BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 9

DOI:10.58240/1829006X-2025.21.9-523

ORIGINAL RESEARCH

EVOLVING TREATMENT STRATEGIES FOR RECURRENT APHTHOUS ULCERS: A COMPREHENSIVE REVIEW

Anlin Anto[1], Jayanth Kumar Vadivel[2], Ashir KR[3], Anuna Laila Mathew[4]

[1]Senior Lecturer Oral Medicine and Radiology Pushpagiri College of dental sciences, Research scholar Saveetha Dental college

[2]Professor Oral Medicine and Radiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India

[3]Professor Oral Medicine, and Radiology, KMCT Dental College, Kozhikode

[4]Professor and HOD department of Oral medicine and Radiology Pushpagiri college of dental sciences[4]

[*]**Corresponding author:** Anlin Anto [1]Senior Lecturer Oral Medicine and Radiology Pushpagiri College of dental sciences, Research scholar Saveetha Dental college annanto161@gmail.com

Received: *Sep.22 2025;* ***Accepted:*** *Oct. 18, 2025;* ***Published:*** *Oct 23,2025*

Background: Recurrent aphthous stomatitis (RAS) is the most prevalent chronic ulcerative condition of the oral mucosa, affecting 5–25% of the population. Despite its benign and self-limiting nature, recurrent painful lesions significantly impair speech, mastication, and quality of life. The precise etiology remains elusive, with multifactorial influences including genetic predisposition, immune dysregulation, nutritional deficiencies, stress, and systemic associations.

Aim: This review synthesizes current evidence on the clinical features, diagnostic considerations, and therapeutic strategies for RAS, with emphasis on evolving modalities and a stepwise management algorithm.

Methods:A comprehensive literature search was conducted across PubMed, Scopus, and ScienceDirect databases, focusing on articles published between 1996 and 2025. Key domains included epidemiology, clinical classification, diagnostic pathways, conventional treatments, novel therapies, and integrative approaches. A total of 50 relevant studies were included in this narrative review.

Results: Conventional management remains centered on topical corticosteroids, antiseptics, and analgesics, while systemic agents are reserved for severe or refractory cases. Adjunctive therapies such as hyaluronic acid, probiotics, zinc and vitamin B12 supplementation, and herbal formulations (e.g., curcumin, aloe vera, *Myrtus communis*) demonstrate promising outcomes. Low-level laser therapy and advanced drug delivery systems, including bioadhesive films and dissolvable microneedles, represent significant innovations. Artificial intelligence–based diagnostic tools and integrative medicine approaches provide additional frontiers. Based on current evidence, a stepwise management algorithm is proposed to guide clinical decision-making.

Conclusion:RAS continues to pose diagnostic and therapeutic challenges due to its multifactorial etiology and recurrent nature. While conventional therapies remain essential, the incorporation of novel pharmacological, technological, and holistic strategies holds promise for personalized, effective, and patient-friendly care.

***Keywords*:** Recurrent aphthous stomatitis, oral ulcers, corticosteroids, laser therapy, curcumin, management algorithm

INTRODUCTION

Recurrent aphthous stomatitis (RAS), also known as recurrent aphthous ulcers, is one of the most common chronic inflammatory conditions of the oral mucosa. Its prevalence is reported to range from 5% to 25% in the general population, with onset often during childhood or adolescence and a tendency for recurrent episodes throughout life [1]. Clinically, RAS manifests as painful, round or oval ulcers with erythematous borders and a fibrinous pseudomembranous base, predominantly affecting non-keratinized mucosal surfaces such as the labial and buccal mucosa, ventral tongue, and soft palate [2,3]. Despite being self-limiting, the recurrent and painful nature of the lesions often interferes with speech, mastication, swallowing, and overall quality of life, making it a significant burden for patients [4]. The precise etiology of RAS remains

elusive. A multifactorial pathogenesis has been proposed, implicating genetic predisposition, nutritional deficiencies, psychological stress, hormonal fluctuations, microbial agents, and immune dysregulation [3,5]. Immunological studies suggest that T-cell–mediated mechanisms and elevated pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), contribute to mucosal injury and delayed healing[6,7]. Moreover, systemic associations have been reported, with RAS presenting as a manifestation of hematological deficiencies, gastrointestinal diseases, and autoimmune conditions such as Behçet's syndrome [2,6].

RAS is generally classified into three clinical variants: minor, major, and herpetiform ulcers. Minor aphthae account for approximately 70–85% of cases, are usually less than 1 cm in diameter, and heal within 7–14 days without scarring. Major aphthae are larger, deeper, and may persist for weeks, often leaving scars. Herpetiform ulcers, although less common, present as multiple small (1–3 mm) lesions that may coalesce into larger irregular ulcerations [3,6,8].

The therapeutic approach to RAS is primarily symptomatic. Conventional management strategies include topical corticosteroids, anesthetics, antimicrobial rinses, and analgesics, which aim to reduce pain and accelerate healing. Systemic therapy, including corticosteroids, colchicine, levamisole, and thalidomide, may be reserved for severe or refractory cases, although their long-term use is limited by adverse effects [4–6,9]. In recent years, novel treatment modalities such as bioadhesive drug delivery systems, amlexanox, rebamipide, and herbal formulations like *Myrtus communis* have gained interest for their anti-inflammatory, immunomodulatory, and wound-healing properties [1,7,8].Given the high prevalence, multifactorial etiology, and lack of a definitive cure, RAS continues to pose diagnostic and therapeutic challenges. This review aims to provide a comprehensive overview of conventional and emerging treatment strategies, highlight evolving drug delivery systems, and propose a stepwise approach to management.

Methodological Background

This review was conducted as a narrative synthesis of the available literature on recurrent aphthous stomatitis (RAS). A comprehensive search of PubMed, Scopus, and ScienceDirect databases was performed for articles published between 2000 and 2025. Search terms included *"recurrent aphthous stomatitis," "oral ulcers," "etiology," "classification," "diagnosis," "treatment,"* *"management,"* and *"therapy."*

All relevant publication types, including epidemiological studies, clinical trials, case reports, systematic reviews, and narrative reviews, were considered. Articles were included if they addressed one or more of the following domains:

1. Epidemiology and clinical features of RAS.
2. Diagnostic approach and differential diagnosis.
3. Conventional and emerging therapeutic strategies.
4. Integrative and holistic management perspectives.

From the initial pool, 50 peer-reviewed studies were identified and included. Data were synthesized thematically to highlight clinical presentation, diagnostic pathways, treatment modalities, and evolving management algorithms. The emphasis was on summarizing established practices while integrating emerging evidence for future perspectives.

2. Clinical Presentation and Classification

Recurrent aphthous stomatitis (RAS) typically presents as painful, round or oval ulcers with well-defined erythematous margins and a fibrinous pseudomembranous base, primarily affecting non-keratinized mucosal sites such as the buccal and labial mucosa, ventral tongue, floor of mouth, and soft palate [10,11]. Patients often report burning or tingling sensations in the prodromal stage, followed by ulcer development within 24–48 hours. These lesions significantly impair eating, swallowing, and speaking, thereby reducing quality of life [12].

The clinical course of RAS is characterized by recurrent episodes with variable severity and duration. Although lesions are self-limiting, recurrence rates remain high, with many patients experiencing multiple episodes annually[10]. Several precipitating factors, such as psychological stress, local trauma, hormonal fluctuations, and nutritional deficiencies, have been implicated in exacerbating the frequency and severity of outbreaks [12,15]. (Table 1)

2.1 Classification

The classification of RAS is essential for guiding diagnosis and treatment planning. Based on clinical features, three principal subtypes are recognized: minor, major, and herpetiform ulcers [11,15].

- Minor RAS (Mikulicz ulcers): Representing 70–85% of cases, these are small (<1 cm), shallow ulcers that heal within 7–14 days without scarring [11].
- Major RAS (Sutton ulcers): Larger (>1 cm), deeper, and more painful lesions that persist for

weeks and often heal with scarring; they account for about 10–15% of cases [10,13].

- Herpetiform ulcers: Characterized by multiple, pinhead-sized ulcers (1–3 mm) that may coalesce into larger irregular lesions; they occur in 5–10% of patients and are more common in females [11,15].

Recent advances in diagnostic imaging and artificial intelligence tools have further enhanced classification accuracy. Deep learning algorithms applied to intraoral photographic datasets have demonstrated promising results in the automated detection and differentiation of RAS subtypes, potentially aiding clinicians in early diagnosis and monitoring [14].

Table 1. Clinical Classification of Recurrent Aphthous Stomatitis

Type	Size	Number	Duration	Healing/Scarring	Prevalence
Minor (Mikulicz)	<1 cm	1–5 lesions	7–14 days	Heals without scarring	70–85% of cases [11,15]
Major (Sutton)	>1 cm	1–10 lesions	2–6 weeks	Heals with scarring	10–15% of cases [10,13]
Herpetiform	1–3 mm (coalescing)	10–100 small ulcers	7–14 days (may persist longer if coalescent)	Rare scarring, more common in females	5–10% of cases [11,15]

2.2 Associated Systemic Conditions

While most cases are idiopathic, RAS may also serve as a mucocutaneous manifestation of systemic disorders, particularly Behçet's disease. This multisystem vasculitis is characterized by recurrent oral and genital ulcers, ocular inflammation, and other systemic features, making the differentiation of idiopathic RAS from Behçet's syndrome clinically crucial [13].

3.3 Contemporary Perspectives

Recent literature emphasizes the need for a multidisciplinary approach, particularly when RAS-like lesions are persistent or refractory to conventional treatment. Del Mazo et al. (2023) highlighted the importance of distinguishing idiopathic RAS from ulcerations associated with systemic inflammatory or autoimmune diseases to prevent misdiagnosis and delayed treatment [18]. Moreover, consensus guidelines for dental practitioners stress the importance of structured algorithms for diagnosis and referral, ensuring timely differentiation between benign recurrent aphthae and more serious mucocutaneous disorders [17]. (Table 2) The diagnostic process should follow a structured pathway, as summarized in Figure 1 [16–20].

Table 2. Differential Diagnosis of Recurrent Aphthous Stomatitis

Condition	Distinguishing Features	References
Herpes simplex virus (HSV)	Vesicular lesions, keratinized mucosa involvement, viral cytopathic effect on biopsy	16,17
Behçet's disease	Oral + genital ulcers, ocular inflammation, skin vasculitis	19
Lichen planus	Reticular white striae, chronic erosive lesions, biopsy confirms lichenoid inflammation	16,20
Pemphigoid / Pemphigus	Multiple widespread bullous or erosive lesions, positive immunofluorescence	16
Lupus erythematosus	Oral ulcers with systemic features (malar rash, ANA positivity)	16,20

Inflammatory bowel disease (IBD)	Oral ulcers associated with GI symptoms (bloody diarrhea, abdominal pain)	19,20
Nutritional deficiencies (iron, B12, folate)	Glossitis, angular cheilitis, systemic anemia features	20
Oral squamous cell carcinoma	Persistent non-healing ulcer, indurated margins, histological evidence of malignancy	16

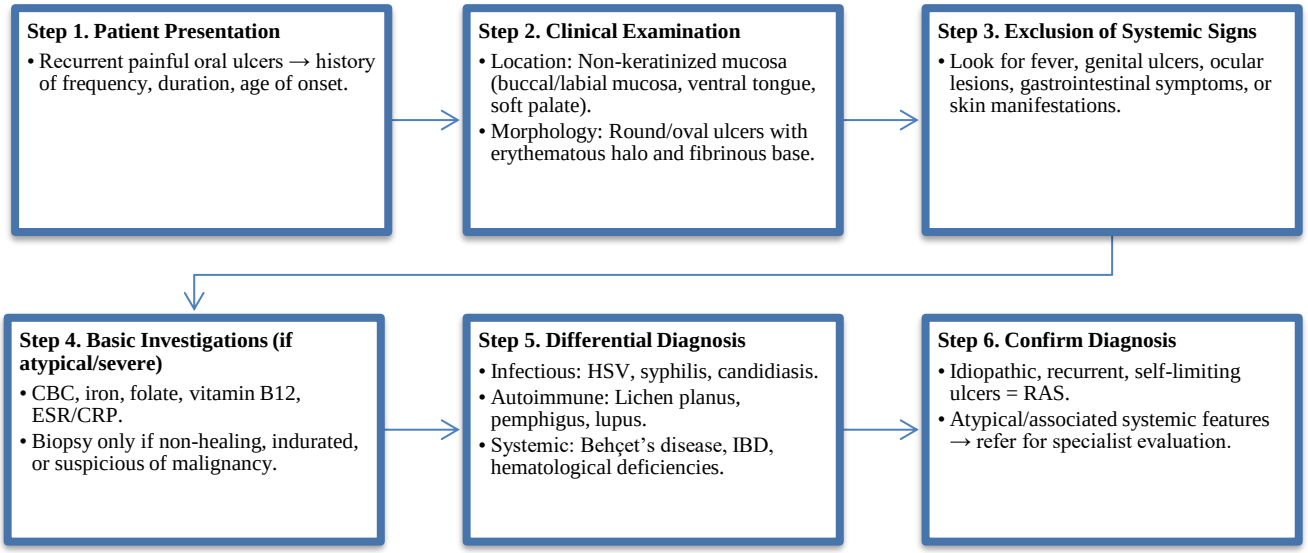

Figure 1. Diagnostic Algorithm for Recurrent Aphthous Stomatitis (RAS)

4. Goals of Therapy

The management of recurrent aphthous stomatitis (RAS) is primarily symptomatic, as no definitive cure exists. Treatment strategies therefore aim to achieve a balance between immediate relief and long-term disease control. The primary therapeutic goals are to reduce pain, accelerate ulcer healing, and restore normal oral functions such as eating, speaking, and swallowing [22,23]. Beyond symptomatic relief, secondary objectives include decreasing the frequency and severity of recurrences, minimizing treatment-related side effects, and improving the patient's overall quality of life [23,24].

Several therapeutic modalities have been studied with these goals in mind. Laser therapy has emerged as an effective tool, providing rapid pain relief and shorter healing time, with some evidence suggesting longer recurrence-free intervals compared to conventional medication [22,27]. Systematic reviews of clinical interventions emphasize that while topical corticosteroids remain the mainstay for acute management, newer interventions such as mucoadhesive films, probiotics, and natural product–based formulations are showing promising outcomes [23].Bioadhesive drug delivery systems, such as chitosan-containing oral films, improve drug retention at the mucosal site and enhance therapeutic effectiveness while reducing systemic exposure [24]. Similarly, the adjunctive use of oral probiotics has been investigated for its ability to restore microbial balance and potentially reduce the recurrence of ulcers [25]. Natural compounds like curcumin, particularly in nanomicelle formulations, have also shown significant anti-inflammatory and wound-healing effects, with better patient acceptance and safety profiles [26]. Taken together, these findings suggest that while the central goals of RAS therapy remain pain reduction and healing acceleration, modern approaches are increasingly focused on targeted, biocompatible, and patient-friendly strategies. The integration of conventional and innovative therapies may thus represent the optimal pathway toward individualized care.

5. Conventional and Established Treatment Strategies

The therapeutic management of recurrent aphthous stomatitis (RAS) has traditionally been focused on symptomatic relief, recurrence prevention, and minimizing complications. Although no curative therapy exists, conventional modalities remain the backbone of treatment, particularly for mild to moderate disease. These include lifestyle modifications, topical agents, and systemic drugs for severe or refractory cases [27,28,36].

5.1 Non-Pharmacological and Dietary Measures

Lifestyle and dietary modifications are frequently recommended as first-line measures. Patients are advised to avoid local irritants such as spicy or acidic foods, sodium lauryl sulfate–containing toothpaste, and mechanical trauma from dental appliances. Psychological stress management has also been shown to reduce the frequency and severity of ulcer outbreaks [28,35]. Nutritional supplementation, particularly with zinc and vitamins, has demonstrated efficacy in decreasing recurrence rates, highlighting the role of systemic deficiencies in disease pathogenesis [33].

5.2 First-Line Topical Therapies

Topical therapy remains the mainstay of treatment for the majority of RAS patients. Corticosteroids (e.g., triamcinolone acetonide, clobetasol propionate) are the most commonly used agents, significantly reducing inflammation and accelerating healing [28,29]. In addition, hyaluronic acid has emerged as an effective adjunct, enhancing mucosal healing and improving patient comfort, as confirmed by systematic reviews [30].

Recent studies have also explored newer topical approaches. Cannabidiol (0.1%) demonstrated analgesic and anti-inflammatory effects in a randomized controlled trial, suggesting its potential as a novel agent in RAS management [31]. Curcumin-based topical gels have been reported to provide comparable efficacy to corticosteroids, with favorable safety profiles [32]. Similarly, plant-derived and herbal therapies—including aloe vera, licorice extract, and propolis—have shown promising results in improving healing rates and reducing pain [34].

5.3 Systemic Therapies for Severe Disease

For patients with major aphthae or recurrent, debilitating disease, systemic medications are warranted. Short courses of systemic corticosteroids may be used for acute control, but their long-term application is limited due to adverse effects [28]. Other immunomodulators, including colchicine, thalidomide, and levamisole, have been reported as effective in refractory cases, though toxicity and regulatory restrictions limit their routine use [28,29,36].

Nutritional supplementation represents a relatively safe systemic option. Zinc and vitamin B12 supplementation have demonstrated benefits in reducing recurrence and severity [33]. These findings suggest that systemic correction of nutritional deficiencies may serve as an adjunctive strategy in patients with frequent relapses.

5.4 Adjunctive Modalities

Laser therapy has gained popularity as an alternative to pharmacological approaches. Clinical evidence suggests that diode and Nd:YAG lasers provide rapid pain relief, shorten healing time, and may prolong remission periods compared to conventional medication [27]. Similarly, drug delivery innovations, such as mucoadhesive systems and nanocarriers, have been proposed to enhance drug bioavailability and prolong mucosal contact [29,35]. (Table 3)

Table 3. Conventional and Established Treatment Strategies for RAS

Category	Examples	Mechanism/Action	Clinical Evidence
Lifestyle & dietary measures	Stress reduction, SLS-free toothpaste, zinc, vitamins	Reduce triggering factors, correct deficiencies	28,33,35
Topical corticosteroids	Triamcinolone, clobetasol, fluocinonide	Anti-inflammatory, accelerate healing	28,29
Topical adjuncts	Hyaluronic acid, anesthetic gels, antimicrobials	Promote healing, reduce discomfort	28,30
Herbal/natural agents	Aloe vera, licorice, curcumin gel, propolis	Anti-inflammatory, wound healing	32,34
Novel topical agents	Cannabidiol 0.1% gel, nanocarrier-based curcumin	Analgesic, anti-inflammatory, targeted release	31,32,35
Systemic therapy	Corticosteroids, colchicine, thalidomide, zinc, vitamin B12	Suppress immune response, correct deficiencies	28,33,36
Physical therapy	Diode laser, Nd:YAG laser	Pain relief, faster healing, prolonged remission	27,29

6. Evolving and Modern Therapeutic Approaches

The last decade has witnessed significant advancements in the management of recurrent aphthous stomatitis (RAS), driven by the need for safer, more effective, and patient-centered therapies. Unlike conventional approaches that primarily focus on symptom relief, modern strategies integrate biotechnological innovations, natural compounds, advanced drug delivery systems, and digital diagnostic tools [37,38].

6.1 Natural and Synthetic Drug Innovations

A wide range of novel pharmacological agents has been evaluated for RAS. Natural compounds such as curcuminoids, long recognized for their anti-inflammatory and antioxidant properties, have shown promising roles in modulating chronic oral mucosal inflammation[42]. Systematic reviews also highlight the effectiveness of curcumin-based nanoformulations, which enhance bioavailability and patient compliance [37]. Vitamin supplementation, particularly vitamin B12, has emerged as a key adjunct in selected patient populations, with evidence supporting its role in reducing recurrence frequency and severity [40].

Synthetic drugs with targeted mechanisms, such as immunomodulators and molecular adjuvants, are being studied as alternatives to corticosteroids, aiming to minimize systemic side effects while maintaining efficacy [37,43].

6.2 Biophysical and Device-Based Therapies

Low-level laser therapy (LLLT) continues to gain prominence in the management of RAS. A systematic review and meta-analysis confirmed its effectiveness in reducing pain intensity and accelerating healing time, with minimal adverse effects [39]. LLLT provides an attractive alternative or adjunct to pharmacological approaches, especially in patients who are unresponsive or intolerant to systemic agents.

6.3 Digital and Artificial Intelligence (AI) Approaches

Recent advances in artificial intelligence have introduced deep learning and neural network models for the automated diagnosis and classification of RAS from clinical oral images [38]. These tools can assist clinicians in differentiating RAS from other ulcerative conditions, enhance early detection, and support longitudinal monitoring of disease progression. Integrating AI-driven diagnostics with therapeutic algorithms may pave the way for personalized treatment protocols.

6.4 Holistic and Integrative Perspectives

Modern research has increasingly explored the overlap between chronic inflammation, systemic diseases, and traditional healing systems. Insights from Ayurvedic sciences emphasize holistic management and systems biology approaches, which may provide complementary strategies in chronic RAS management [44]. Similarly, cross-disciplinary work in periodontology and oral mucosal immunology points toward the potential of shared adjuvant drug strategies to address mucosal inflammation across oral diseases [43].

Furthermore, the association of RAS with systemic inflammatory conditions, such as Behçet's disease, underscores the importance of tailored systemic therapies that address underlying pathophysiological mechanisms [41]. (Table 4)

Table 4. Emerging and Innovative Therapies for RAS

Therapy/Approach	Mechanism/Target	Clinical Evidence	Reference(s)
Curcuminoids (nanoformulations)	Anti-inflammatory, antioxidant, improved bioavailability	Reduced recurrence, safe, well tolerated	37,42
Vitamin B12 supplementation	Corrects deficiency, modulates mucosal immunity	Effective in select patients	40
Novel synthetic agents/adjuvants	Immunomodulation, targeted drug action	Under investigation, adjunctive potential	37,43
Low-level laser therapy (LLLT)	Pain reduction, accelerated wound healing	Meta-analysis supports efficacy	39
AI/Deep learning models	Automated diagnosis, subtype classification	High accuracy in image-based studies	38
Ayurvedic/holistic approaches	Systems biology, integrative inflammation control	Emerging, complementary evidence	44

Link with Behçet's disease	Systemic vasculitis, shared pathogenesis	Requires tailored systemic therapy	[41]

7. A Stepwise Approach to Management Algorithm

Management of recurrent aphthous stomatitis (RAS) should follow a stepwise algorithm tailored to severity, recurrence pattern, and systemic risk factors. The primary objectives are pain relief, accelerated healing, recurrence reduction, and improved quality of life.

Step 1: Initial Assessment. Diagnosis is based on history, lesion morphology, and recurrence pattern. Common triggers such as trauma, stress, or dietary irritants should be identified. Laboratory screening for deficiencies (iron, folate, vitamin B12) is indicated in atypical or persistent cases [45,49].

Step 2: Patient Education and Prevention. Counseling focuses on avoiding irritants, adopting stress control measures, and correcting nutritional deficiencies. Zinc and vitamin B12 supplementation are recommended where relevant [33,40].

Step 3: First-Line Therapy (Topical). Topical corticosteroids (triamcinolone, clobetasol) remain the standard of care [28,29]. Adjuncts such as hyaluronic acid gels, anesthetic rinses, and bioadhesive films enhance mucosal healing [30,24]. Natural products including curcumin gels, aloe vera, and propolis provide safe alternatives [32,34,42].

Step 4: Second-Line Therapy. For recurrent or painful lesions, low-level laser therapy offers rapid pain relief and shorter healing time [22,27,39]. Novel delivery systems—such as mucoadhesive films, nanocarriers, and microneedles—improve local drug retention [24,29,50].

Step 5: Systemic Therapy. Severe or refractory RAS may require short systemic corticosteroids. Immunomodulators like colchicine, thalidomide, or roflumilast are reserved for resistant cases, with multidisciplinary evaluation for systemic associations such as Behçet's or IBD [41,46–48].

Step 6: Monitoring and Long-Term Care. Patients should undergo regular review to assess recurrence, efficacy, and adverse effects. Management should be individualized, incorporating lifestyle, systemic, and integrative approaches [44].

Figure 2. Stepwise management algorithm for recurrent aphthous stomatitis (RAS). The algorithm outlines sequential management beginning with clinical assessment and identification of triggers, followed by preventive measures and first-line topical therapies. Adjunctive and novel approaches, including laser therapy and advanced delivery systems, are considered when initial measures are insufficient. Systemic therapy is reserved for severe or refractory cases, with emphasis on multidisciplinary referral in patients with associated systemic diseases. Long-term care requires monitoring, individualized combination strategies, and incorporation of integrative approaches.

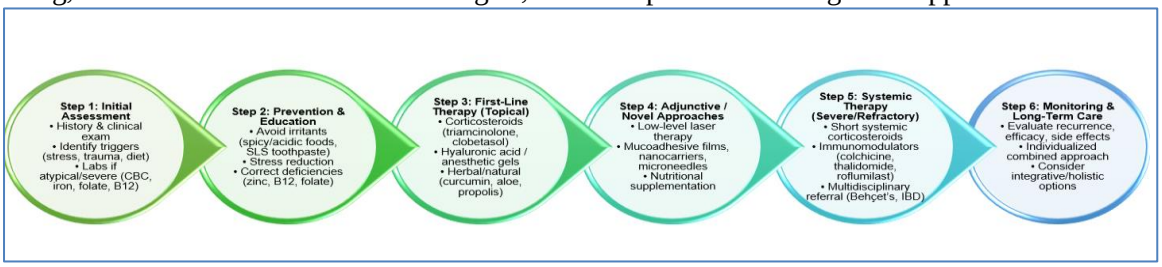

Figure 2. Stepwise management algorithm for recurrent aphthous stomatitis (RAS)

8. DISCUSSION AND FUTURE PERSPECTIVES

Recurrent aphthous stomatitis (RAS) remains a multifactorial and enigmatic condition, with unclear etiology and diverse clinical presentations. Despite significant advances in topical and systemic treatments, no single therapy achieves permanent remission. This review highlights how management has evolved from empiric corticosteroid use to targeted and innovative strategies that integrate modern drug delivery systems, natural compounds, and device-based approaches.

From a conventional standpoint, topical corticosteroids and antiseptic rinses remain the most effective first-line therapies for acute relief. However, concerns over recurrence, resistance, and side effects drive the exploration of alternatives such as hyaluronic acid gels, probiotics, and curcumin-based formulations. The role of nutritional supplementation, especially zinc and vitamin B12, has been supported in systematic reviews, emphasizing the need for routine screening of hematological and micronutrient status in RAS patients [45,49]. Emerging therapies reflect a paradigm shift toward personalization and precision

medicine. Dissolvable microneedles and nanocarriers offer site-specific delivery with minimal systemic exposure [50]. Laser therapy has gained robust evidence for its ability to reduce pain and shorten healing time [39]. Biologics and systemic agents such as thalidomide and roflumilast show promise in severe cases, though long-term safety data remain limited [47,48]. At a broader level, the recognition of RAS as a potential marker of systemic disease underscores the importance of multidisciplinary care. Associations with Behçet's disease, inflammatory bowel disease, and autoimmune disorders highlight the need for clinicians to view RAS not only as an isolated mucosal disorder but also as a window to systemic pathology [41,46].

Future perspectives emphasize the integration of artificial intelligence (AI) in diagnostic pathways, enabling earlier detection and improved differentiation from other ulcerative disorders [38]. Additionally, cross-disciplinary approaches drawing from periodontology, immunology, and traditional medicine provide fresh insights into inflammation and mucosal healing [42–44]. With growing interest in personalized, holistic, and technology-driven care, future management will likely adopt a hybrid model combining conventional, innovative, and systemic strategies tailored to individual patient profiles.

9. CONCLUSION

Recurrent aphthous stomatitis is a common yet challenging oral mucosal disorder that significantly impairs quality of life. While the precise etiology remains elusive, advances in diagnostics and therapeutics have broadened the management landscape. Conventional treatments, particularly topical corticosteroids, remain central to care, but their limitations necessitate adjunctive and innovative approaches. Recent developments—such as laser therapy, bioadhesive films, curcumin formulations, probiotics, and microneedle-based delivery systems—offer promising results, particularly when integrated with preventive and nutritional measures. For severe or refractory cases, systemic agents such as thalidomide and novel immunomodulators provide options, though careful patient selection is essential.

Moving forward, stepwise management algorithms incorporating diagnostic markers, individualized risk factors, and evolving therapies will be critical. The integration of AI-driven diagnostics and holistic, multidisciplinary perspectives may further enhance patient outcomes. Ultimately, the goal is to transition from symptom suppression toward sustained remission and improved quality of life.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Conflicts Of Interests

None

Author Contribution

Funding

None

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