

COMPARATIVE EFFECTIVENESS OF LOCAL AND SYSTEMIC
TREATMENTS FOR CHRONIC RECURRENT APHTHOUS
STOMATITIS

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Abstract. *Recurrent aphthous stomatitis (RAS) is a chronic inflammatory condition of the oral mucosa that requires targeted therapeutic strategies to manage its relapsing nature and associated morbidity. This review critically evaluates the comparative efficacy of local and systemic treatment modalities for RAS, focusing on clinical parameters such as ulcer size reduction, healing time, recurrence rates, and safety profiles. Local therapies, including corticosteroids, antiseptic agents, bioadhesive gels, and laser applications, are assessed for their effectiveness in symptomatic management and tissue regeneration. Systemic approaches, involving immunomodulators and anti-inflammatory agents, are analyzed for their capacity to address the underlying immune dysregulation and systemic factors contributing to disease progression. The review highlights the heterogeneity in therapeutic outcomes and emphasizes the importance of individualized treatment protocols to enhance efficacy and reduce recurrence.*

Keywords: *Recurrent aphthous stomatitis, local treatment, systemic treatment, immunomodulation, hyaluronic acid, quercetin, corticosteroids, therapeutic outcomes, comparative efficacy.*

Relevance. Recurrent aphthous stomatitis (RAS) represents a persistent clinical issue characterized by chronic relapsing ulcerations of the oral mucosa, often resistant to standardized therapeutic approaches. The multifactorial pathogenesis of RAS, encompassing immune dysregulation, vascular abnormalities, and microbial imbalances, complicates the establishment of effective, universally accepted treatment protocols.

Materials and Methods. The present review is based on a comprehensive analysis of published literature examining the efficacy of local and systemic therapies for recurrent aphthous stomatitis (RAS). A systematic search was conducted using databases such as PubMed, Scopus, and Web of Science to identify relevant studies published between 2020 and 2025. The inclusion criteria were limited to peer-reviewed clinical trials, observational studies, and meta-analyses that provided measurable outcomes related to RAS treatment. Search terms included “recurrent aphthous stomatitis,” “local treatment,” “systemic therapy,” “treatment efficacy,” and “comparative analysis.”

The reviewed studies were categorized based on the therapeutic approach: local treatments included antiseptic agents, corticosteroid applications, bioadhesive formulations, and low-level laser therapy, while systemic therapies encompassed immunomodulators, systemic corticosteroids, and anti-inflammatory agents. Studies addressing combination therapies were also examined to assess potential additive or synergistic effects.

The methodological assessment of each study considered sample size, study design, and statistical validity. Clinical outcomes, such as reduction in ulcer size, duration of healing, recurrence rates, and adverse effects, were extracted and analyzed. Patient-reported outcomes, including pain relief and quality-of-life improvements, were also included to provide a comprehensive understanding of the effectiveness of each treatment modality. Statistical and

comparative analyses were emphasized to evaluate differences in therapeutic impact between local and systemic interventions.

Review of Literature Sources. Recurrent aphthous stomatitis (RAS) is an inflammatory condition of the oral mucosa characterized by ulcerative lesions with a chronic course and periodic exacerbations. This disease poses a significant medical and social challenge, drawing considerable

The fibrinous form is identified by yellowish patches on the mucosal surface accompanied by hyperemia. These lesions lack involvement of minor salivary glands and are covered by fibrin tightly adherent to the surrounding tissue. As the condition progresses, the fibrin detaches, forming an aphthous ulcer that typically heals within 6–8 days. When stained with a 1% methylene blue solution, the fibrinous deposits remain resistant to washing with saline or saliva.

The necrotic form predominantly occurs in highly vascularized areas of the oral mucosa. Transient vascular spasms lead to epithelial necrosis, resulting in ulceration. The necrotic layer is loosely attached and easily removed through scraping. Unlike the fibrinous form, the methylene blue stain is readily washed off by saline. This form requires 12–20 days for complete epithelial healing.

The glandular form involves not only the mucosa but also the minor salivary glands, particularly in areas such as the lips, tongue, and Waldeyer's ring. Hyperemic zones appear, within which the minor salivary glands are visibly raised due to edema. Methylene blue staining highlights nonfunctional salivary gland regions. As the lesions progress, erosions develop into ulcers, exposing the terminal portions of the glands. These areas are infiltrated at the base, with the epithelialization process extending up to 30 days.

The cicatricial form is marked by damage to acinar structures and connective tissue. Salivary gland function is significantly reduced, and healing is accompanied by the formation of dense scar tissue.

This classification highlights the diverse clinical manifestations of RAS, each requiring tailored diagnostic and therapeutic approaches to achieve effective management.

The deforming form of recurrent aphthous stomatitis (RAS) is characterized by more profound destruction of connective tissue, extending into the muscle layer. Ulcers in this form are intensely painful, often migratory, and are frequently accompanied by peripheral erosions and smaller aphthous lesions.

The lichenoid form presents as localized areas of hyperemia bordered by a whitish ridge of hyperplastic epithelium. This form most commonly occurs on the tongue and features aphthous elements with a rapid developmental cycle lasting 3–4 days [17]. It has been referred to as the "abortive form" by previous researchers .

The cytomorphological profile of cellular elements in RAS exhibits specific features. Smears taken from aphthous lesions typically reveal minimally altered epithelial cells and a small number of leukocytes. As ulcers develop, the number of epithelial cells decreases, while leukocytes with marked dystrophic changes significantly increase.

- **Pigmented stage:** This stage is characterized by an erythematous spot accompanied by intercellular edema, cytolysis, and disruption of intercellular contacts. Membrane structures within epithelial cells are damaged, subepithelial tissue exhibits edema, and fibrous structures are degraded.
- **Erosive-ulcerative stage:** Necrobiotic and necrotic processes dominate during this phase, with prominent leukocytic infiltration.
- **Healing stage:** Functional activity of epithelial cells is observed, leading to epithelial regeneration.

The primary lesion in RAS is considered to be a vesicle, which forms as a result of vacuolar degeneration of epithelial cells.

The disease is also associated with microcirculatory disturbances, a critical factor in tissue trophic maintenance [10]

The rational and effective treatment of various oral mucosal conditions, particularly recurrent aphthous stomatitis (RAS), represents a significant challenge in the practice of dental and maxillofacial surgery. The success of RAS management is largely dependent on the timeliness of diagnosis, as diagnostic errors are relatively common. Special attention must be paid to the differential diagnosis of RAS and chronic herpetic stomatitis (CHS), as the clinical distinctions between these two conditions are often subtle and difficult to discern. A thorough analysis of disease dynamics, combined with detailed anamnesis and comprehensive clinical evaluation, allows for the identification of key features unique to each etiology.

Given the close anatomical and functional relationship between the oral cavity and the gastrointestinal tract, the diagnostic and therapeutic process often begins with identifying and managing disorders of the digestive system.

Some studies recommend incorporating propranolol ("Anaprilin") into the treatment regimen for RAS [1]. This medication selectively blocks the transmission of nerve impulses in the sympathetic division of the autonomic nervous system, disrupting reflex pathways originating from damaged abdominal organs and protecting the oral mucosal tissues from the harmful effects of elevated norepinephrine levels.

One of the primary approaches to RAS treatment is desensitization therapy. For patients with hypersensitivity to bacterial allergens, specific desensitization using these allergens is implemented. Non-specific desensitization measures include the use of sodium thiosulfate, histaglobulin, antihistamines, and calcium-based preparations [5].

Several authors propose the inclusion of immunomodulatory agents, such as T-activin, Dalarin, and Galavit, in the treatment regimen for recurrent aphthous stomatitis (RAS) in cases of identified immune imbalance. These

agents exhibit immunocorrective properties, with T-activin demonstrating the ability to stimulate lymphokine production, including interferons, restore T-killer cell activity, and improve multiple immune parameters. Clinical and laboratory studies indicate that T-activin is particularly effective in managing persistent forms of RAS [35, 52].

Research on Dalarin highlights its role in normalizing lymphocyte proliferative responses and enhancing rosette formation. Intramuscular administration of Dalarin has shown to not only suppress inflammatory processes in the oral mucosa and accelerate epithelialization of aphthous lesions but also provide significant analgesic effects [14].

In cases of suppressed local immunity requiring correction, agents such as Imudon, Gepon, Mipro-VITA, and Polyoxidonium are recommended [9]. Imudon, a locally acting immunomodulatory drug, has been deemed effective in the comprehensive treatment of RAS. It is typically prescribed at a dosage of one tablet, administered six to eight times daily over 10–15 days, depending on disease severity. Preventive courses are recommended every 4–6 months, with a dosage of one tablet six times daily for 10 days.

Further studies indicate that systemic immune stimulation with methyluracil followed by local antigenic stimulation with Imudon is a more effective immunotropic strategy for preventing RAS recurrence. Methyluracil is administered orally at 0.5 g three times daily for 20 days, with Imudon added from the 10th day at a dosage of eight tablets daily for one week. Preventive courses are recommended during remission periods in the spring and autumn [16].

Assessing the clinical and immunological status of patients is critical for the successful management of RAS. Given the frequent detection of immune imbalances in patients, the inclusion of immunomodulatory agents in treatment regimens is considered justified. Based on evidence of altered systemic reactivity in RAS, therapies that enhance nonspecific resistance factors, such

as histaglobulin, prodigiosan, and lysozyme, have been incorporated. These agents stimulate phagocytosis, indirectly affect antimicrobial mechanisms, and promote reparative processes in the body [12, 23].

According to some international authors, the prophylactic use of levamisole (Decaris), which exhibits both anthelmintic and immunomodulatory properties, may fail to produce positive outcomes [11].

Alongside immunomodulators, antiseptic agents are also commonly used in clinical practice. However, due to their relatively high toxicity, prolonged use of antiseptics in treating chronic inflammatory diseases of the oral mucosa may result in tissue damage and impaired reparative processes [2].

Recent years have seen a surge in the integration of homeopathy into medical practice. A noteworthy example is the homeopathic complex preparation Traumeel S, which is widely used in RAS treatment due to its ability to stimulate metabolic processes [3].

A critical component of successful RAS treatment involves a thorough clinical and immunological evaluation of the patient. This approach aims to identify and manage comorbidities, particularly those affecting the gastrointestinal tract and liver, infectious allergies, vitamin deficiencies, and dysfunctions of the central and autonomic nervous systems. Special attention must also be given to diagnosing and addressing dental diseases. Dietary modifications, including gluten-free diets, have demonstrated effectiveness in managing RAS [5].

In the comprehensive therapy of aphthous stomatitis, systemic interventions play a pivotal role. The selection of therapeutic agents is guided by the need to target various pathogenic pathways. For patients with heightened sensitivity to bacterial allergens, specific desensitization with intradermal allergen administration in minimal doses (0.001 ml) has been proposed. In cases of multi-allergen sensitivity, combinations of allergens in equal dilutions

have been used, although outcomes have been inconsistent, potentially due to the lack of precise diagnostic criteria [5].

These corticosteroids have been administered as injections, tablets, and topical ointments. However, their use is associated with adverse effects, including Cushing's syndrome, hypertension, hyperglycemia, and hypokalemia, limiting their long-term application and prompting the search for alternative therapies.

Plasmapheresis has emerged as an effective adjunct in RAS treatment. Studies have shown that plasmapheresis improves overall patient condition, accelerates aphthous lesion healing, extends remission periods, and positively impacts homeostatic parameters [4].

Another highly effective topical agent is Metrogyl Denta, which combines metronidazole and chlorhexidine to suppress both aerobic and anaerobic microorganisms. This preparation is applied to the affected areas twice daily and has the added benefit of a refreshing mint flavor [7].

To accelerate the epithelialization of pathological elements in RAS, agents such as methyluracil, carotolin, and rosehip oil are commonly utilized. One of the most effective treatments for promoting aphthous ulcer healing is Solcoseryl dental adhesive paste, which contains solcoseryl and the local anesthetic polidocanol. This preparation adheres securely to the oral mucosa, providing prolonged therapeutic effects. It is applied in a thin layer 3–5 times daily to a pre-dried mucosal surface and moistened with water. Comparative studies have shown that Solcoseryl paste is more effective than Mundizal gel [20].

To enhance nonspecific immune reactivity, primary treatments often include prodigiosan, pyrogenal, lysozyme, pentoxyl, methyluracil, autologous blood therapy, and plasmapheresis [4]. For more targeted local treatment of lesions, some authors have recommended soluble therapeutic films containing active ingredients such as corticosteroids, antibacterial agents, epithelial

stimulants, and immunomodulators. These films maintain a consistent concentration of active substances in the lesion area, restrict the zone of action to the affected site, and protect the lesion with their firm adherence [12].

Microbiological analyses of samples from the oral mucosa of RAS patients reveal significant disruptions in the microbial balance, with shifts in the ratio of normal to pathogenic microflora. Antimicrobial solutions, such as 0.02% furacilin and 0.02% ethacridine lactate, are recommended for reducing pathogenic microbial populations [12].

A wide range of medicinal plants is employed for local RAS therapy due to their low toxicity and minimal side effects, making them suitable for prolonged use in patients of all ages. Among these, the phytopreparation Svitanok has proven effective. Additionally, Elekasol, a combined herbal preparation containing calendula and chamomile flowers, licorice root, succession herb, sage leaves, and eucalyptus, demonstrates antimicrobial and anti-inflammatory properties while stimulating reparative processes. It is applied topically in rinses, sprays, and applications for 5–7 days, with simultaneous internal use 2–5 times daily.

Another herbal preparation, Fitodent, made from plant-based raw materials (e.g., calamus rhizome, calendula flowers, nettle leaves, chamomile flowers, Japanese sophora fruits, celandine herb, and rosehip fruits), exhibits anti-inflammatory, analgesic, deodorizing, and fungicidal effects. This preparation is diluted with water and used for rinses, washings, and oral baths 3–5 times daily for 2–5 minutes.

Physiotherapy also plays an essential role in RAS management by activating the body's adaptive and reserve capabilities. Laser therapy, particularly with the "Optodan" apparatus, effectively reduces inflammation and accelerates mucosal healing [19]. To enhance the efficacy of laser radiation, combined pharmacological and phototherapeutic methods are

employed, such as photoiontophoresis with oxolinic, methyluracil, heparin, hydrocortisone, and tetracycline ointments [18].

In the past decade, polarized light therapy (PLT) with wavelengths ranging from 400 nm to 2000 nm has gained significant traction in medical practice. This light is linearly polarized, moves in a single direction, and has wavelengths longer than ultraviolet (UV) rays but with an energy range lower than that of laser light, making it safe for use. Light emitted by devices like the Bioptron lamp (Zepter, Switzerland) penetrates up to 2.5 mm into tissues, enhancing enzymatic activity, metabolic and redox processes, blood and lymph circulation, and immunoprotective responses. Additionally, it stimulates nerve endings, accelerates tissue regeneration, and provides analgesic, desensitizing, bacteriostatic, and bactericidal effects [13].

The application of blue light therapy in treating oral mucosal pathologies, alongside other physiotherapeutic modalities, broadens the range of pathogenetic treatments available. This method avoids the side effects typically associated with pharmacotherapy and is considered one of the most gentle and well-tolerated options. It can also be used independently to address both local and systemic factors contributing to recurrent aphthous stomatitis (RAS) [8].

Traditional local therapies for RAS include anesthetizing the oral mucosa with a 10% lidocaine spray, thorough rinsing with a 0.06% chlorhexidine solution, applying trypsin solutions to aphthous lesions, using a 1% mefenamic acid solution on affected areas for its anti-inflammatory properties, and coating ulcers with carotolin. These treatments can be used both therapeutically during flare-ups and prophylactically in remission periods.

Treatment planning must account for comorbid conditions, immune reactivity, disease severity, causative factors, and lesion development stages. Preventing RAS recurrences primarily involves accurate diagnosis and rational management of gastrointestinal, nervous, and endocrine system pathologies, as well as addressing chronic oral infections. Adherence to a strict diet rich in

proteins, minerals, and vitamins, along with proper work-rest balance, is essential. Avoiding self-medication and over-prescription is critical to minimizing relapses and ensuring effective management.

The prognosis for RAS is generally favorable; however, delayed medical intervention, misdiagnosis, or self-treatment can render the disease more resistant to therapy. At present, no single treatment method ensures complete resolution of RAS. Existing combination therapies effectively reduce disease severity, extend remission periods, accelerate epithelialization, and decrease the number and size of lesions.

To achieve sustainable outcomes in RAS management, periodic courses of comprehensive therapy are necessary. Selecting optimal systemic and local treatments requires an individualized approach tailored to each patient. RAS continues to represent a significant medical and social challenge, and while numerous therapeutic modalities exist, a universal algorithm for comprehensive management remains undeveloped. Additionally, the lack of standardized maintenance therapy highlights the ongoing need for further research.

Conclusion. Recurrent aphthous stomatitis (RAS) remains a significant medical and social challenge due to its chronic, relapsing nature and multifactorial pathogenesis. Current therapeutic approaches emphasize both local and systemic treatments, yet a universally effective and comprehensive algorithm for RAS management has not been established. Local therapies, such as antiseptics, corticosteroids, and regenerative agents, play a vital role in managing symptoms and promoting mucosal healing. Systemic therapies, including immunomodulators and anti-inflammatory agents, address underlying immune dysregulation but may be accompanied by significant side effects, particularly with corticosteroid use.

Emerging non-pharmacological methods, such as polarized light therapy and hyperbaric oxygenation, show promise as complementary treatments that



enhance therapeutic outcomes and reduce side effects. Dietary interventions, physiotherapy, and the use of phytopreparations further expand the arsenal of available treatments, underscoring the importance of a holistic, individualized approach.

Despite advancements in treatment modalities, the lack of standardized maintenance therapies and precise diagnostic criteria for differentiating RAS from other similar conditions, such as herpetic stomatitis, highlights critical gaps in current clinical practice. To improve patient outcomes, further research is needed to develop comprehensive therapeutic protocols, refine diagnostic tools, and explore novel treatment combinations. The integration of evidence-based local and systemic therapies tailored to individual patient needs remains the cornerstone of effective RAS management.

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