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Original Research Paper

Oral Pathology

# CURRENT PERSPECTIVES ON COVID-19 COMPLICATIONS IN 2025: FOCUS ON THE ORAL CAVITY AND SYSTEMIC EFFECTS.

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**ABSTRACT** The COVID-19 pandemic, driven by SARS-CoV-2, exhibits significant oral and systemic complications mediated by viral binding to **ACE2 receptors** densely expressed in oral mucosa (50× higher than lungs). Recent evidence confirms **oral manifestations** in 20–45% of cases, including dysgeusia (38–47%), xerostomia (17.8–46.3%), and mucosal ulcers (20.5%), often serving as early disease indicators. Pathogenic mechanisms involve **direct viral cytopathy** in salivary glands, cytokine storm-induced microthrombosis, and autoimmune cross-reactivity, with viral RNA persisting in oral tissues for ≤60 days. Systemically, **Long COVID (10–35% of patients)** manifests with fatigue (58%), neurological sequelae ("brain fog" RR 2.68), cardiovascular injury (myocarditis: 2.3% in athletes), and new-onset autoimmune disorders (e.g., Guillain-Barré syndrome).

**KEYWORDS :**

### Introduction (Expanded References)

SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) receptors for cellular entry, which are abundantly expressed in oral mucosal tissues (tongue, salivary glands) and pulmonary alveoli (1),(7). Global epidemiological data reveal **over 770 million confirmed infections** and **6.9 million deaths** as of 2023, with variants of concern (VOCs) like Omicron lineages exhibiting enhanced immune evasion through spike protein mutations (N501Y, E484K) (11) . The oral cavity serves as a primary viral reservoir due to **50-fold higher ACE2 density** in tongue epithelium compared to lung tissue, facilitating early viral replication and salivary shedding (7), (10).

### Pathophysiology of SARS-CoV-2 Infection (Enhanced Mechanisms)

#### Viral Entry and Immune Dysregulation

SARS-CoV-2 spike glycoproteins bind ACE2 receptors, primed by transmembrane protease serine 2 (TMPRSS2), triggering endocytosis. Single-cell RNA sequencing confirms **co-expression of ACE2/TMPRSS2** in 80% of minor salivary gland ductal cells and oral keratinocytes, enabling direct viral damage (7). Post-infection, a **dysregulated cytokine cascade** (IL-6, TNF- , IFN- ) promotes endothelial injury and microthrombosis in oral vasculature, exacerbating mucosal lesions (6),(10). Autopsy studies reveal **viral RNA persistence** in oral epithelial cells up to 60 days post-infection, correlating with chronic xerostomia (1),(7).

#### Autoimmune Cross-Reactivity

Molecular mimicry between SARS-CoV-2 spike proteins and host antigens triggers **autoantibody production** against epithelial components. CD68+ macrophage infiltrates in oral submucosa drive fibroblast activation, potentially leading to **oral submucous fibrosis**(1),(10) . Complement system overactivation (elevated factor D) correlates with ulcer severity and poor healing (6).

### Oral Manifestations (Updated Prevalence Data)

***Table 1: Prevalence and Mechanisms of Oral Manifestations in COVID-19***

| Manifestation | Prevalence | Key Pathogenic mechanisms | Clinical Management |
|---|---|---|---|
| Dysgeusia | 38-47% | Inflammation of taste bud sustentacular cells; ACE2-mediated neural damage (1), (10) | Olfactory training, zinc supplementation |
| Xerostomia | 17.8-46.3% | Viral invasion of salivary acinar cells; reduced aquaporin-5 expression (1),(7) | Pilocarpine, artificial saliva |
| Aphthous-like Ulcers | 20.5% | Vasculitis from anti-endothelial antibodies; TNF- mediated necrosis (10) | Topical corticosteroids, photobiomodulation |
| COVID Tongue | 22% | ACE2-mediated papillitis; geographic tongue patterns (1) | Antifungal rinses for superimposed candidiasis |
| Hemorrhagic Crusts | 26% | Thrombotic microangiopathy; platelet dysfunction (10) | Anticoagulation optimization |
| Bruxism | 59% increase | Pandemic-related stress; trigeminal nerve hyperactivation (1) | Occlusal splints, behavioral therapy |

**Pathogenic Insights:**

- Salivary Gland Dysfunction: SARS-CoV-2 infects serous acinar cells via ACE2, reducing salivary flow and antimicrobial peptides (e.g., histatins), increasing caries risk (7).

- Mucosal Lesions: Biopsies show viral cytopathic effects in basal keratinocytes (karyorrhexis, ballooning degeneration), with 40% of lesions positive for SARS-CoV-2 RNA (10).

- Periodontal Complications: Upregulation of MMP-9 in gingival fibroblasts by spike protein enhances collagen degradation, accelerating attachment loss (1).

### Systemic Complications (Extended Evidence)

#### Long COVID Syndrome

Defined by WHO as **symptoms persisting >3 months post-infection**, affecting 10-35% of patients (2),(5). Meta-analysis of 47,910 patients identifies >50 long-term effects, with fatigue (58%), headache (44%), and dyspnea (24%) most prevalent (5). Oral sequelae include **persistent xerostomia** (12%) and dysgeusia (9%) at 6-month follow-up (1),(2).

#### Organ-Specific Sequelae:

**Pulmonary**: Fibrotic lung disease in 25-71% of hospitalized patients; reduced DLCO in 16% (6).
**Cardiovascular**: Myocarditis in 2.3% of athletes; POTS incidence increases 3-fold (6).
**Neurological**: "Brain fog" (RR 2.68) linked to microglial activation and hippocampal atrophy (5),(8).

#### Immune-Mediated Disorders

Autoantibodies against phospholipids emerge in 30-50% of severe cases, associated with:
**Guillain-Barré syndrome**: 21-fold risk after adenoviral vaccines (3).
**Thrombocytopenia**: Antibody-mediated platelet destruction (4/million) (3).

**Type 1 Diabetes:** New-onset cases from pancreatic -cell ACE2 infection (6).

**Table 2: Systemic Adverse Events of COVID-19 Vaccines (Updated 2025)**

| Vaccine Platform | Myocarditis | Thrombosis | GBS Incidence |
|---|---|---|---|
| mRNA (Pfizer/ Moderna) | 2.13/million doses | Not elevated | 0.5/million doses |
| Adenoviral Vector | 1.3/million doses | TTS: 4/million doses | 21-fold increase |
| Protein Subunit | Rare | Rare | Rare |

*Data sources: CDC pharmacovigilance (3),(9).

### Management Strategies (Expanded Therapeutics)

#### Oral Interventions

**Ulcer Management**: Chlorhexidine 0.12% mouthwash reduces pain by 60% in RCTs (10).
**Xerostomia** Therapy: Cevimeline (30mg TID) increases unstimulated salivary flow by 40% (1).
**Taste Dysfunction**: Theophylline nasal irrigation + olfactory training improves recovery by 75% (2).

#### Systemic Treatments

**Anticoagulation**: Rivaroxaban 10mg/day reduces microthrombosis in Long COVID (HR 0.72)(6).
**Immunomodulators**: Low-dose naltrexone (4.5mg/day) improves fatigue in 67% of patients (2).
**Rehabilitation**: Graded exercise therapy prevents post-exertional malaise in POTS (5).

#### Vaccine Efficacy

2024-2025 bivalent boosters targeting Omicron XBB.1.5 subvariant show 85% efficacy against severe disease. Myocarditis risk remains lower than from SARS-CoV-2 infection (150/million cases) (9),(11).

### Conclusion And Future Directions

COVID-19 manifests as a multisystemic disorder with significant oral involvement, reflecting shared ACE2-related pathogenesis. Oral manifestations serve as early indicators of systemic complications, necessitating integrated care models involving dentists. Research priorities in clude:

1.Variant-Specific Pathogenesis: Impact of emerging lineages (e.g., JN.1, KP.2) on oral mucosa (11).
2. Biomarker Validation: Salivary viral load as a predictor for Long COVID (7).
3. Therapeutic Innovations: Antifibrotic agents (pirfenidone) for post-COVID oral fibrosis (10).

#### Health Disparities:

Marginalized populations exhibit 2-fold higher Long COVID risk due to limited healthcare access (3),(8). Global collaboration through WHO pandemic preparedness networks is critical for surveillance of oral-systemic interactions in future variants.

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