



# Mouth Ulceration

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**Declaration of Competing Interests:**  
None declared.

**M**outh ulceration results most commonly from local causes such as trauma, and recurrent aphthous stomatitis (RAS), but similar multiple ulcers can arise from systemic disease (especially haematological, infectious, gastrointestinal and dermatological disorders), or drug reactions. Recurrent oral ulceration may clinically resemble RAS but if it either does not commence in childhood, or it fails to resolve with age, the presentations have been termed aphthous-like ulceration (ALU) and are found in some immunodeficiency states, chronic viral infections, rheumatological disorders, skin diseases and autoinflammatory syndromes. Chronic infections such as tuberculosis, and malignant neoplasms, may cause single chronic ulcers. This article reviews oral ulceration, with a focus on the more common causes – especially RAS.

## Introduction

Mouth ulceration can arise from multiple causes<sup>1,2</sup> ranging from systemic disorders (such as diseases of blood, infections, gastrointestinal system and skin); to malignancy; to local mechanical trauma or burns; to aphthae (recurrent aphthous stomatitis, RAS); and to various drugs (Box 1).

Ulcers are among the most common mouth lesions. The epidemiology varies, depending upon the cause of the ulceration. Systemic diseases causing ulcers are multiple (Box 1). Blood diseases can affect

patients at any age, whereas most infections are in childhood. Herpes virus infections are common in this group and cause multiple ulcers often with fever. Oral ulcers due to *Mycobacterium tuberculosis* and *Treponema pallidum* infection though rare in the developed world are increasingly seen in patients with, or at particular risk of, HIV/AIDS. Other ulcers in HIV/AIDS include viral (mainly herpes viruses) or fungal, Kaposi's sarcoma, or lymphoma.<sup>3</sup> Gastrointestinal and skin diseases are seen predominantly in adults.

### BOX 1: MAIN CAUSES OF MOUTH ULCERATION

#### SYSTEMIC CAUSES

##### Blood (haematological) disease

- Anaemia
- Leukaemias and myelodysplastic syndromes
- Neutropenias
- Hypereosinophilic syndrome
- Hypoplasminogenaemia

##### Infections

- Viral
- HSV
- VZV
- EBV
- CMV
- HIV
- Coxsackie viruses
- ECHO viruses
- Bacterial
- Mycobacteria
- *Treponema pallidum*
- Mycotic (candidosis, histoplasmosis, paracoccidioidomycosis)
- Parasitic
- Leishmania
- Others

##### Gastrointestinal disease

- Coeliac disease
- Crohn's disease
- Ulcerative colitis
- Others

##### Skin disease

- Lichen planus
- Pemphigus
- Pemphigoid
- Erythema multiforme
- Dermatitis herpetiformis
- Linear IgA disease
- Epidermolysis bullosa
- Others

##### Vasculitides

- Lupus erythematosus
- Behçet's disease
- Wegener's granulomatosis
- Sweet's syndrome
- Reiter's syndrome
- Periarteritis nodosa
- Others

##### MALIGNANT DISEASE

- Oral carcinoma
- Antral carcinoma

- Lymphomas
- Kaposi's sarcoma
- Salivary neoplasms
- Others

##### LOCAL CAUSES

- Trauma
- Burns
- Necrotising sialometaplasia
- Others

##### APHTHAE and APHTHOUS-LIKE ULCERS

- PFAPA (periodic fever, aphthae, pharyngitis, adenitis)
- Other periodic syndromes

##### DRUGS

- Cytotoxic agents
- Alendronate
- Nicorandil
- Phenytoin
- NSAIDs
- Lamotrigine
- Mycophenolate
- Sirolimus
- Tiotropium
- Others (many)



Figure 1: Oral carcinoma.



Figure 2: Aphthous stomatitis.

Oropharyngeal squamous cell carcinoma, which often presents as an oral ulcer, is mainly still a disease of older people and produces a single persistent ulcer (Figure 1). Traumatic ulceration due to ill-fitting dentures also generally occurs in this age group.

Recurrent aphthous stomatitis (RAS) is prevalent mainly in childhood and early adulthood (Figure 2), with a natural history of spontaneous resolution with age. Drugs causing ulcers are seen mainly in the older population.

**Recurrent aphthous stomatitis**

RAS is the most common oral ulcerative condition. The onset is usually during childhood, with a tendency to diminish in frequency and severity with age. Onset in later years suggests a possibility of a more complex disorder or definable predisposing factors, and the term aphthous-like ulcers (ALU) is applied.

**Clinical features**

Ulcers are painful, clearly defined, shallow, round or oval, with a shallow necrotic centre covered with a yellow-greyish pseudo-membrane and surrounded by raised margins and erythematous haloes. There are three clinical presentations;

*Minor aphthae* (Mikulicz's aphthae, or mild aphthous ulcers), account for 75%-85%.<sup>2</sup> They can involve non-keratinised mucosae (usually the labial and buccal mucosae, floor of the mouth and ventral or lateral tongue), are smaller than 8-10mm

and tend to heal within 10-14 days without scarring.

*Major aphthous* ulcers (peradenitis mucosa necrotica recurrens (PMNR) or Sutton's disease) account for 10-15% of RAS. Usually appearing after puberty, they typically involve mucosae overlying minor salivary glands and are round or ovoid with clearly defined margins, but the ulcers are usually deeper, larger and last significantly longer than do minor aphthae. They have a raised irregular border and frequently exceed 1cm, are painful, can last up to months and often leave a scar after healing.

*Herpetiform aphthous* ulcers are multiple (5-100) 1-3mm rounded crops of small painful ulcers resembling ulcers of herpes simplex. Seen anywhere on the mucosa, they tend to fuse and produce much larger ulcers, lasting 10-14 days, have a predisposition for women and generally have a later age onset than the other RAS.

**Aetiopathogenesis**

**Family tendency:**

Over 42% of RAS patients have first degree relatives with RAS.

**Immunopathogenesis:**

A mononuclear (lymphocytic) cell infiltrate in the epithelium in the pre-ulcerative stage is followed by a localised papular swelling due to keratinocyte vacuolisation surrounded by a reactive erythematous halo representing vasculitis. The painful

papule then ulcerates and a fibrous membrane covers the ulcer which is infiltrated mainly by neutrophils, lymphocytes and plasma cells. Cell-mediated responses, involving T-cells and tumour necrosis factor alpha (TNF alpha) production by these and other leukocytes (macrophages and mast cells) are involved. TNF-alpha affects endothelial cell adhesion and neutrophil chemotaxis and induces inflammation. Other cytokines such as interleukin-2 (IL-2) and IL-10 and natural killer (NK) cells activated by IL-2 also play a role.

**Aphthous-like ulcers (ALU)**

Classic RAS is a locally limited condition; similar ulcers may be seen in some systemic conditions. The aetiology of these aphthous-like ulcers (ALU) is probably multifactorial with a variety of predisposing factors, and immunologic changes provoked by a range of factors. These include:

**Stress:** can provoke ulcers.

**Foods:** such as chocolate, coffee, peanuts, cereals, almonds, strawberries, cheese, tomatoes as well as wheat flour (containing gluten) may be implicated in some patients.

**Drugs:** Various drugs may produce aphthous-like ulcers.

**Immune defects:** Large aphthous-like ulcers may be seen in immunodeficiencies.

**Hormonal imbalance:** in some patients, ulcers remit with oral contraceptives or during pregnancy.

**Tobacco smoking:** patients are usually non-smokers and there is a lower prevalence and severity of ulcers in heavy compared to moderate smokers. Some patients report

*A single ulcer lasting more than three weeks may well represent malignancy or a chronic infection*

an onset of ulcers parallel to smoking cessation, while others report control on re-initiation of smoking. The use of smokeless tobacco is also associated with a significantly lower prevalence of ulcers. Nicotine containing tablets also appear to control the frequency of ulcers.

**Associated systemic diseases:** in a minority of patients, systemic diseases may be associated, especially haematinic deficiencies or gastrointestinal disease, or other rare syndromes.

**Haematinic deficiency states:** Though some studies deny an aetiological relationship with deficiencies of folic acid or iron, deficiencies of vitamin B1, B2, B6 or B12, folic acid or iron have been found in 18-28% of patients compared to about 8% in healthy individuals. Replacement of the deficiency improves ulcers in some patients only.

**Gastrointestinal diseases:** coeliac disease, gluten-sensitive enteropathy (GSE) is seen in over 4% of patients whose initial presentation was ALU and patients diagnosed with GSE typically remit completely on a gluten-free diet. Crohn's disease and ulcerative colitis, may also be accompanied by mouth ulcers.

**Behçet's syndrome:** manifests with ALU and a range of systemic complications, notably affecting the eyes, joints, neurological system and skin.

**PFAPA Syndrome:** (periodic fever, aphthae, pharyngitis, and adenitis) and other periodic syndromes are occasionally seen in younger people.

**Sweet's syndrome:** (acute febrile neutrophilic dermatosis) is characterised by fever, neutrophil leukocytosis, erythematous skin plaques or nodules on the face and extremities and often aphthous-like ulcers. It may occur in conjunction with malignant conditions, such as leukaemia.

**Cyclic neutropenia:** manifests with recurrent ulcers, fever, malaise, skin infections and cervical adenopathy at approximately 21 day intervals.<sup>26</sup>

### Management of patients with mouth ulcers

#### Diagnosis

The diagnosis of mouth ulceration depends largely upon the history. Most

#### BOX 2: TOPICAL CORTICOSTEROIDS FOR CONTROL OF SOME MOUTH ULCERS

##### Adhesive paste

Apply 5mm of a moderate-potency topical corticosteroid in adhesive paste (triamcinolone acetonide in orabase 0.1%) on the wetted finger and transfer it onto the ulcer, and avoid eating/drinking for 5-10 minutes. Repeat 3-4 times a day for 5-7 days.

##### Spray

Spray fluticasone propionate aqueous nasal spray 2-3 times onto the oral ulcer and avoid eating/drinking for 5-10 minutes. Repeat 3-4 times a day for 5-7 days.

##### Mouth rinse

Betametasone sodium phosphate: 500 micrograms soluble tablets, use as a mouthwash for 2-3 minutes, repeated 3-4 times a day for 5-7 days. The patient should dissolve 1 tablet in 10-15 ml water to make the mouthwash.

ulcers affect the non-keratinised mucosae (lips; ventrum of tongue and cheek [buccal] mucosae). *Ulcers in the palate* are uncommon but are seen in skin diseases such as pemphigus or pemphigoid, and necrotising sialometaplasia.

The most important diagnostic point however, is the *number of ulcers* and *their persistence* or otherwise. A single ulcer lasting more than three weeks may well represent malignancy or a chronic infection. Such ulcers must be further investigated, and biopsy is usually indicated. Oral cancer most frequently affects the lateral margin of the tongue. *Multiple* chronic ulcers are more typical of systemic disease or drug reactions. *Multiple recurring* ulcers starting in childhood are typical of RAS but at other ages, ALU may have a systemic basis.

The diagnosis of RAS is made on the basis of history and clinical criteria since there are no specific laboratory findings. A medical history should be taken to exclude ALU and other ulcerative conditions. Lesions affecting skin, other mucosae (ocular/ano-genital), gastrointestinal and respiratory tracts in particular must be excluded. A complete blood cell count and haematinic estimation is indicated to exclude immune disorders, vitamin and iron deficiencies, and malabsorption (e.g. coeliac disease).

#### Treatment

The treatment of patients with mouth ulcers depends on the aetiology: the fun-

damental cause should, where possible, be corrected.

The medical history should exclude relevant systemic disorders (haematological, infections, gastrointestinal, or skin diseases) or causal drug use.

The possibility of trauma from local factors including sharp and/or broken teeth, the wearing of dentures and other appliances, and biting during chewing should be checked.

For aphthous ulceration and some other ulcers such as ALU caused by mucocutaneous disorders, topical corticosteroids or tacrolimus can help (Box 2). ■

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#### Recommended websites:

Visiting Professor, University of Helsinki:  
[http://www.hammas.helsinki.fi/english/eng\\_index.htm](http://www.hammas.helsinki.fi/english/eng_index.htm)  
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