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Recurrent Aphthous Stomatitis: Etiology, Morphology, Pathogenesis, And Contemporary Treatment Methods

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Abstract: *Recurrent aphthous stomatitis (RAS) is one of the most common ulcerative conditions affecting the oral mucosa, characterized by recurring, painful ulcers that significantly impair quality of life. Despite its prevalence, the exact etiology of RAS remains unclear, though it is considered multifactorial. Genetic predisposition, immunological dysfunction, nutritional deficiencies (e.g., iron, folate, vitamin B12), hormonal fluctuations, stress, and local trauma are known contributing factors. Morphologically, RAS is classified into three main types: minor, major, and herpetiform aphthae, each differing in size, number, duration, and healing patterns. Pathogenetically, the condition is thought to result from a T-cell mediated immune response that leads to epithelial ulceration and inflammation. In recent years, considerable advancements have been made in the treatment of RAS, ranging from topical corticosteroids and antiseptics to systemic immunomodulators and novel biological agents. Additionally, laser therapy and probiotics are emerging as promising adjunctive therapies. Despite the variety of treatments available, management primarily focuses on symptom relief, reducing recurrence, and improving patient comfort. A better understanding of the underlying mechanisms and risk factors may lead to more targeted and effective treatment strategies in the future.*

Keywords: recurrent aphthous stomatitis, oral ulcers, etiology, morphology, pathogenesis, immune response, treatment methods, topical therapy, systemic therapy, biological agents.

Introduction: Recurrent aphthous stomatitis (RAS), commonly referred to as recurrent oral ulcers or canker sores, represents one of the most prevalent forms of non-infectious ulcerative diseases affecting the oral mucosa [1]. RAS typically manifests as round or oval painful ulcerations on non-keratinized mucosal surfaces such as the labial and buccal mucosa, tongue, and floor of the mouth. These ulcers characteristically have a grey-to-yellow fibrinous base with an erythematous halo and recur with variable frequency, often causing significant discomfort, difficulty in eating, speaking, and reducing quality of life [2]. Epidemiological evidence suggests a global prevalence ranging from 5 % to 25 %, with onset often during adolescence or early adulthood and a predilection for females. Despite extensive study, the precise etiology remains uncertain. However, a multifactorial origin is widely accepted, involving a complex interplay between genetic predisposition, immune dysregulation, local trauma, microvascular disturbances, nutritional deficiencies, hormonal fluctuations, stress, and microbial influences. Morphologically, RAS lesions demonstrate superficial mucosal necrosis with inflammatory infiltrate dominated by neutrophils, lymphocytes, and macrophages. Pathogenesis is believed to stem from an aberrant T-cell mediated immune response targeting altered epithelial cells or local antigens, leading to cycles of ulceration and healing [3, 4].

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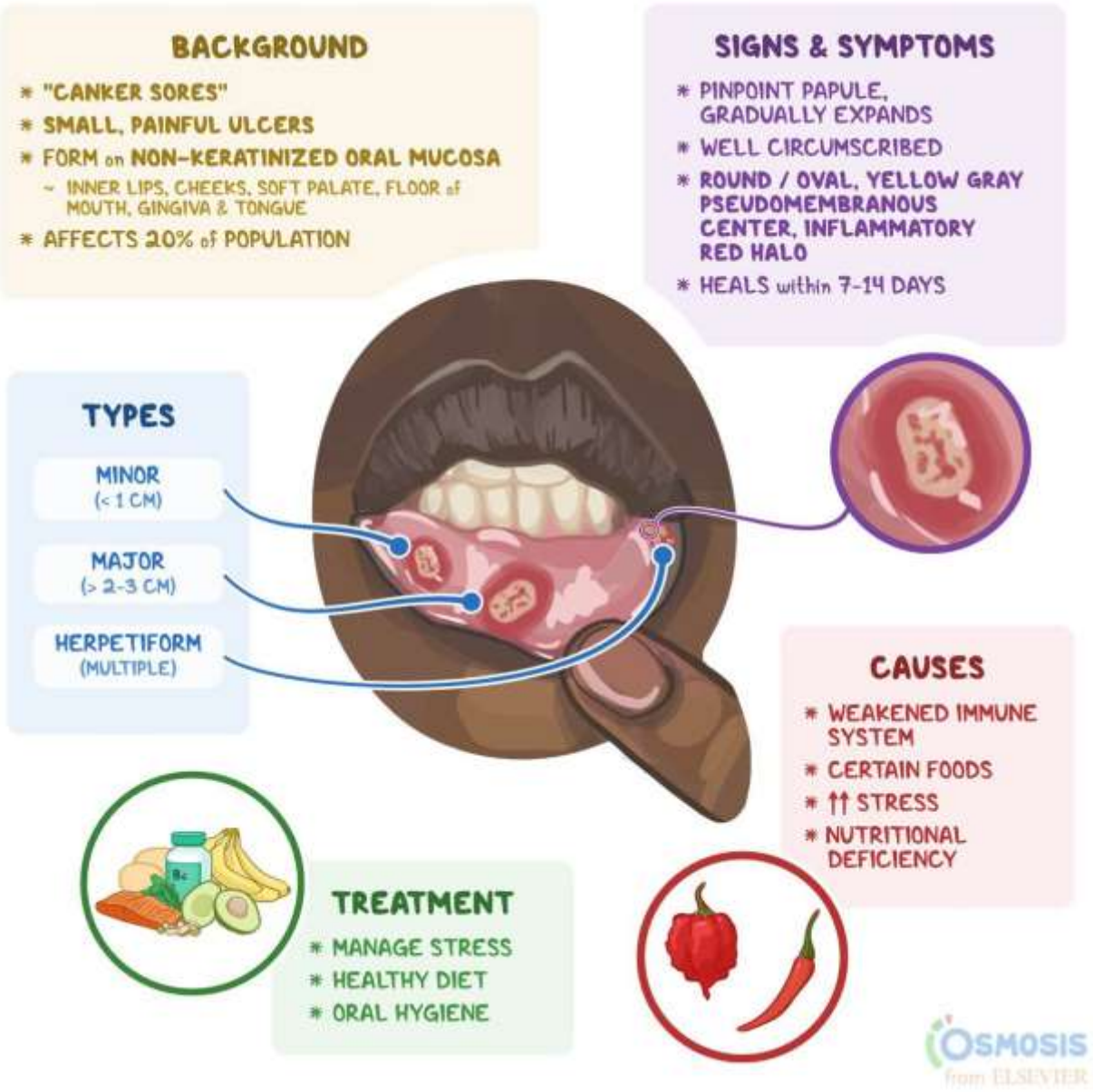

Figure 1: Located in the oral cavity APHTHOUS STOMATITIS.

Contemporary management strategies focus on symptom relief, reduction in ulcer frequency, and promotion of healing. These include topical corticosteroids, analgesics, antimicrobial mouth rinses, laser therapy, systemic immunomodulators, and in some cases, nutritional supplementation [5]. This comprehensive review aims to elucidate RAS etiology, morphological characteristics, patho--genic mechanisms, and modern therapeutic approaches to improve patient outcomes and guide future research.

Literature Review: Review of the extant literature on recurrent aphthous stomatitis indicates that genetic predisposition plays a significant role, with familial clustering and associations with HLA-B12, HLA-DR2, HLA-DR7 alleles documented in various studies [6]. Immune mechanisms are central to the disease process; numerous investigations highlight elevated levels of proinflammatory cytokines—such as interleukin-2, interleukin-6, and tumor necrosis factor-alpha—in the saliva and serum of affected individuals. Mucosal biopsy studies consistently show superficial ulceration with a perivascular inflammatory infiltrate, characterized initially by neutrophils and followed by lymphocytes and macrophages, signifying a localized immune response. Nutritional factors have also been implicated: deficiencies in iron, vitamin B12, folate, and zinc appear more frequently in RAS patients [7], and supplementation trials have demonstrated varied rates of ulcer reduction. Psychological stress has been linked to both onset and exacerbation of aphthous ulcers, with stress biomarkers correlating with clinical severity.

The role of microbial factors remains controversial; some studies detect higher prevalence of Helicobacter pylori or streptococcal species in RAS patients, though causality remains unproven. Hormonal influences have been inferred from menstrual cycle-related flares in many female patients [8]. Treatment research has ranged from topical therapies, such as 0.1 % triamcinolone acetonide and amlexanox paste, to systemic agents like colchicine, pentoxifylline, and low-dose corticosteroids. Laser therapy has emerged as a promising modality, demonstrating faster pain relief and lesion healing in randomized controlled trials [9]. However, sustained long-term remission remains elusive. Overall, the literature underscores RAS as a multifactorial condition requiring individualized therapeutic approaches that target symptom management, immune modulation, and potential nutritional correction.

Materials and Methods: This review synthesizes data from clinical, histopathological, immunological, and therapeutic studies on RAS published in peer-reviewed journals over the past two decades. Research articles were identified using electronic databases, focusing on recurrent aphthous stomatitis, oral ulcer morphology, immune biomarkers, nutritional assessments, and treatment efficacy. Inclusion criteria comprised original articles, clinical trials, cohort studies, case-control analyses, and meta-analyses involving human participants. Exclusion criteria included non-English language papers, case reports with fewer than ten subjects, or studies lacking clear methodology. Histological data were derived from biopsy-based investigations that documented mucosal architecture, cellular composition, and immune marker expression via immunohistochemistry or flow cytometry. Immunological studies measuring cytokine profiles utilized enzyme-linked immunosorbent assays, multiplex bead assays, or RT-PCR. Nutritional assessments included serum or saliva measurements of iron indices, vitamins B12 and folate, zinc, and associated supplementation trials. Treatment modalities evaluated span topical agents (e.g., corticosteroid ointments, analgesics), systemic therapies (e.g., colchicine, pentoxifylline, corticosteroids, thalidomide), low-level laser therapy, and adjunctive interventions.

Outcomes measured included ulcer count, size, duration, pain intensity using visual analogue scale, and recurrence frequency. Statistical analyses from source studies comprised t-tests, ANOVA, chi-square, Kaplan-Meier survival curves, and logistic regression as appropriate for controlled versus observational data. In randomized controlled trials reviewed, blinding and allocation methods were appraised. Literature findings were categorized into etiological factors, morphological features, immunopathogenesis, and treatment outcomes for clearer comparison. Wherever possible, quantitative data were extracted to summarize effectiveness and safety. Limitations of each methodology—such as small sample sizes, heterogeneity in diagnostic criteria, and variable follow-up durations—were noted to contextualize findings. By integrating these diverse methodologies, this review aims to present a cohesive understanding of RAS's multifaceted nature and contemporary management strategies.

Results:

Etiological Factors: Genetic investigations consistently reveal familial aggregation of RAS, with up to 40 % of patients reporting a first-degree relative with similar lesions. Specific HLA associations—such as HLA-B12, HLA-DR2, and HLA-DR7—have been overrepresented in RAS cohorts compared with healthy controls. Twin studies show higher concordance among monozygotic twins, supporting a genetic predisposition. However, genetic factors alone do not fully explain disease occurrence, underscoring a multifactorial etiology.

Morphological Findings: Histopathological examinations across multiple studies consistently describe superficial epithelial necrosis, central fibrin deposition, and a dense subepithelial inflammatory infiltrate. Early lesions demonstrate neutrophil predominance, while later lesions are dominated by T lymphocytes (both CD4+ and CD8+), macrophages, and occasional eosinophils. No specific pathogen has been consistently identified within lesions, supporting a sterile inflammatory response. Microvascular alterations, including perivascular edema and endothelial activation, have also been documented, suggesting localized vascular contributions to ulcer development.

Immunopathogenesis Immunological profiling reveals elevated salivary and serum levels of IL-2, IL-6, IL-8, TNF-alpha, and IFN-gamma in RAS patients compared to controls. Flow cytometry studies indicate increased CD8+/CD4+ ratio within lesions. These data support a T cell–mediated cytotoxic response as a central mechanism. Additionally, regulatory T cell (Treg) deficiencies and altered Th17/Treg balance have been observed, indicating impaired immune regulation. Neutrophil activation markers and reactive oxygen species levels are elevated in early ulceration stages. Mast cells have been detected near ulcer margins, releasing histamine and proteases that may exacerbate local tissue damage.

Nutritional and Hormonal Influences: Controlled studies demonstrate statistically significant correlations between RAS occurrence and deficiencies in serum ferritin, vitamin B12, folate, and zinc. Supplementation trials indicate that correcting deficiencies reduces ulcer frequency and severity in approximately 60 % of participants, suggesting a modifiable risk component. Hormonal influences are inferred from cyclical patterns in women, though direct hormonal assays yield inconsistent results; estrogen and progesterone fluctuations are hypothesized to modulate mucosal immunity.

Psychological and Microbial Factors: Psychological stress scales are elevated in RAS patients, and stress management interventions correlate with modest reductions in flare frequency. The role of microbial agents remains inconclusive; occasional

detection of Helicobacter pylori DNA in oral swabs lacks reproducibility, and no consistent microbial pathogen has been definitively linked to RAS pathogenesis.

Treatment Outcomes: Topical corticosteroids, including triamcinolone acetonide and clobetasol propionate, produce significant symptomatic relief within 24–48 hours and accelerate healing by 2–3 days in approximately 70–80 % of cases. Topical analgesics and antimicrobial rinses, such as chlorhexidine and benzydamine, aid in pain control but exert minimal effects on healing time. Low-level laser therapy has shown rapid pain reduction and shorter ulcer duration by approximately 40 % compared with placebo. Systemic agents like colchicine and pentoxifylline have been evaluated in moderate-to-severe recurrent RAS with reductions in recurrence frequency by 50–60 %, though gastrointestinal side effects are common. Systemic corticosteroids are used in severe cases to achieve rapid remission but are limited by systemic adverse effects. Newer immunomodulators (e.g., thalidomide, levamisole) demonstrate efficacy in refractory cases but raise safety concerns.

A summary of treatment efficacy:

Treatment Modality Symptom Relief Healing Time Reduction Recurrence Frequency Reduction

Topical corticosteroids High Moderate–High Low–Moderate

Low-level laser therapy High High Moderate

Systemic colchicine/pentoxifylline Moderate Moderate Moderate–High

Systemic corticosteroids High High Moderate

Nutritional supplementation Variable (~60 %) N/A Moderate

Overall, a multimodal treatment strategy incorporating topical agents, immunomodulation, nutritional correction, and behavioral interventions appears most effective in managing RAS and improving patient quality of life.

Discussion: Recurrent aphthous stomatitis (RAS) manifests as episodic ulceration of the oral mucosa with complex etiology encompassing genetic, immunologic, nutritional, hormonal, psychological, and possibly microbial aspects. Familial aggregation and specific HLA associations, such as HLA-B12, HLA-DR2, and HLA-DR7, underscore a genetic susceptibility that likely facilitates disease onset when combined with triggering factors [10, 11]. However, genetic predisposition alone does not guarantee disease expression, signaling the importance of environmental and immunological contributors. Morphologically, RAS lesions are characterized by superficial mucosal necrosis and inflammatory infiltrate predominantly composed of neutrophils and T lymphocytes. This pattern suggests a cascade of initial innate immune activation followed by adaptive immune response. The absence of a consistent infectious agent reinforces the concept of a sterile [12], immune-mediated ulcerative process. Histopathological evaluation often reveals endothelial activation and perivascular edema, indicating localized microvascular involvement that may exacerbate tissue breakdown and prolong healing.

Immunologically, elevated levels of Th1 cytokines (IL-2, IFN-gamma) and Th17-associated mediators (IL-6, IL-8, TNF-alpha) suggest that both cell-mediated immunity and neutrophil-chemoattraction play pivotal roles [13]. The observed imbalance between effector T cells (CD8+) and regulatory T cells contributes to loss of immune tolerance, facilitating recurrent mucosal damage. Neutrophil activation with enhanced reactive oxygen species generation may further drive tissue injury. These immunological findings not only enhance our understanding of RAS pathophysiology but also offer potential targets for novel therapeutic interventions, such as biologics or small-molecule inhibitors [14].

Nutritional deficiencies—particularly iron, vitamin B12, folate, and zinc—appear to be significant co-factors in RAS development and severity. These nutrients are essential for epithelial regeneration, immune regulation, and mucosal integrity. Clinical trials demonstrating decreased ulcer frequency after supplementation argue for routine screening of RAS patients for deficiencies and corrective interventions where indicated [15]. Hormonal influences, while less studied, may modulate immune responses in the oral mucosa and help explain gender disparities and cyclical patterns of ulcer recurrence.

Psychological stress has a bidirectional relationship with RAS: stress can induce ulcers via neuroimmunomodulation [16], while painful lesions amplify psychological distress. Research supports integration of behavioral interventions such as relaxation training, cognitive-behavioral therapy, or mindfulness as adjunctive therapies to medical treatment. The therapeutic landscape for RAS includes topical corticosteroids as first-line agents due to their anti-inflammatory potency and favorable safety profile. Triamcinolone and clobetasol pastes provide rapid pain relief and shortened healing duration [17]. For patients with frequent or severe episodes, low-level laser therapy offers non-pharmacological relief, with studies demonstrating significant acceleration of healing and reduction of pain scores. Lasers may modulate inflammation and stimulate cellular repair mechanisms without systemic side effects.

Systemic agents—colchicine, pentoxifylline, corticosteroids, and immunomodulators like thalidomide and levamisole—are reserved for cases refractory to topical or laser therapies. Colchicine and pentoxifylline reduce recurrence rates, though gastrointestinal tolerability may limit use. Systemic corticosteroids deliver swift therapeutic effect but their long-term side effects warrant caution [18]. Agents like thalidomide are effective but carry risks of teratogenicity and neuropathy, necessitating stringent monitoring.

Recent exploratory studies have evaluated emerging biologics targeting specific immune pathways. For example, anti-TNF agents have anecdotal benefits in recalcitrant cases, but high cost and infection risk limit adoption. Similarly, topical immunomodulators—such as tacrolimus ointment—show promise but require further evaluation of safety, particularly regarding malignancy risk with long-term use [19].

An integrated treatment algorithm may begin with topical corticosteroids for mild to moderate disease. In patients with nutritional deficiencies, supplementation should follow confirmation of deficiency. Weak evidence supports prophylactic low-dose colchicine or pentoxifylline in patients with frequent recurrences. Low-level laser therapy can be offered as an adjunct or alternative for individuals contraindicated for steroids or who prefer non-drug options. Referral to a specialist may be warranted for lesions unresponsive after three months or when systemic agents are considered [20, 21]. Despite advances, several challenges remain. Diagnostic standardization is lacking: RAS is often diagnosed clinically without universally agreed classification criteria. Heterogeneity in clinical trial designs and outcome measures complicates evidence synthesis. Further understanding of molecular immunopathogenesis may identify biomarkers for disease severity, recurrence risk, and treatment response. Development of targeted biologic therapies based on immune profiling remains a potential future direction [22].

Long-term follow-up studies are needed to evaluate sustainability of remission and safety. Specifically, trials comparing outcomes between topical-only regimens, systemic immunomodulators, and combined multimodal therapies would inform best practice. Studies exploring microbiome profiles in the oral cavity might help clarify the ambiguous role of microbial agents in RAS. In summary, RAS is a multifaceted disease requiring personalized treatment plans that integrate topical anti-inflammatory agents [23], nutritional management, stress reduction, and immunomodulatory therapies when necessary. A holistic approach improves patient quality of life and may reduce lesion frequency. Future research should focus on biomarker-guided therapy and novel targeted agents to achieve sustained remission with minimal adverse effects.

Conclusion: Recurrent aphthous stomatitis is a common, multifactorial ulcerative condition of the oral mucosa characterized by painful, recurrent ulcers that disrupt daily life. Genetic predisposition, immune dysregulation—characterized by elevated Th1 and Th17 cytokines and altered T effector/regulator balance—nutritional deficiencies, hormonal fluctuations, psychological stress, and possibly microbial components collectively drive disease expression. Histopathologically, RAS is defined by superficial mucosal necrosis and inflammatory infiltrate without evidence of infectious agents, confirming its immune-mediated etiology. Modern management strategies are centered on rapid symptom relief, lesion healing, and reduction in recurrence frequency. Topical corticosteroids remain first-line due to their efficacy and safety, while low-level laser therapy provides a non-pharmacologic alternative that accelerates healing. Systemic agents such as colchicine, pentoxifylline, and corticosteroids are reserved for moderate-to-severe or refractory cases, while emerging biologic and immunomodulatory therapies hold promise for future targeted interventions. Addressing modifiable factors—such as nutritional deficiencies and psychological stress—through supplementation and behavioral interventions enhances treatment outcomes. Despite progress in understanding RAS, challenges persist due to heterogeneity in clinical presentation, diagnostic criteria, and trial methodology. Future research should aim to standardize diagnostic definitions, validate immunobiomarkers, and explore targeted therapies with favorable safety profiles. Interdisciplinary collaboration involving dental practitioners, immunologists, and nutritionists will be essential to developing comprehensive guidelines. Ultimately, a personalized, multimodal treatment paradigm offers the best pathway to improving quality of life for patients suffering from recurrent aphthous stomatitis.

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