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REVIEW ARTICLE **OPEN ACCESS**

Erosive and Bullous Oral Lesions: Diagnostic Challenges and Clinical Algorithms

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Abstract:

Introduction: Diagnosing oral ulcers is challenging due to their nonspecific symptoms and variable microscopic/histopathological features, which lead to low sensitivity in immunological tests and significant diagnostic delays. Therefore, we aimed to review the existing literature to present current approaches to this problem.

Methods: We conducted a non-systematic review of existing guidelines for the differential diagnosis of oral lesions and published diagnostic algorithms using the PubMed database. The search strategy included the keywords as follows: “oral lichen planus” combined with “diagnosis”, “differential diagnosis”, “guidelines”, “AI”, “artificial intelligence”, or “machine learning”.

Results: There are few official guidelines for the diagnosis of oral lichen planus, and most of the existing ones are either too general, focused primarily on treatment, lacking decision-making algorithms, or limited to specific conditions.

Discussion: In the absence of comprehensive recommendations, independent authors have proposed diagnostic algorithms; however, these have been considered either insufficiently detailed or overly cautious. Neural networks demonstrate high accuracy in classifying oral lesions, but there are issues with overfitting and the limited dissemination of tools developed by individual research teams. These tools are classified as medical devices and require proper authorization. Therefore, we developed our own diagnostic “roadmap”, integrating patient history, histopathological evaluation, and immunochemical testing, along with a practical summary tailored for general practitioners.

Conclusion: Until comprehensive official guidelines addressing the diagnosis of oral lesions are introduced and AI-based tools are approved and commercialized, diagnostic schemes, such as the one presented here, may serve as helpful adjuncts for physicians.

Keywords: Differential diagnosis, Oral cavity, Blisters, Erosions, Ulcers, Lesions.

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1. INTRODUCTION

Diagnosing oral ulcers poses many challenges for clinicians because they can represent a wide array of pathological entities from inflammatory/reactive, infectious, immune-mediated, systemic, and malignant neoplastic processes (Table **1**) [1-22]. The same microscopic features may be present in different medical conditions, and the histopathological characteristics may vary along a spectrum, possibly influenced by factors, such as the disease's activity level at the time of the biopsy, recent treatments, the clinical presentation, and the specific anatomical location. Particular importance lies in the site of biopsy material collection; it should be taken not from the lesion itself, but from the periphery around a fresh blister. In consequence, the sensitivity of immunological tests aimed at detecting targets specific to diseases within this group is limited, although it remains the gold standard. It is critically important, therefore, for the diagnostic process to be carried out efficiently, avoiding exposing the patient to both unnecessary delays and unnecessary procedures.

Table 1. Possible causes of lesions in the oral cavity, along with basic information regarding their diagnosis and therapy.

Lichen planus [1-3]	
Surface Shape, size, pattern Colour	Atrophic, erosive, bullous, papular, plaque-like Irregular, large, reticular, symmetrically distributed bilaterally White (72.6%), red (27.4%)
Typical location in the oral cavity	Tongue, gingiva, buccal mucosa, lips. Typically, the bilaterality of distribution, especially involving the buccal mucosa and gingiva
Other locations	Skin and/or genital mucosa
Other features	Lesions, painful or not; desquamative gingivitis
Healing	Slow, with scarring
Histopathology	Dense subepithelial lymphocytic band on hematoxylin-eosin staining; keratotic epithelium with basilar degeneration; presence of Civatte bodies (degenerating keratinocytes); a sawtooth appearance of the rete ridges may be present
Immunology	Globular deposits of several immunoglobulins, especially IgM and complement or fibrinogen, mixed with apoptotic keratinocytes (Civatte bodies) in DIF (sensitivity: 75%)
Mucous membrane pemphigoid [1-5]	
Surface Shape, size, pattern Colour	Tense serous or hemorrhagic bullae that easily rupture; erosions or ulcers; patches or widespread erythema Irregular Yellowish slough surrounded by an erythematous halo
Typical location in the oral cavity	Gingiva (most often, permanently exclusive sites), buccal mucosa, lips, palate, tongue
Other locations	Ocular mucosa (65%), nasal mucosa (20-40%), pharyngeal (20%), laryngeal (5-10%), esophageal (5-15%), anogenital region (20%), skin (head, neck, upper torso)
Other features	Lesions are painful; Nikolsky's sign is positive only on the gingiva; dysphagia, foetor, bleeding, and/or peeling of the mucosa; relapsing and remitting course; desquamative gingivitis
Healing	With or without scaring
Histopathology	Subepithelial blistering with an infiltrate consisting of eosinophils, lymphocytes, and/or neutrophils
Immunology	IgG (97%), C3 (78%), IgA (27%), and IgM (12%) against targeting bullous antigens 1 and 2, laminin 332, 311, type VII collagen, α6 β4-integrin, and non-identified basal membrane zone antigens in epithelial basement membrane zones/hemidesmosomes (BP180 and BP230). Continuous, linear deposition of IgG, C3, less commonly, IgA, along the basement membrane zone. IIF is usually negative. Salt-split skin discriminates between pemphigoid subtypes: in classic MMP, autoantibodies against BP180 or BP230 bind to the epithelial side, and in other subtypes, antibodies against p200, laminin-332, and type VII collagen bind to the dermal side
Pemphigus vulgaris [1-4]	
Surface Shape, size, pattern Colour	Erosions rather than blistering; fluid-filled, thin-walled blisters that easily rupture (intact blisters are less likely to persist and remain intact due to their thin roofs secondary to acantholysis) Irregular; localized or diffuse with a tendency to spread; ill-defined, with fragile margins Ragged whitish margin; yellowish slough may develop as infection supervenes
Typical location in the oral cavity	Any

(Table 1) contd.....

Other locations	Pharyngeal and nasal mucosa, rarely genital, ocular, laryngeal, and esophageal mucosa. Flaccid bulla on the skin (face, scalp, and upper chest) that easily rupture, leaving erosions and crusts. Nikolsky's sign on the gingiva and skin
Other features	Pain; desquamative gingivitis in 25% cases; secondary infection of oral erosive or ulcerative lesions is actually quite uncommon
Healing	Slow, without scarring
Histopathology	Intra-epithelial blistering; acantholysis with rounding up of keratinocytes, and a suprabasilar cleft. Basal keratinocytes attached to the basement membrane, and lining the blister floor (tombstone appearance); eosinophils infiltrating the epidermis
Immunology	Autoantibodies against desmoglein 1 and 3, sometimes also against E-cadherin, desmoplakin, and alpha-9 acetylcholine receptor. In DIF, the binding of IgG to the epithelial cell surface. Deposition pattern, smooth or granular. Characteristic net-like, honeycomb-like intercellular pattern. Complement C3 deposits in 61% of cases
Lupus [2, 4, 6]	
Surface Shape, size, pattern Colour	Different morphological features ranging from plaques to erythema and ulcerations Shallow, poorly defined; symmetrical distribution; 'sun-ray'-like lesions No red border; white, feathery border or striated white component
Typical location in the oral cavity	Gingiva, buccal mucosa, lips, and palate
Other locations	Multiorgan involvement (joints, skin, muscles, eyes, lungs, central nervous system, and kidneys); butterfly malar rash
Other features	Xerostomia; burning sensation
Healing	With scarring
Histopathology	Lymphocytic infiltrate and necroptotic keratinocytes at the dermo-epidermal junction
Immunology	Antinuclear (anti-DNA) antibodies in serum
Lichenoid lesion (hypersensitivity reaction) [3, 7]	
Surface Shape, size, pattern Colour	Atrophic/erosive patches, plaque-like appearance, ulceration Striae (reticular, linear, or annular) White or red
Typical location in the oral cavity	Localized to the site in contact with the allergenic material, usually unilaterally
Other locations	Skin (rarely)
Other features	Indistinguishable from oral lichen planus
Healing	Within 1-2 weeks
Histopathology	Inflammatory infiltrate deep in the corium (as opposed to a band-like distribution in lichen planus), a focal perivascular infiltrate, formation of germinal centres made of chronic inflammatory cells, and a mixed cellular infiltrate with plasma cells in the connective tissue. In contrast to OLP, lack of increased vascularity, a lack of increased PAS-positive basement membrane thickness, and a lack of increased numbers of granulated mast cells in areas of basement membrane degeneration
Immunology	Patch testing; in drug-related lesions, "string of pearls" or basal cell cytoplasmic autoantibody reaction seen in direct immunofluorescence, in contrast to OLP
Erythema multiforme [1, 2]	
Surface Shape, size, pattern Colour	Superficial erosions Red
Typical location in the oral cavity	Tongue, buccal mucosa
Other locations	Lips; skin pathognomonic targets or iris lesions on the extremities; an influenza-like prodrome (moderate fever, malaise, sore throat)
Other features	Pain; crusting (particularly of the lips) being pathognomonic
Healing	7-10 days

(Table 1) contd.....

Histopathology	liquefaction degeneration of the basal epidermal cells, necrotic keratinocytes, exocytosis of lymphocytes, intense lymphocytic infiltration at the basement membrane, papillary oedema, vascular dilatation and perivascular mononuclear infiltrate
Immunology	Not specific
Behçet's disease [2, 4]	
Surface Shape, size, pattern Colour	Evolution into ulcers From a few millimeters to centimeters Red
Typical location in the oral cavity	Tongue, buccal mucosa, palate
Other locations	Genital ulcers and eye inflammation
Other features	Pain; cyclic presentation
Healing	-
Histopathology	Lack of typical features, diagnosis by exclusion
Immunology	Lack of typical features, diagnosis by exclusion
Pyostomatitis vegetans [8]	
Surface Shape, size, pattern Colour	Abscess and pustular lesions; "snail track" ulcers Miliary White or yellow contents
Typical location in the oral cavity	Gingiva, buccal mucosa, lips
Other locations	-
Other features	Erythematous and oedematous mucosal bases
Healing	-
Histopathology	Intraepithelial and subepithelial microabscesses, infiltration of neutrophils and eosinophils, hyperkeratosis, acanthosis, and focal acantholysis
Immunology	ANCA (sensitivity 56%, specificity 89%)
Recurrent ulcerative colitis [9-12]	
Surface Shape, size, pattern Colour	Shallow ulcers with clear boundaries Rounded or ovoid with red and slightly raised margins Yellow or white pseudomembranes
Typical location in the oral cavity	Gingiva, buccal mucosa, lips, palate
Other locations	Other non-masticatory mucosa
Other features	Pain; non-specific gingivitis
Healing	-
Histopathology	Not specific
Immunology	ANCA (sensitivity 56%, specificity 89%)
Crohn's disease [1-3, 9-12]	
Surface Shape, size, pattern Colour	Ulceration resembling aphthous sores Deep, linear ulcers in the grooves, with hyperplastic edges, firm or boggy to palpation
Typical location in the oral cavity	Gingiva, buccal mucosa, lips, palate
Other locations	Retromolar regions; swelling of the lips, cheeks, and face
Other features	Buccal mucosa exhibiting a 'cobblestoned' appearance; swelling in the labial and buccal mucosa; angular cheilitis; 'stag horning' appearance noticed in the floor of the mouth; xerostomia
Healing	2-6 weeks
Histopathology	non-caseous granulomatous inflammation

(Table 1) contd.....

Immunology	-
Herpes simplex virus [3, 13]	
Surface Shape, size, pattern Colour	Blisters that eventually rupture lead to ulcerations Small, numerous, encircled by an erythematous halo. In hard cases, diffuse large whitish ulceration consisting of an erythematous halo surrounded by a scalloped border Yellowish pseudo-membrane
Typical location in the oral cavity	Gingiva, lips
Other locations	Headache, malaise, pharyngitis, fever, cervical lymphadenopathy in primary infection
Other features	Pain
Healing	5-7 days, without scarring
Histopathology	Acantholysis with solitary keratinocytes within the blister cavity; margination of the nuclear chromatin, multinucleation, and nuclear inclusions in keratinocytes; viral inclusions (small pink deposits with a clear halo within the nucleus)
Immunology	-
Herpangina [4]	
Surface Shape, size, pattern Colour	Blisters and ulcers Small Red
Typical location in the oral cavity	Palate
Other locations	Posterior part of the mouth (palate and throat)
Other features	Sore throat, fever
Healing	7 days
Histopathology	Not specific
Immunology	Not specific
Hand, feet, and mouth disease (Coxsackie virus infection) [14-16]	
Surface Shape, size, pattern Colour	Blisters Multiple Red
Typical location in the oral cavity	Any
Other locations	Erythematous macular rash, mainly on palms and feet
Other features	Pain; rarely muscles involved (Bornholm disease), meningitis
Healing	7-10 days
Histopathology	Similar to erythema multiforme (lymphocytic infiltrate, epidermal necrosis, spongiosis, ballooning, reticular alteration); a) necrotic keratinocytes are emphasized in the upper third of the epidermis, b) neutrophils are more numerous
Immunology	Not specific
Necrotizing ulcerative gingivitis [17]	
Surface Shape, size, pattern Colour	Punched-out, crater-like ulceration Red
Typical location in the oral cavity	Gingiva
Other locations	Lymphadenopathy, general malaise
Other features	Pain; interproximal necrosis, bleeding, soreness, fetid odor, pseudomembrane formation
Healing	Lack of spontaneous healing, but it can be expected in a few days if proper treatment is administered
Histopathology	Four layers: a bacterial area of fibrous mesh composed of epithelial cells, leukocytes, a variety of bacterial cells, a neutrophil-rich zone, a necrotic zone, and spirochete infiltration
Immunology	-

(Table 1) contd.....

Primary syphilis [2, 14, 18, 19]	
Surface Shape, size, pattern Colour	Single solitary ulcer Deep Brown or red-purple base and ragged rolled border
Typical location in the oral cavity	Lip, tongue, buccal mucosa, palate, gingiva, or tonsillar pillar
Other locations	Genital mucosa
Other features	Painless; occuring 1-3 weeks after oro-genital or oro-anal contact; cervical lymphadenopathy
Healing	-
Histopathology	Dense lymphoplasmacytic inflammation, often with inflammatory exocytosis or ulceration at the surface, and perivascular inflammation
Immunology	A positive test for *T. pallidum* on direct immunofluorescence or biopsy with immunohistochemistry
Secondary syphilis [2, 4, 18, 19]	
Surface Shape, size, pattern Colour	Patches, ulcers, “snail tracks” Multiple, irregular, surrounded by erythema Grey-white necrotic membrane
Typical location in the oral cavity	Lip, tongue, buccal mucosa, palate, gingiva, or tonsillar pillar
Other locations	Maculopapular, subtle, not pruritic skin rashes on ≥1 area of the body or mucous membrane lesions
Other features	2-12 weeks after the primary stage; general symptoms: malaise, fatigue, myalgia, sore throat, fever, headache
Healing	A few weeks
Histopathology	Dense lymphoplasmacytic inflammation, often with inflammatory exocytosis or ulceration at the surface, and perivascular inflammation
Immunology	A positive test for *T. pallidum* on direct immunofluorescence or biopsy with immunohistochemistry
Candida infection [3, 18]	
Surface Shape, size, pattern Colour	Membranes or confluent plaques that resemble milk curds Confluent plaques that resemble milk curds can be wiped off to reveal a raw, erythematous, and sometimes bleeding base White
Typical location in the oral cavity	Tongue, gingiva, buccal mucosa, lips, palate
Other locations	Oro-pharynx
Other features	Can be wiped off to reveal a raw, erythematous base (sometimes bleeding)
Healing	-
Histopathology	Inflammatory response; the level of inflammation varies from minimal to suppurative based on the individual's immune status
Immunology	-
Recurrent aphthous stomatitis [2, 9, 14, 20]	
Surface Shape, size, pattern Colour	May merge, producing large ulcerative areas Rounded, erythematous border
Typical location in the oral cavity	Major RAS - most commonly lips, soft palate, and fauces; occasionally, dorsum of tongue or gingiva Minor RAS - labial mucosa, buccal mucosa, and floor of the mouth
Other locations	None
Other features	Pain; rare onset in the third decade of life
Healing	Major: up to 6 weeks, with scarring Minor: 10-14 days without scarring
Histopathology	Nonspecific; a superficial stratum comprised of a fibrinous discharge infused with polymorphonuclear leukocytes, epithelial ulceration, and profound inflammation

(Table 1) contd.....

Immunology	Negative
Chronic ulcerative stomatitis [1]	
Surface Shape, size, pattern Colour	Erosive, ulcerative, vesicular Widespread in 30% of cases; bilaterally on the buccal mucosa may suggest lichen planus
Typical location in the oral cavity	Tongue, gingiva, buccal mucosa, and rarely lips or palate
Other locations	Rarely skin
Other features	Pain; gingival soreness; xerostomia
Healing	Without scarring
Histopathology	Very similar to lichen planus (partially atrophic epithelium with saw-toothed rete ridges); possible leukocytic exocytosis and a dense band-like inflammatory infiltrate composed mainly of lymphocytes and a few plasma cells in the epithelium-connective tissue
Immunology	Mucosal damage by CD8 T cell activity; IgG deposition targets deltaNp63alpha. This specific antinuclear antibody signal, termed stratified epithelial-specific antinuclear antibody (SES-ANA), is localized to the basal cells and the lower one-third portion of the spinous layers
Graft-*versus*-host disease [1, 2, 21, 22]	
Surface Shape, size, pattern Colour	Erosions, ulcerations, striae, papules, mucoceles Lichenoid appearance White striae, generalized mucosal erythema; heavy pseudomembranous clot on ulcerations Grayish-white to yellowish
Typical location in the oral cavity	Any
Other locations	Acute GVHD: skin, liver, oral mucosa, gastrointestinal tract; chronic GVHD: liver, lungs, skin, oral and gastrointestinal mucosa; reduced production of tears and saliva
Other features	Pain; xerostomia; decreased oral opening (trismus); history of transplantation
Healing	-
Histopathology	Lichenoid lymphocytic (CD3+ and CD68+ T cells) infiltrate, necrosis, dyskeratotic epithelial cells
Immunology	DIF usually negative
Traumatic ulcer/frictional and reactive keratoses [2, 4, 14]	
Surface Shape, size, pattern Colour	Ulcer/papule or plaque Poorly-demarcated, macerated, ragged-appearing, keratotic White or yellow with red margins/white
Typical location in the oral cavity	Tongue, buccal mucosa, lips, palate (sharp food)/buccal mucosa, tongue, and lip
Other locations	No
Other features	Pain/painless
Healing	10 days
Histopathology	Parakeratosis, acanthosis, alveolar ridge keratosis; minimal to no inflammation unless the lesion has been ulcerated or traumatized
Immunology	-

Diagnostic difficulties in this area, resulting in treatment delays, have been reported by several authors. Literature research conducted in 2022 by Petruzzi *et al*. [23] revealed 16 studies indicating an 8-month delay from the initial signs/symptoms to proper diagnosis in oral autoimmune vesiculobullous diseases and 73 months in Sjögren syndrome; no data exist for oral lichen planus, oral lupus erythematosus, orofacial granulomatosis, and oral erythema multiforme. The authors concluded that diagnosing oral autoimmune diseases can pose challenges because their signs/symptoms are often non-specific, and there is a lack of awareness among dentists, physicians, and dental and medical specialists regarding these conditions. In a British study, the time to diagnosis for erosive lichen planus (LP) patients was longer than in reticular LP (median: 452 days *vs*. 312 days); additionally, the process took longer when patients were referred by their general medical practitioner than by a dentist (median 606 *vs*. 313

days) [24]. In comparison, according to NICE (NG12) Suspected Cancer: Recognition and Referral guidelines (2020), red or red/white patches require an appointment with a dentist within 2 weeks, and unexplained ulceration lasting >3 weeks should be consulted within 2 weeks with a head and neck cancer unit [25].

Proper diagnosis is additionally complicated by biological factors, such as secondary colonization of the lesions. Moreover, despite the increasing number of tools to facilitate diagnosis, its quality is debatable. For example, the use of commercial patch tests to distinguish between lichen planus and type 4 delayed-type hypersensitivity response to some component of the restoration, mediated by dendritic cells and CD4+/CD8+ lymphocytes, is very controversial since some authors have reported a positive correlation between a positive patch test result and the improvement or healing of lichenoid lesion after amalgam replacement, while others have not confirmed this association [26]. As a result, the criteria for replacing restorations vary significantly among different clinics and studies; in some studies, restoration replacement has been done only in cases with a positive patch test, while other authors have replaced all restorations in contact with the lesion, regardless of the patch test result. Also, another study considered a positive patch test result and contact of the restoration with lesion as essential for replacement, whereas others replaced restorations based solely on a strong or very strong topographic association [27]. Various other adjunctive aids, such as autofluorescence imaging with the VelScope, acetowhitening with chemiluminescence, and vital staining with toluidine blue, are commercially available, but the sensitivity and specificity of these methods are poor (84.1%, 77.3%, 56.8%, 15.3%, 27.8%, and 65.8%, respectively) [28]. Nonetheless, a systematic review focusing on optical fluorescence imaging, which analyzed data from twenty-seven studies, revealed that optical fluorescence imaging enhanced lesion detection and visualization more effectively than comprehensive oral examination alone in the clinical evaluation of oral potentially malignant disorders [29]. As cancer may arise during the natural history of oral potentially malignant disorders, including lichen planus, the key feature is to undertake patient follow-up at appropriate intervals. The follow-up intervals should be chosen based on the individual's risk assessment and considering patient compliance.

Throughout history, the identification of many conditions resulting in oral ulcers has primarily relied upon clinical presentation, sometimes supported by tissue biopsy. However, not all cases may display the usual clinical or histological indicators linked to a particular condition. There is a distinct requirement for further research into the molecular origins of these conditions. This research study could pave the way for pinpointing more precise molecular targets, which could then be used to create diagnostic tests and guide therapeutic strategies. However, until substantial progress is made in the basic sciences, the focus should be on optimizing the other two strategies, *i.e.*, the creation of tools that integrate data from history, immunology, and histopathology, and the use of artificial intelligence to analyze images. First and foremost, a thorough history of the ulcerative findings, alongside clinical examination and, potentially, a tissue biopsy, must be an integral and indispensable component of the diagnostic database. This triple-component approach must form the basis of diagnostic algorithms for oral ulcerative conditions and any other types of oral lesions that pose a diagnostic challenge.

2. METHODS

To identify relevant literature on OLP diagnostics guidelines, a non-systematic search was conducted in the PubMed and Google Scholar databases. The search covered publications up to September 2024.

The following keywords were used: “oral lichen planus” AND (“diagnosis” OR “differential diagnosis” OR “guidelines” OR “AI” OR “artificial intelligence” OR “machine learning”). Only peer-reviewed articles published in English and available in full-text were included. Opinion pieces, conference abstracts without full text, and publications not directly related to OLP were excluded. The selection process consisted of 1) the screening of titles and abstracts, and 2) full-text analysis of the selected articles. To ensure comprehensiveness, a snowballing strategy was also applied by manually reviewing the reference lists of key articles.

3. RESULTS

3.1. Official Guidelines

There are a few materials regarding the management of lichen planus that have official guideline status. Diagnostic criteria for OLP, established in 1978 by the WHO [30], were modified twice by very small teams: in 2003 by van der Meij and van der Waal [31], and then in 2016 by Cheng *et al*. [32]. The guidelines published by the American Association of Oral Medicine in 2016 were extremely brief and recommended only periodic biopsies to rule out malignant transformation [33]. The American Academy of Oral and Maxillofacial Pathology guidelines, also published in 2016, extensively discussed potential lichenoid-mimicking diseases; however, they too did not propose a decision-making algorithm. Their practical aspect was limited to an 11-point checklist designed to draw clinicians' attention to issues to be determined during the subjective and objective examination [32]. The guidelines published in 2020 by the European Dermatology Forum with the European Academy of Dermatology and Venereology [34] primarily addressed the treatment, rather than the diagnosis of OLP, and did not include a diagnostic algorithm. Similar guidelines focused on mucous membrane pemphigoid contained diagnostic algorithms, but were limited to mucous membrane pemphigoid (MMP) only [35]. Another was dedicated solely to bullous pemphigoid [36]. In 2021, official French guidelines [37] were released, which, in the case of typical white reticulations, did not recommend routine biopsies, and in the absence of such changes, they suggested obtaining samples from areas outside of erosive or ulcerated regions. Furthermore, these recommendations discouraged the routine initiation of OLP diagnosis with DIF, suggesting the use of this method only in cases of

ulcerated, erosive, bullous types, and in cases of diffuse erythematous gingivitis with the absence of reticulated lines (Wickham striae). We find it challenging to agree with these guidelines for two reasons. Firstly, Wickham striae can be mistaken for signs of other diseases, including secondary syphilis or graft-*versus*-host disease [38]. Secondly, in mucous membrane pemphigoid, erosions were present in 75.6% of the 126 patients with oral cavity involvement, blisters in 48.8%, and erythema in 43.9%, while white lines were observed in 17.9% [39]. Adhering to the French guidelines exposes patients to the risk of missing diagnoses of diseases that, when left untreated, can have serious health consequences, while aiming to avoid a relatively low-risk examination with questionable benefit. In our clinical practice, we diagnosed MMP in two patients at a very early stage solely through the simultaneous performance of histopathological and DIF examinations in patients with suspected OLP. This enabled the initiation of treatment at a very early stage and the protection of the patients' eyesight. Chinese guidelines have also been published, but only a brief abstract is available in English, and the language barrier prevents most global readers from accessing the full document [40].

3.2. Diagnostic Algorithms

As long as no novel tools are available, algorithms aiming to shorten the path to correct diagnosis play a particularly important role. In the absence of comprehensive, up-to-date guidelines, several independent authors have attempted to fill this gap by proposing their own diagnostic schemes.

In 2019, Bilodeau and Lalla [41] presented a diagnostic algorithm for oral lesions that relied solely on clinical signs. A year later, researchers introduced an electronic version of The Atlas of Oral Mucosal Diseases, a case-based database developed in collaboration with clinicians from the Faculty of Medicine at Masaryk University. Their algorithm for blistering diseases of the oral mucosa was based on histopathological and immunological findings, but it did not incorporate clinical signs [42]. Also, in 2019, Rashid *et al*. proposed a flowchart focused narrowly on blistering disorders, such as mucous membrane pemphigoid, pemphigus vulgaris, and paraneoplastic pemphigus [43]. That same year, another team published a conservative and non-committal diagnostic pathway [44], which recommended specialist referral and a wide range of diagnostic tests, but did not offer categorical decisions or probabilistic estimates. While this caution likely reflects the complexity of oral mucosal disorders, it reduces the utility of such tools in routine clinical decision-making. In our view, none of these prior diagrams is comprehensive enough to serve as a reliable clinical aid. A review of the literature indicates that building an effective decision-support algorithm is inherently difficult due to the heterogeneity of clinical presentations and the limitations of current diagnostic methods. To address this, we have synthesized available material and developed a new diagnostic roadmap integrating information from patient history, histopathology, and immunochemical studies (Fig. **S1**). Additionally, we have proposed a practical summary for general practitioners (Tables **1**-**3**).

Table 2. Recommendations for general practitioners.

Differential diagnosis of oral ulcers	Infectious diseases (viral, bacterial, fungal)
	Autoimmune disorders (*e.g.*, OLP, MMP, pemphigus vulgaris)
	Malignancies
	Systemic diseases (*e.g.*, Crohn’s disease, systemic lupus erythematosus)
	Adverse drug reactions
	Mechanical or chemical trauma
Red flag symptoms - indication for urgent evaluation or referral	Ulcer persisting for more than 2-3 weeks
	Unilateral lesion
	Indurated or infiltrated margins
	Associated pain, bleeding, or difficulty with eating/speaking
	Regional lymphadenopathy
	Systemic symptoms (*e.g.*, weight loss, fever)
	Lesions in patients with known cancer risk factors (*e.g.*, tobacco use, alcohol consumption)
When to suspect an autoimmune or premalignant condition	Multifocal, symmetrical lesions (*e.g.*, cheeks, gingiva, tongue)
	Patient reports burning sensation, pain during eating, or sensitivity to spicy foods
	Presence of reticular (Wickham’s striae), erosive, or bullous lesions
	Associated autoimmune conditions (*e.g.*, Sjögren’s syndrome, rheumatoid arthritis, autoimmune thyroiditis)
	Desquamative gingivitis, which is often a clinical feature of MMP
Biopsy is safe and essential in cases of	Chronic, unexplained lesions
	Suspected OLP, MMP, pemphigus, or lupus erythematosus
	Suspected malignancy (especially SCC)

(Table 2) contd.....

Recommended actions for general practitioners	Thorough history (duration, recurrence, medications, chronic conditions)
	Clinical assessment: number, location, lesion borders, induration, symmetry
	Referral to a specialist (dermatologist, ENT, oral and maxillofacial surgeon) for suspicious lesions
	Arrange or prepare the patient for a biopsy and provide education on its necessity
	Consider systemic disease and order appropriate tests (*e.g.*, morphology, CRP, ANA, vitamin B12, ferritin)
Impact of diagnostic delays	Irreversible ocular damage, including vision loss
	Permanent mucosal scarring and structural damage
	Malignant transformation of premalignant lesions (*e.g.*, to SCC)
	Significant decline in quality of life due to pain and discomfort
Artificial intelligence - future potential, not yet standard of care	AI-based algorithms are under development and show promise in the image analysis of oral mucosal lesions
	In the future, AI may assist in diagnosing conditions, such as OLP or cancer

Abbreviations: AI - Artificial intelligence, ANA - Antinuclear antibodies, CRP - C-reactive protein, DIF - Direct immunofluorescence, MMP - Mucous membrane pemphigoid, OLP - Oral lichen planus, SCC - Squamous cell carcinoma.

Table 3. Diagnostic approach to chronic oral ulcerations and suspected oral lichen planus.

Patient history	Duration of symptoms (>2-3 weeks)
	Recurrence of similar lesions in the past
	Pain, burning, sensitivity to spicy foods
	Associated systemic symptoms (fever, weight loss, malaise)
	Medication history (especially NSAIDs, antihypertensives, antimalarials)
	History of autoimmune disease or malignancy
Clinical examination	Number of lesions (single *vs.* multiple)
	Location (buccal mucosa, gingiva, tongue, lips, palate)
	Symmetry (bilateral *vs.* unilateral)
	Appearance (reticular white striae, erosions, ulcers, bullae, erythema)
	Borders (indurated, irregular, raised)
	Presence of desquamative gingivitis
	Regional lymphadenopathy
Red flags (immediate referral indicated)	Lesion >3 weeks without healing
	Unilateral and indurated ulcer
	Bleeding, pain on palpation, or dysphagia
	Suspicion of malignancy (especially in smokers or alcohol users)
	Weight loss or systemic signs
	Visual symptoms or ocular involvement (suggestive of MMP)
Initial work-up (optional at primary level)	Morhology, CRP, ESR
	Iron, vitamin B12, folate, ferritin
	ANA, RF (if autoimmune disease suspected)
	Consideration of viral swabs (HSV, VZV) if acute ulcers are present
When to recommend biopsy and direct immunofluorescence*	Chronic ulcer(s) without clear etiology
	Suspected OLP, MMP, pemphigus, lupus, leukoplakia, or SCC
	Non-healing erosive or atrophic lesions
	Unilateral or indurated lesion
	DIF necessary for suspected autoimmune blistering diseases
Referral pathways	Dermatologist (autoimmune suspicion, complex ulcers)
	ENT specialist or oral surgeon (for biopsy, malignancy suspicion)
	Ophthalmologist (if ocular symptoms in MMP suspected)
	Gastroenterologist (if systemic disease, like Crohn's disease, is suspected)
Follow-up and patient education	Educate the patient about the need for a biopsy and specialist evaluation
	Emphasize that early diagnosis can prevent irreversible complications
	Provide written instructions and specialist referral documentation
	Schedule follow-up to ensure biopsy and diagnosis have been completed

Abbreviations: ANA - Antinuclear antibodies, CRP - C-reactive protein, DIF - Direct immunofluorescence, ESR - Erythrocyte sedimentation rate, HSV - Herpes simplex virus, MMP - Mucous membrane pemphigoid, NSAIDs - Nonsteroidal anti-inflammatory drugs, OLP - Oral lichen planus, RF - Rheumatoid factor, SCC - Squamous cell carcinoma, VZV - Varicella-zoster virus.

***Note:** Biopsy should be taken from the lesion margin and adjacent normal mucosa (for DIF).

4. DISCUSSION

Our step-by-step algorithm provides a structured clinical pathway for evaluating patients with chronic oral erosions and ulcerations. It begins with the exclusion of infectious and emergency conditions, followed by stratification based on chronicity, lesion morphology, anatomical distribution, and systemic associations. Particular emphasis is placed on “red flag” features indicative of malignancy or severe immunobullous disease. When immune-mediated pathology is suspected, histopathological examination and direct immunofluorescence are positioned as pivotal decision tools. This approach facilitates early recognition of conditions, such as oral lichen planus, mucous membrane pemphigoid, and erythema multiforme, allowing timely referrals and targeted interventions. The integration of such algorithms into clinical practice, especially when enhanced with AI-based triage support, could significantly improve diagnostic accuracy and reduce time to treatment in both primary and outpatient care settings.

Our diagnostic flowchart not only offers a practical clinical tool, but also highlights areas of greatest diagnostic risk. High-stakes decision points include the early identification of systemic symptoms and the need for prompt referral in suspected autoimmune blistering diseases or neoplastic conditions. Failure to recognize warning signs, such as fever, odynophagia, persistent unilateral ulceration, or mucocutaneous desquamation, may result in delayed diagnosis of life-threatening diseases, like pemphigus vulgaris, mucous membrane pemphigoid, Stevens-Johnson syndrome, or oral squamous cell carcinoma.

Beyond identifying these critical junctures, the algorithm introduces several refinements to current diagnostic reasoning. It distinguishes oral lichen planus from lichenoid lesions of systemic, pharmacological, or iatrogenic origin, offering a more nuanced interpretive path. The framework also incorporates lesion laterality, symptom chronicity and severity, and the presence of systemic manifestations into the differential diagnosis, factors that improve specificity in complex conditions, such as systemic lupus erythematosus, Behçet’s disease, or adverse drug reactions. Moreover, the algorithm helps standardize the timing of mucosal biopsy and direct immunofluorescence testing, promoting earlier specialist engagement. In summary, our proposed scheme enhances clinical safety and bridges the gap between theoretical recommendations and practical application, particularly for general practitioners and dental clinicians managing ulcerative or bullous oral lesions.

While we hope that it proves useful, we must also emphasize its limitations. First, it was developed from an unstructured review of existing reviews, lacking the rigor of formal guideline development methods, such as systematic review and the Delphi process. Second, its broad scope necessitated certain simplifications and a focus on the most common clinical presentations. Atypical cases may not conform to the flowchart, and users should remain vigilant for unusual features. In such situations, we encourage consulting the underlying literature that informed this graphical and tabular synthesis.

In recent years, rapidly advancing artificial intelligence has found applications in an increasing number of fields, including dermatology. This has led to the integration of image recognition methods by neural networks alongside conventional histopathological and immunological techniques. Machine learning (ML) represents a branch of artificial intelligence dedicated to the task of making predictions through the identification of data patterns. Within the realm of ML, deep learning emerges as a specialized subset, concentrating on prediction-making through the utilization of multi-layered neural network algorithms inspired by the intricate structure of the human brain. ML assimilates image features from training data to detect distinctive characteristics in medical images and subsequently categorizes them into various disease types. Neural network learning can be supervised (indications of correct answers) or unsupervised, when the network performs clustering of objects based on similarities between them. The reliability of ML's performance is assessed through the validation of these acquired features using separate validation data, followed by further confirmation through testing with a dedicated dataset [45]. In detail, key metrics designed to monitor and measure the performance of a model and differences between particular methods (such as random forest, support vector machine, artificial neural network, and convolutional neural networks) were described by Ghaffari in a way that is understandable for clinicians [46].

Neural networks have shown high accuracy in classifying lesions as (1) papule/nodule; (2) macule/spot; (3) vesicle/bullous; (4) erosion; (5) ulcer; and (6) plaque (95.09%) [47], and in differentiation, listed as follows: OLP *vs*. healthy mucosa (100%) [48], oral lichen planus, oral lichenoid lesions, and oral epithelial dysplasia with lichenoid host response (94.62%) [49], OLP *vs*. non-OLP (88.18%) [50], LP *vs*. mucocele (84.0%) [51], nonmalignant lesions, potentially malignant, and malignant (80%) [52, 53], oral dysplasia *vs*. other types of lesions (93.3%) [54], oral precancerous lesions (90%) [55], pemphigus vulgaris *vs*. other lesions (78.7-99.0%) [56], recurrent aphthous ulcer (98.70%) [57], and bullous pemphigoid *vs*. pemphigus vulgaris (AUROC 0.82-0.94) [58]. Errors in the classification of images of oral lesions have been found to be associated with problems of sharpness, resolution, focus, human errors, and the influence of data augmentation [59]. NNs have also made it possible to predict with 90% accuracy a positive OLP response to immunosuppressive treatment [60]. In the study by Keser *et al*. [48], a network trained on photographic images of buccal mucosa with 65 healthy and 72 oral lichen planus lesions achieved 100% correct classifications, verified by Oral Medicine and Maxillofacial Radiology experts. However, the test and validation sample sizes were very small (n=7). Idrees *et al*. created an AI-based model able to identify and count mononuclear cells and granulocytes in the inflammatory infiltrates in a set consisting of 24 samples from OLP patients and a retrospective cohort of 130 cases with confirmed diagnoses of OLP, oral lichenoid lesions (OLLs), or oral epithelial dysplasia (OED) with lichenoid host response [49]. The model effectively

detected OLP cases by analysing the number of inflammatory and mononuclear cells, achieving an area under the curve of 0.982 and 0.988, respectively. Establishing a cut-off point between OLP and other lichenoid conditions based on the number of mononuclear cells resulted in a sensitivity of 100% and an accuracy of 94.62%. These results are very encouraging, but the main problem with neural networks is the risk of overfitting, *i.e.*, the false high performance achieved in validation on one database that is not confirmed on subsequent datasets. As a result, tools developed by a single research team are not easy to popularize and, consequently, to implement quickly on larger populations. The most high-profile example of a software bug detected and disclosed that led to the death of patients is the story of Therac-25 [61]. Since 2017, under Regulation (EU) 2017/745 of the European Parliament and of the Council, diagnostic software is classified as a medical device and, therefore, must obtain marketing authorization along with all associated regulatory requirements.

An interesting issue is the comparison of the effectiveness of classification models with the experience of clinicians. In the case of skin cancer lesions, a marketized neural network proved to be much more effective than humans; its sensitivity and specificity were 96.2% and 68.8%, respectively, whereas the dermatologists' management decisions demonstrated an average sensitivity of 84.2% and specificity of 69.4% [62]. However, in patients with oral cavity blistering lesions, the comparison outcome depended on the clinician's experience (<5 years *vs*. ≥5 years) in the multimodal model created by He *et al*. [58], exhibiting a sensitivity of 85% and a specificity of 95%, which were better than the average result of junior dermatologists (sensitivity: 68%, specificity: 78%) and comparable to the average of senior dermatologists (sensitivity: 80%, specificity: 87%), with a few outliers among senior consultants who far exceeded the result obtained by neural networks. Another comparison, performed by Cai *et al*., showed similar accuracy obtained by NN and clinicians in the differential diagnosis of autoimmune bullous diseases [67.5% accuracy on the broader disease classes (pemphigus *vs*. pemphigoid *vs*. other diseases) and 56.7% accuracy on the finer partitions (pemphigus vegetans *vs*. vulgaris *vs*. foliaceous; bullous pemphigoid *vs*. linear IgA disease; erythema multiforme *vs*. urticaria *vs*. bullous lupus)] [8]. A meta-analysis performed by Rokhshad *et al*. [63], aggregating data from 36 eligible studies involving patients with various skin conditions, showed that AI's accuracy in detecting oral mucosal lesions ranged from 74% to 100%. In comparison, clinicians unaided by AI had an accuracy range of 61% to 98%.

Although some people fear that artificial intelligence will eliminate more and more jobs and threaten areas previously reserved for humans, including in medicine, doctors, especially dentists, can leverage AI to expedite important decision-making processes. This technology has the potential to alleviate the dentists' workload, eliminate human errors in decision-making, and thus ensure high-quality and consistent medical care. Its utility is particularly evident in rural areas that are distant from highly specialized healthcare facilities. It is, therefore, inevitable that diagnostic techniques and computer-assisted decision-making processes will continue to develop, the need for which is particularly evident in the area of oral blistering and erosive lesions.

This review involved several limitations that should be acknowledged. First, the inclusion of studies was limited to those published in English, which may have led to language bias and the exclusion of relevant findings from non-English sources. Second, the review was restricted to articles indexed in selected databases (PubMed and Google Scholar), and it is possible that some relevant studies published in grey literature or other repositories were missed. Third, the synthesis of results was qualitative, which may limit the generalizability of the conclusions. Fourth, as with all literature reviews, the interpretation of results may be inherently influenced by the selection and extraction process, introducing unintentional bias. Future research should aim to address these limitations by including broader language and source criteria, improving methodological rigor, and exploring quantitative synthesis where feasible.

CONCLUSION

In summary, the differential diagnosis of oral cavity lesions is a complex diagnostic challenge. Our proposed roadmap schema is a collective representation of previously published work brought together in one place for the convenience of healthcare practitioners. Until AI-based tools are expanded, validated on a broad population, registered, and commercialized on a large scale, this roadmap may serve as a diagnostic aid for physicians, with the caveat of limitations inherent to the signs.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: K.O.: Allocated the resources and wrote the initial draft; P.T.: Performed review and editing. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

AI	=	Artificial intelligence
AUROC	=	Area under the receiver operating characteristic
CD4+	=	Cluster of differentiation 4 positive
CD8+	=	Cluster of differentiation 8 positive
DIF	=	Direct immunofluorescence
LP	=	Lichen planus
ML	=	Machine learning
MMP	=	Mucous membrane pemphigoid
NICE	=	National Institute for Health and Care Excellence
NN	=	Neural network
OED	=	Oral epithelial dysplasia

OLLs = Oral lichenoid lesions

OLP = Oral lichen planus

WHO = World Health Organization

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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