of saliva can further exacerbate the situation, affecting oral pH levels, buffering capacity, and antimicrobial properties, thereby increasing the risk of dental caries and periodontal disease. The inflammation also results in changes to vascular permeability, which may lead to mucosal edema and tenderness, creating an environment that is conducive to opportunistic infections, such as oral thrush or other fungal infections [18].

Management options for CRS, such as tocilizumab, an anti–IL-6 receptor monoclonal antibody, along with corticosteroids, can effectively mitigate some of the systemic inflammatory effects [19]. However, it is crucial to be aware that these treatments may also introduce immunosuppressive risks for oral health. This immunosuppression can hinder the body's natural defense mechanisms, making the oral cavity more susceptible to infections and complicating the management of existing oral health issues. Thus, a careful balance must be achieved in treating CRS while safeguarding oral health.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS is a neurotoxic complication that occurs specifically in the context of immune effector cell therapies, such as CAR T-cell therapy. This condition can affect a concerning 30–64% of patients, often presenting alongside CRS [17]. The underlying pathophysiology of ICANS is believed to involve a series of pathological events, including endothelial activation, which contributes to inflammation and disruption of the blood-brain barrier. This disruption allows inflammatory mediators, like cytokines and chemokines, to enter the central nervous system, causing a variety of neurological symptoms. The clinical signs of ICANS can range from mild cognitive issues-such as confusion, difficulty concentrating, and short-term memory problems-to severe neurological complications, including aphasia, seizures, coma, and, in rare cases, cerebral edema.

In terms of oral health implications, ICANS can have secondary effects that lead to diminished oral hygiene. Patients may experience decreased self-care capabilities due to cognitive challenges, impaired motor coordination, and dysphagia, compounded by reduced oral sensory perception. Additionally, patients may sustain traumatic oral lesions stemming from involuntary biting during seizure episodes or from a reduction in protective reflexes, which heightens the risk of oral injuries. Management of ICANS typically encompasses a regimen of supportive care that prioritizes patient safety and comfort. For cases classified as moderate to severe, corticosteroids are administered to mitigate inflammatory responses. In specific scenarios, anticonvulsants may be prescribed for proactive seizure prevention. While these interventions are crucial for preserving neurological function, it is essential to note that they may inadvertently impact the patient's immune competence and hinder mucosal healing, necessitating careful consideration and monitoring throughout the treatment process.

Other recognized toxicities

In addition to the clinical manifestations of CRS and ICANS, recipients of CAR T-cell therapy frequently experience a variety of hematologic and immune-related complications. These complications can significantly affect the patient's quality of life, impairing their ability to eat, speak, and maintain adequate oral hygiene:

- **Prolonged Cytopenias:** Extended periods of neutropenia, anemia, and thrombocytopenia, which are often observed in patients following hematopoietic cell transplantation or CAR T-cell therapy, can last beyond 30 days post-infusion. These prolonged cytopenias not only contribute to increased fatigue and weakness but also significantly elevate the risk of developing severe oral mucosal ulcerations, opportunistic Candida infections, herpetic reactivations, and gingival bleeding. The resulting mucosal damage can lead to difficulties in eating and swallowing, ultimately affecting nutritional intake and quality of life [20].

- **Hypogammaglobulinemia:** The use of anti-CD19 CAR T-cell constructs may lead to a state of B-cell aplasia characterized by persistently low levels of immunoglobulins, specifically IgG, IgA, and IgM. This immunodeficiency renders patients more susceptible to recurrent infections, particularly those affecting the oral cavity (such as oral candidiasis) and the sinus passages. The lack of adequate B-cell response hampers the body's ability to mount effective immune responses, putting patients at higher risk for both bacterial and viral infections [21].
- **Opportunistic Infections:** The oral cavity and oropharynx can become vulnerable to a range of opportunistic infections, which are more likely to proliferate during periods of prolonged immunosuppression. Common culprits include fungal infections (primarily from Candida species), viral infections (such as Herpes Simplex Virus [HSV], Varicella-Zoster Virus [VZV], and Cytomegalovirus [CMV]), and bacterial infections (notably those caused by Streptococcus and Actinomyces species). These infections can cause substantial discomfort and clinical complications, including severe oropharyngeal pain, dysphagia, and, in some cases, systemic dissemination [22].
- **Metabolic Derangements:** Patients undergoing aggressive treatment regimens may experience metabolic derangements, such as electrolyte imbalances like hypokalemia and hypophosphatemia, alongside nutritional deficiencies typically seen during acute toxicity phases. These imbalances can significantly hinder the process of oral wound healing, exacerbate mucosal discomfort, and contribute to overall clinical morbidity. It's crucial to monitor and correct these metabolic disturbances promptly to facilitate recovery and reduce the risk of secondary complications in the oral mucosa [22].

Oral side effects: Current evidence

Despite the extensive characterization of oral toxicities associated with various oncologic treatments-including conventional chemotherapy, radiotherapy, and hematopoietic stem cell transplantation (HSCT) [11,12]-the presence, types, and impact of these toxicities in the context of CAR T-cell therapy remain largely underexplored and inadequately documented. In the established settings of chemotherapy and radiation therapy, oral complications such as mucositis, opportunistic infections that can arise due to immunosuppression, xerostomia characterized by dry mouth resulting from reduced saliva production, dysgeusia affecting taste perception, and salivary gland dysfunction are well-recognized. These complications are not merely frequent adverse effects; they play a clinically significant role in several key aspects, including negatively impacting nutritional intake, heightening the risk of infections, diminishing overall quality of life, and potentially jeopardizing adherence to treatment regimens [11-13]. Hence, understanding the full spectrum of oral toxicities in CAR T-cell therapy is essential for improving patient care and outcomes (Figure 2).

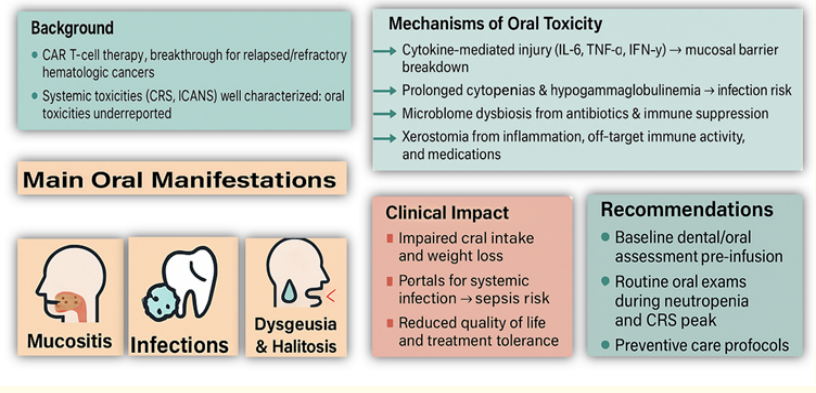

Figure 2

The current literature surrounding CAR T-cell therapy reveals a notable deficiency in comprehensive studies, as the available evidence largely consists of isolated case reports and small-scale single-institution series [23], as well as indirect extrapolations from related hematologic interventions like HSCT (24,25). This scarcity of focused research is particularly significant considering that CAR T-cell therapy recipients share numerous risk factors with other immunocompromised cancer populations [20]. These factors include profound cytopenias, which result in reduced blood cell counts and heightened susceptibility to infections; immune dysregulation, where the body's immune response is compromised or overactive; disruption of mucosal barriers, which can lead to increased vulnerability to pathogens; and significant exposure to broad-spectrum antimicrobials, often necessitated by the management of opportunistic infections [20-22]. Moreover, the distinctive immune activation and inflammatory cascades initiated by CAR T-cell therapy, including CRS and prolonged B-cell aplasia [15,16,20,21], may introduce unique pathways of oral injury. These pathways might manifest as conditions such as mucositis, xerostomia, or other forms of oral complications that are not typically seen with conventional therapies. Understanding these specific mechanisms is crucial for developing targeted preventive and therapeutic strategies for managing oral health in patients undergoing CAR T-cell therapy.

Despite the current lack of comprehensive systematic data, the available clinical observations yield valuable mechanistic insights into the oral health challenges faced by patients undergoing CAR T-cell therapy. For instance, the presence of documented oral mucosal ulcerations during neutropenic phases indicates significant similarities to chemotherapy-induced mucositis, a painful inflammation of the mucous membranes [24]. This observation suggests that the mechanisms of injury overlap between these two treatment modalities, pointing to a need for further investigation into preventive measures. Moreover, the rising reports of invasive fungal infections during the post-infusion immunosuppressive period highlight a concerning risk for severe opportunistic oral-maxillofacial diseases. These infections can lead to significant morbidity in immunocompromised patients, underscoring the importance of vigilant oral health monitoring [23].

Furthermore, insights from broader immunotherapy studies-particularly regarding adverse effects like xerostomia, a condition characterized by dry mouth, and dysgeusia, which refers to altered taste perception, associated with the use of checkpoint inhibitors-offer plausible frameworks for understanding the potential off-target effects or immune-mediated complications in CAR T-cell recipients [25,26]. Taken together, these emerging findings critically underscore the immediate necessity for well-designed prospective studies aimed at systematically capturing oral health outcomes within CAR T-cell clinical trials. Such initiatives would provide essential data on the incidence rates, temporal patterns, and associated risk factors for oral health complications. Ultimately, this information would be pivotal in developing targeted preventive and therapeutic strategies designed to safeguard oral function and enhance the overall quality of life for patients undergoing CAR T-cell therapy.

Mucositis

Currently, there is a lack of large-scale prospective studies that establish the incidence of oral mucositis in patients receiving CAR T-cell therapy. However, evidence from other cancer treatments suggests that this side effect may be both prevalent and clinically significant. In standard chemotherapy regimens, approximately 30–40% of patients report developing oral mucositis [24]. For patients undergoing HSCT, the incidence rises significantly, with 60–85% experiencing this debilitating side effect [24]. Furthermore, in cases of concurrent chemoradiotherapy specifically for head and neck cancer, studies indicate that up to 90% of patients may suffer from oral mucositis, underscoring the serious nature of this complication [24]. The high prevalence and severity of oral mucositis can primarily be attributed to several interrelated factors, including the rapid turnover of epithelial cells in the oral cavity, which cytotoxic agents can easily disrupt.

Additionally, the oral mucosa's inherent susceptibility to inflammatory injury, combined with the multifaceted impact of systemic immunosuppression, contributes to the heightened risk. While specific data regarding CAR T-cell therapy and oral mucositis is still

lacking, small observational studies and anecdotal cases have documented instances of painful, erythematous, or ulcerative lesions occurring during the neutropenic phase that typically follows cell infusion [15,16]. These lesions often arise at the peak of systemic toxicity, coinciding with the onset of various complications such as CRS, cytopenias, and an increased susceptibility to infections.

Potential mechanisms underlying mucositis in CAR T-cell therapy recipients include several interconnected factors: (I) Indirect epithelial injury due to systemic cytokine surges during CRS: The infusion of CAR T-cells can trigger a profound immune response characterized by a rise in pro-inflammatory cytokines, particularly IL-6 and TNF-α. Elevated levels of these cytokines during CRS have been shown to disrupt the normal processes of epithelial regeneration, leading to heightened mucosal inflammation and contributing to mucositis. This inflammatory response can result in increased permeability of the epithelium, further exacerbating tissue damage and the subsequent inflammatory cascade [15,16]. (II) *Microbial overgrowth during prolonged neutropenia*: Following CAR T-cell therapy, patients often experience significant immune suppression, particularly due to neutropenia. This immunocompromised state diminishes the patient's ability to fend off infections, allowing for opportunistic bacterial and fungal colonization of the mucosal surfaces. As a result, these pathogens can infiltrate necrotic tissue and lead to secondary infections, which complicate mucositis and delay recovery [21,22]. The risk of infections is further amplified by the breakdown of the epithelial barrier caused by the mucositis itself. (III) *Delayed epithelial regeneration linked to cytopenia-induced impaired healing:* Persistent lymphopenia and thrombocytopenia following CAR T-cell infusion pose significant challenges to tissue repair and regeneration. The depletion of these critical cell types not only impairs the immune response but also inhibits essential healing processes, leading to a failure in restoring the integrity of the mucosal barrier. The combination of impaired healing and increased bleeding risk due to thrombocytopenia can exacerbate the severity of mucositis, leading to more significant patient morbidity [20].

Clinically, mucositis in this context can significantly impact oral intake, resulting in weight loss, reducing quality of life, and potentially serving as a pathway for systemic infections in immunocompromised patients [11,12]. In high-risk populations, these complications may require hospitalization, parenteral nutrition, or systemic antibiotics. Furthermore, severe mucositis can delay supportive care and complicate the administration of other essential post-CAR T-cell therapies. Therefore, incorporating pre-treatment dental evaluations, stringent oral hygiene protocols, and encouraging early symptom reporting into CAR T treatment plans may help to mitigate mucositis-related complications [11,12,24]. Additional prospective research is needed to understand its prevalence, better identify risk factors, and determine the most effective prevention strategies within this specific therapeutic context.

Oral infections

Profound immunosuppression following CAR T-cell infusion-resulting from persistent cytopenias, hypogammaglobulinemia, and the immunomodulatory effects of concurrent supportive treatments-creates a highly favorable environment for the emergence of opportunistic oral infections [20-22]. Neutropenia may persist for weeks, while B-cell aplasia can endure for months or even years. This prolonged immunosuppression significantly elevates the risk of both early infectious complications, such as bacterial infections, and late complications, including viral and fungal infections [20,211]. Moreover, therapeutic interventions such as corticosteroids, which are often employed to mitigate CRS, or IL-6 receptor blockers like tocilizumab, can further compromise immune defenses [15,16]. A striking illustration is a 2024 case report that documents a fatal instance of invasive fungal rhinosinusitis in an adolescent patient with relapsed ALL following T-cell therapy [23]. While the infection primarily impacted the paranasal sinuses, it likely originated from or was aggravated by microbial colonization at the oral–nasal interface, emphasizing the vulnerability of the maxillofacial region during the immunosuppressed state that follows CAR T-cell infusion. This case underscores a critical clinical insight: oral or sinonasal infections in CAR T-cell recipients can

rapidly escalate into life-threatening systemic conditions if not recognized and addressed with urgency. Hence, prompt identification and targeted management of such infections are essential to prevent severe complications and ensure the safety of these immunocompromised patients.

Reported oral infections encompass a variety of pathogens and clinical presentations: (I) *Fungal infections:* Fungal infections are primarily caused by Candida albicans along with non-albicans species such as C. glabrata and C. tropicalis, can lead to several manifestations, including pseudomembranous candidiasis, characterized by white, cheese-like patches; erythematous candidiasis, marked by red, inflamed tissues; or angular cheilitis, which presents as painful fissures at the corners of the mouth [20,21]. In patients with severe immunosuppression, particularly those undergoing chemotherapy or living with HIV, these infections have the potential to disseminate to the oropharynx or esophagus, resulting in symptoms like odynophagia (painful swallowing) and subsequent nutritional deficiencies due to difficulty in eating. (II) *Viral infections:* Reactivation of dormant herpes simplex virus (HSV) can cause vesiculoulcerative stomatitis, presenting as clusters of painful blisters and ulcers in the oral cavity. In addition, while varicella-zoster virus (VZV) may lead to painful oral or facial lesions that follow a dermatomal distribution, typically appearing in areas innervated by specific spinal nerves [20]. Although such occurrences are less frequent, reactivation of **cytomegalovirus** (CMV) has been documented in various immunocompromised cohorts; it usually manifests as deep oral ulcers that are slow to heal, which can cause further complications and discomfort for the affected individuals [20]. (III) *Bacterial infections:* The presence of neutropenia, or low neutrophil counts, coupled with the disruption of the protective mucosal barrier, significantly elevates the risk for severe periodontal and odontogenic infections. These can manifest as necrotizing ulcerative gingivitis, which involves painful, necrotic lesions of the gums; periodontal abscesses, characterized by localized collection of pus; and odontogenic cellulitis, a diffuse inflammation of the soft tissues surrounding the teeth [11,12]. These infections can lead to serious complications, including deep space infections in the head and neck area, which may require surgical intervention and extended antibiotic treatment if managed promptly and effectively.

Factors that significantly increase the risk of infection in patients receiving CAR T-cell therapy include: (I) The loss of mucosal integrity, which can occur as a consequence of aggressive chemotherapy conditioning regimens and/or the development of mucositis [24]. (II) Disturbances in the oral microbiome arising from the extensive use of broad-spectrum antibiotics may lead to dysbiosis, reducing the diversity of the microbial community and allowing opportunistic pathogens to proliferate [14,21]. (III) Xerostomia, or dry mouth, results in reduced salivary flow, thereby diminishing the natural delivery of antimicrobial peptides, immunoglobulins, and other protective factors present in saliva that are crucial for maintaining oral health [11,13,26].

From a clinical perspective, oral infections in CAR T-cell recipients can severely impact patient comfort and normal oral functions, such as chewing and swallowing. More alarmingly, they may serve as a primary source of systemic sepsis, particularly when central venous catheters are in place, creating a direct pathway for pathogens to enter the bloodstream. To mitigate these risks, it is essential to implement regular oral examinations as part of the comprehensive follow-up care for patients treated with CAR T-cell therapy. These examinations should ideally be conducted by dental or oral medicine specialists who can identify and manage potential oral complications early on. In such patients, the use of prophylactic antifungal and antiviral therapies may be advantageous for certain patients undergoing CAR T-cell therapy, particularly for those with a higher risk of infections due to their treatment regimens. These preventive measures, already established in many protocols for treating hematologic malignancies, could provide an additional layer of protection against opportunistic infections [20,21].

Salivary gland dysfunction and xerostomia

Xerostomia, defined as the subjective sensation of dry mouth, has not been formally documented as a specific adverse event in clinical trials involving CAR T-cell therapy. However, the occurrence of xerostomia in this patient population is biologically plausible due to the immunological and pharmacological mechanisms inherent in the treatment. CAR T-cell therapy involves the modification of T-cells to target and eliminate cancer cells, which can inadvertently affect other tissues, including the salivary glands. Although

there is a lack of direct evidence from trials specifically addressing this issue, prior clinical experiences in both oncologic treatments and immunotherapy suggest that salivary gland dysfunction, manifesting as symptoms such as dry mouth, could be a significant and often overlooked complication in patients undergoing CAR T-cell therapy.

Potential mechanisms contributing to salivary dysfunction include: (I) *Cytokine-driven inflammation during CRS:* The elevated systemic levels of pro-inflammatory cytokines such as IL-6, IFN-γ, and TNF-α, which are hallmark features of CRS [15,16], can induce transient sialadenitis. This condition leads to inflammation of the salivary glands, impairing the function of acinar cells responsible for saliva production and subsequently reducing overall salivary flow. Comparable inflammatory pathways are implicated in the xerostomia commonly observed in autoimmune conditions like Sjögren's syndrome, where persistent immune activation results in glandular infiltration and cytokine-mediated apoptosis of epithelial cells, ultimately disrupting normal saliva secretion. (II) *Off-target CAR T-cell activity against salivary gland epitopes:* Although anti-CD19 CAR constructs are primarily designed to target CD19-expressing malignant B cells and are not expected to affect salivary tissues directly, there exists a theoretical risk of cross-reactivity if the selected antigen is expressed, albeit at low levels, in the epithelial cells of the salivary glands. This risk echoes cases of immune-mediated salivary dysfunction that have arisen in patients undergoing treatment with immune checkpoint inhibitors, where the mechanism has been attributed to the infiltration of immune cells into salivary glands and subsequent damage to glandular tissue [26]. (III) *Medication-induced xerostomia:* A range of supportive care medications that are frequently administered around the onset of CAR T-cell therapy, such as opioids for pain management, anticholinergic agents to control secretion, and antiemetic drugs to mitigate nausea, are known to adversely impact salivary flow through various neural or direct glandular pathways [11,26]. The combined effects of these pharmacological agents may synergistically worsen the sensation of dryness in the mouth, leading to significant discomfort and complications for patients undergoing treatment.

Increasing evidence supports the likelihood of xerostomia developing in patients who have undergone CAR T-cell therapy. This condition has been frequently reported in patients receiving immune checkpoint inhibitors or other targeted immunotherapies, often in conjunction with clinical manifestations such as stomatitis and dysgeusia, at significant rates [26]. Pathological investigations into these patient populations have demonstrated key features, including lymphocytic infiltration of minor salivary glands, acinar atrophy, and damage to ductal epithelial cells, all indicating an immune-mediated injury to the salivary glands. These histopathologic findings may bear relevance in the context of CAR T-cell therapy, particularly if immune activation persists post-treatment, leading to prolonged damage to salivary tissues. Clinically, xerostomia in CAR T-cell-treated patients can have profound implications for their overall health: (I) The impairment of saliva's critical functions, such as mechanical cleaning of the oral cavity, buffering capacity to neutralize acids, and antimicrobial action against pathogenic bacteria, can increase the risk of various complications. These complications include oral mucosal damage, fungal infections like Candida, and dental decay which can arise due to decreased salivary flow and protective mechanisms [11-13]. (II) Furthermore, reduced lubrication in the mouth may exacerbate swallowing difficulties (dysphagia), impede clear speech articulation, and diminish the ability to taste, creating compounded nutritional deficits and diminished quality of life for patients already burdened by the adverse effects of their treatment. In severe cases, xerostomia may also contribute to the development of oral mucositis by hindering epithelial healing processes and reducing the delivery of essential salivary growth factors that promote tissue repair and regeneration.

From a managerial perspective, early detection and timely intervention are paramount in addressing issues related to dry mouth, particularly in patients undergoing treatments like CAR T-cell therapy. Supportive strategies for alleviating xerostomia include frequently sipping small amounts of water-ideally, every 15 to 30 minutes-to help maintain oral hydration and comfort. The use of sugar-free gum or lozenges can effectively stimulate saliva production, providing a convenient means of relief throughout the day. For candidates who meet specific criteria, the application of topical

sialogogues such as pilocarpine or cevimeline can significantly enhance salivary flow and improve overall oral health. Additionally, implementing a strict regimen of preventive dental care, including regular check-ups and professional cleanings, is essential to reducing the risk of cavities and maintaining oral hygiene. Moreover, it is crucial to carefully evaluate and, whenever possible, minimize the prescription of xerogenic medications, especially in patients at high risk for developing this condition. Considering the current lack of prospective data regarding the incidence and impact of dry mouth related to CAR T-cell therapy, incorporating structured oral symptom questionnaires and objective salivary flow measurements into clinical trials is critical. This approach could provide valuable insights, helping to clarify the actual prevalence, duration, and risk factors associated with this side effect, ultimately enhancing patient care and support strategies during treatment.

Dysgeusia and halitosis

Taste disturbances (dysgeusia) and halitosis are relatively uncommon findings in reports on CAR T-cell therapy; however, these conditions are biologically plausible due to the therapy's intricate effects on the immune system, inflammatory responses, and the oral microbiome. In the realm of other oncological treatments and immunotherapy, studies have documented dysgeusia in as many as 40-56% of patients undergoing chemotherapy, targeted therapies, or immune checkpoint inhibitors [25,27]. Halitosis, although less frequently measured in clinical settings, is increasingly recognized as a secondary outcome associated with oral microbial dysbiosis-an imbalance in the microbial community of the mouth-and a decline in salivary clearance mechanisms [28]. Several mechanisms may underlie the occurrence of dysgeusia and halitosis in patients receiving CAR T-cell therapy: (I) *Increased levels of circulating pro-inflammatory cytokines:* During cytokine release syndrome (CRS), which can occur post-treatment, there are marked increases in circulating levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IFN-γ. These elevated cytokine levels can provoke localized inflammation in the taste buds, disrupt the normal turnover of taste receptor cells, and alter the signaling pathways of gustatory nerves [15,16,29]. Similar cytokine-induced changes in taste perception have been documented in cases of viral infections and various post-vaccination syndromes, where the inflammatory response affects gustatory function. (II) *Oral microbiome dysbiosis resulting from prolonged immunosuppression:* The immunosuppressive effects of CAR T-cell therapy can lead to conditions such as neutropenia, exposure to antibiotics, and significant shifts in the oral microbial ecosystem. These factors can result in an overgrowth of harmful gram-negative anaerobes, such as Porphyromonas and Fusobacterium, while simultaneously decreasing the diversity of beneficial oral microbiota [14,21,30]. The proliferation of these pathogenic bacteria can result in the production of volatile sulfur compounds (VSCs), which are key biochemical contributors to halitosis. Additionally, these microbial changes can further modify taste perception by altering the metabolic by-products that accumulate on the tongue. (III) *Xerostomia impairing taste perception and odor clearance:* Saliva plays a pivotal role in solubilizing taste molecules and the adequate clearance of odor-causing debris from the oral cavity. In patients undergoing CAR T-cell therapy, salivary gland dysfunction may lead to reduced salivary flow [11,12,26]. This impairment can dampen the gustatory stimuli by limiting the availability of taste compounds and facilitating the accumulation of VSCs, thereby exacerbating both dysgeusia and halitosis. Restoring salivary function and maintaining oral hygiene are critical to mitigating these side effects in affected patients.

Although the symptoms associated with dysgeusia and halitosis are not considered life-threatening, they can have a profound impact on an individual's appetite, enjoyment of food, and overall nutritional intake. This is particularly evident in recipients of CAR T-cell therapy, who often face additional challenges such as treatment-related anorexia, oral mucositis, and altered swallowing capabilities [11,24,26]. Dysgeusia may result in strong aversions to specific food groups, especially protein-rich foods, which can exacerbate the risk of malnutrition and hinder recovery. Halitosis, while primarily recognized as a social and psychological concern that can affect self-esteem and interpersonal relationships, may also be indicative of more serious underlying issues. It could suggest the presence of oral infections, breakdown of mucosal tissue, or imbalances in the oral microbiome, each of which may require prompt medical or dental intervention.

Addressing dysgeusia and halitosis symptoms is crucial not only for improving dietary habits but also for enhancing overall quality of life for individuals undergoing such intensive treatments. Management strategies for taste and odor disturbances should be meticulously tailored to address the specific underlying causes: (I) In cases of inflammatory-mediated dysgeusia, which can arise from conditions such as oral lesions, infections, or systemic diseases, the application of topical corticosteroids, such as triamcinolone acetonide, has been shown to provide symptomatic relief. These corticosteroids work by reducing inflammation in the oral mucosa, thereby soothing sensitive tissues and alleviating discomfort. Other supportive therapies may include anti-inflammatory mouthwashes containing agents like lidocaine, which not only numb the area but also help reduce local inflammation, potentially improving taste perception. (II) For halitosis associated with microbiome imbalances, effective interventions are crucial. One of the primary strategies involves the mechanical cleaning of the tongue using specialized tongue scrapers, which can effectively remove biofilms and debris that harbor odor-causing bacteria. Furthermore, the use of antimicrobial mouth rinses, including chlorhexidine gluconate or cetylpyridinium chloride, has been proven beneficial in targeting and eliminating harmful bacteria responsible for bad breath. Additionally, incorporating probiotic therapy, particularly strains of Lactobacillus, offers promising results in restoring a balanced oral microbiome, which, in turn, can mitigate halitosis across diverse populations [30,31].

Given that xerostomia can significantly alter taste and odor perception due to a decrease in saliva production, this condition should be managed through the administration of sialogogues, which are substances that stimulate saliva flow and can include medications like pilocarpine. Additionally, the use of saliva substitutes may play a vital role in maintaining oral moisture, while diligent hydration practices-ensuring adequate fluid intake throughout the day-are essential in combating dryness and improving overall oral health. This multifaceted approach will not only address the symptoms of dry mouth but also will help restore a healthier taste and odor experience.

Conclusion

CAR T-cell therapy has significantly altered the treatment landscape for relapsed and refractory blood cancers, offering patients with limited options the possibility of durable remissions. However, like all highly effective immunotherapies, it comes with a complex and varied toxicity profile. While systemic side effects such as CRS and ICANS are well-documented, oral toxicities often receive less attention, tend to be underreported, and remain insufficiently researched. However, CAR T-cell therapy may potentially lead to mild to severe mucositis, opportunistic infections, salivary gland dysfunction or xerostomia, and taste alterations along with halitosis, stemming from a combination of systemic inflammation, prolonged low blood counts, hypogammaglobulinemia, disruption of the microbiome, and the effects of various medications. Notably, these toxicities not only deteriorate the quality of life but can also lead to systemic infections and nutritional complications, thereby impacting overall treatment outcomes. Effective oral health management for patients undergoing CAR T-cell therapy necessitates a proactive, team-based approach, which involves baseline dental evaluations, regular oral assessments during high-risk phases, preventive strategies against infections, and prompt treatment of any emerging symptoms as part of clinical protocols. Additionally, it is crucial to incorporate standardized oral health outcome measures into CAR T-cell therapy trials to accurately track the incidence of these complications, identify risk factors, and evaluate effective interventions.

In conclusion, oral toxicities constitute an emerging and clinically significant area within the broader safety profile of CAR T-cell therapy. By transitioning from incidental recognition to systematic assessment, the oncology community can more effectively safeguard oral function, improve patient comfort, and ultimately enhance survivorship in this rapidly advancing therapeutic landscape.

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