BMJ Best Practice

Recurrent aphthous stomatitis (episodic mouth ulcers)

Straight to the point of care

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Table of Contents

Summary

Clinically, three forms of recurrent aphthous ulceration exist: major, minor, and herpetiform.

Recurrent aphthous stomatitis is distinguished from aphthous-like ulceration by exclusion of underlying systemic conditions (e.g., inflammatory bowel disease, Behcet syndrome, HIV/AIDS, or cyclic neutropenia).

Diagnosis is based on the history and clinical examination with exclusion of a systemic etiology; there are no specific laboratory findings.

Topical corticosteroids and anti-inflammatory agents are the mainstay of treatment. Severe or refractory cases may require systemic therapy.

Definition

Recurrent aphthous stomatitis (RAS) is a common condition of the oral mucosa that presents in patients who are otherwise healthy. It is characterized by recurrent episodes of round or ovoid ulcers with circumscribed erythematous margins and a grayish-yellow base. These typically present in childhood or adolescence.[1] [2] Similar presentations of recurrent oral ulceration (aphthous-like ulceration) may occur associated with systemic disease, including autoinflammatory syndromes (e.g., periodic fever with adenitis, pharyngitis, and aphthae [PFAPA syndrome], Behcet syndrome, Crohn disease), and immunodeficiency states (e.g., nutritional defects such as in celiac disease and other gastrointestinal disorders, immune defects such as HIV/AIDS, or neutrophil defects such as cyclic neutropenia); therefore, to avoid confusion, the term RAS should be reserved for ulceration seen in the absence of systemic disease.[1] [2]

Other causes of oral ulceration include trauma, inflammatory conditions such as oral lichen planus or graft versus host disease, medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], nicorandil), infections (herpes simplex virus infection, syphilis), and malignancy (i.e. oral squamous cell carcinoma).

Epidemiology

Recurrent aphthous stomatitis (RAS) is prevalent mainly in childhood and early adulthood, with a natural history of spontaneous resolution with age.[2] If similar ulcers start later in life or are associated with fever or systemic disease, they may be aphthous-like ulcers rather than RAS.

RAS is the most common idiopathic intraoral ulcerative disease.[4] The prevalence of RAS varies according to the ethnic and socioeconomic group studied, with a range of 5% to 60% being reported.[5] [6] The prevalence in the general population is accepted at approximately 20%.[7] It is slightly more prevalent in women and in higher socioeconomic groups.[8] [9]

Etiology

A genetic predisposition may contribute to recurrent aphthous stomatitis (RAS). A positive family history may be found in up to 40% of patients.[1] [10] Studies show a high correlation between stress, depression and anxiety, and RAS.[11]

An association with a variety of human leukocyte antigen (HLA) haplotypes has been reported.[12] Further clarification is required.[13]

In addition, further predisposing factors such as cytokine polymorphism have been suggested.[14]

Patients with RAS are usually nonsmokers, and there is a lower prevalence and severity of ulcers in heavy compared with moderate smokers.[15] [16] Some patients report an onset of ulcers parallel to smoking cessation, whereas others report control on reinitiation 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 aphthae.[6]

Hematinic (iron, folic acid, or vitamin B12) deficiencies may be twice as common in some groups of patients with RAS as in healthy control subjects.[1] [6] [17] [18]

There are patients whose ulcers coincide with the luteal phase of the menstrual cycle and often remit with oral contraceptives or during pregnancy.[6]

Local trauma may trigger ulcers in susceptible people.[1] [6] [19] Increased level of anxiety has been reported in some patients with RAS.[6]

RAS may be more prevalent in cows' milk-fed children.[20] Certain foods (e.g., chocolate, peanuts, coffee, and gluten products) have been reported to trigger episodes of RAS.[3] An increased frequency of RAS related to sodium lauryl sulfate-containing dentifrice has been reported, although other studies found no such association.[21] In another trial, researchers found that sodium lauryl sulfate-free toothpaste did not reduce the number or frequency of ulcers, but the participants self-reported feeling less pain and that they thought the ulcers healed slightly faster.[22]

Pathophysiology

A mononuclear (lymphocytic) cell infiltrate in the epithelium in the pre-ulcerative stage is followed by a localized papular swelling as a result of keratinocyte vacuolization surrounded by a reactive, erythematous halo representing vasculitis.[23] The lesion then ulcerates and a fibrous membrane covers the ulcer, which

is infiltrated mainly by neutrophils, lymphocytes, and plasma cells. Finally, there is healing with epithelial regeneration.

Evidence suggests that immunopathogenesis may involve cell-mediated responses, involving T cells and tumor necrosis factor alpha (TNF-alpha) production by these and other infiltrating leukocytes (macrophages and mast cells).[24] TNF-alpha induces inflammation by its effect on endothelial cell adhesion and neutrophil chemotaxis.[25] There has also been evidence of the association of toll-like receptors (TLR).[26] [27]

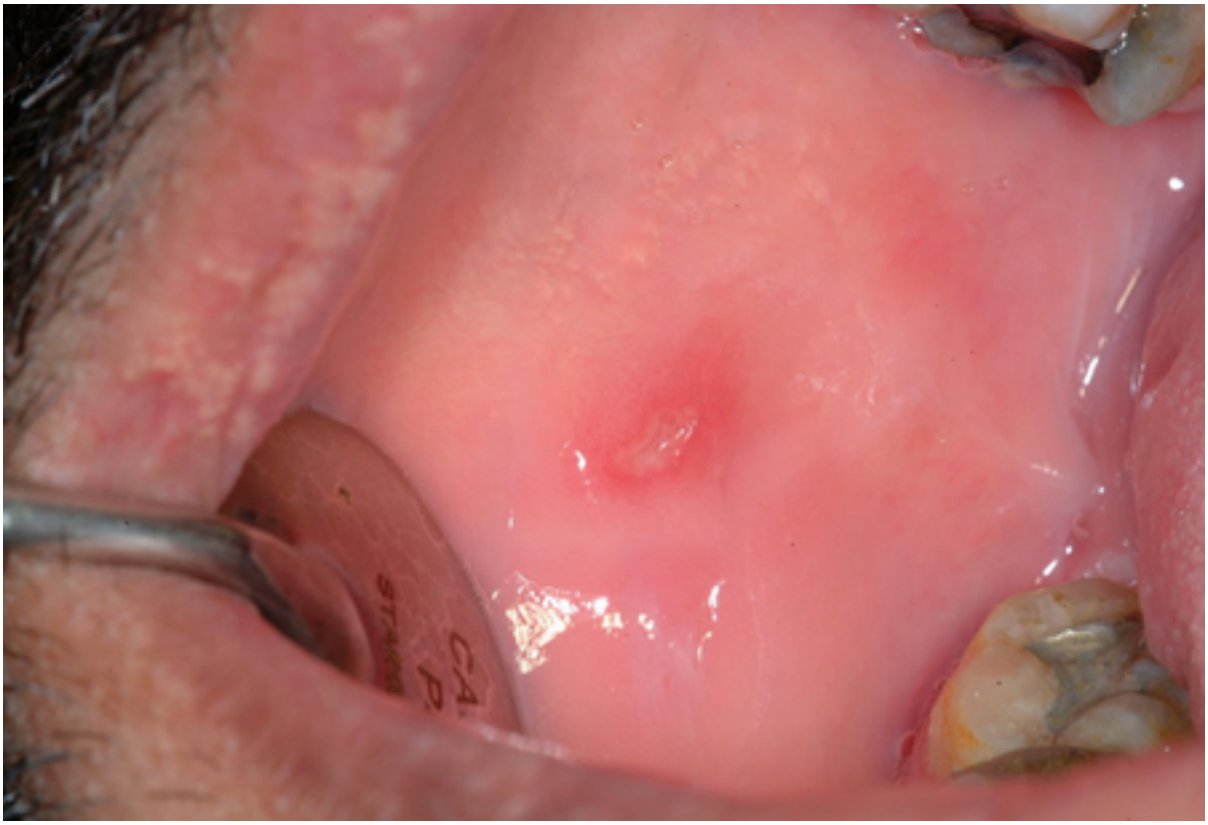
Other cytokines, such as interleukin (IL)-2 and IL-10, and natural killer cells activated by IL-2 also have a role in RAS.[1] [23]

Classification

Clinical classification[1] [2] [3]

There are three clinical presentations of recurrent aphthous stomatitis (RAS), which suggests disease heterogeneity.

Minor aphthous ulcers (around 75% to 85% of all RAS cases):



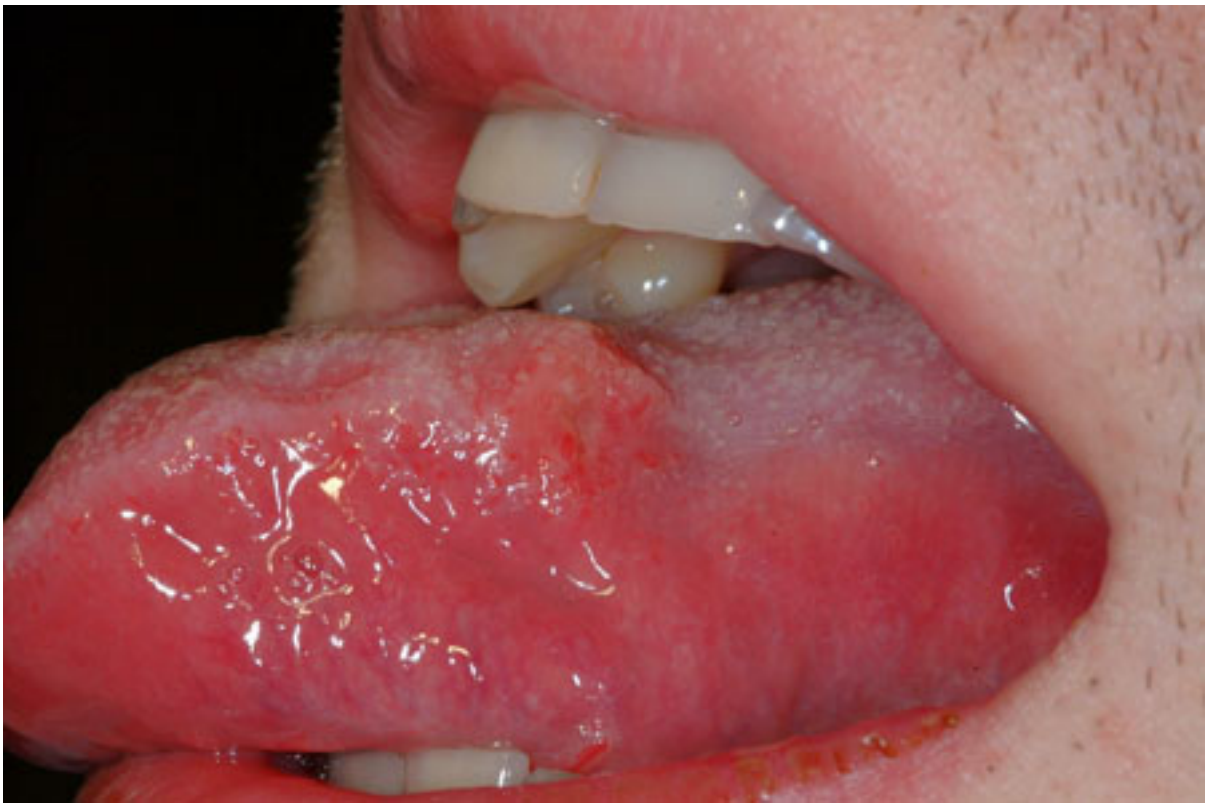
Recurrent aphthous stomatitis (RAS): minor aphthae

From the personal collection of Crispian Scully, MD, PhD, FDSRCS, FRCPath

- Small round or ovoid ulcers less than 10 mm in diameter (usually less than 5 mm in diameter)
- Occur in groups of 1 to 6 at a time
- Found mainly on the nonkeratinized mucosa of the lips, cheeks, floor of the mouth, sulci, or ventrum of the tongue

- Heal in 7-10 days without scarring
- Frequency of episodes varies and patients can experience ulcer-free periods
- Occur mainly in people ages between 10 and 40 years.

Major aphthous ulcers (around 10% to 15% of all RAS cases):

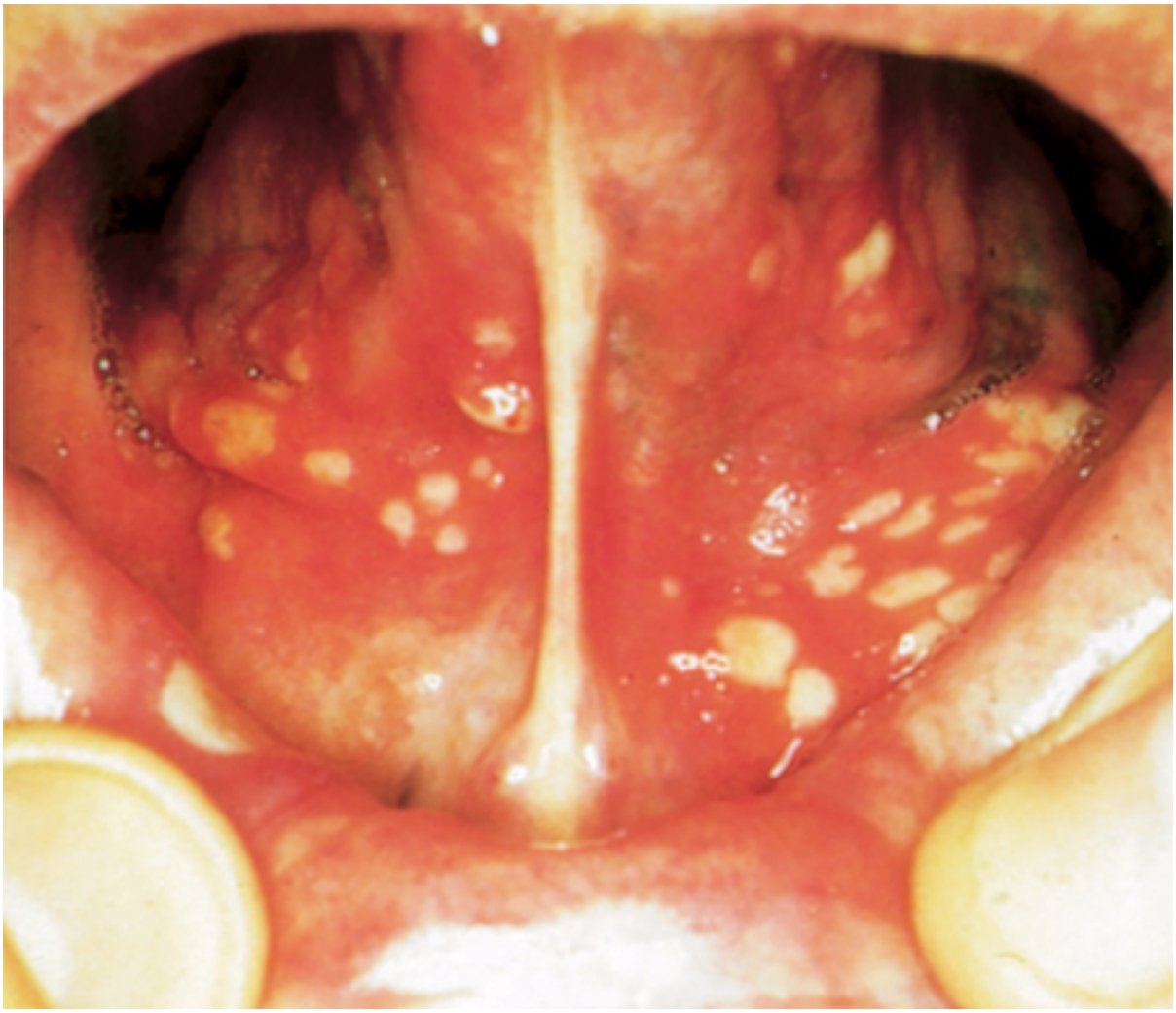


Recurrent aphthous stomatitis (RAS): major aphthae

From the personal collection of Crispian Scully, MD, PhD, FDSRCS, FRCPath

- Often more painful and persistent than minor aphthae
- Large round or ovoid ulcers greater than 10 mm in diameter
- Occur in groups of 1 to 6 at a time
- Involve any oral site, including the keratinized mucosa (palate and dorsum of tongue)
- Heal slowly over 10-40 days, or occasionally longer
- Recur frequently and may heal with scarring
- Occur mainly in people ages 10-40 years.

Herpetiform aphthous ulcers:



Recurrent aphthous stomatitis (RAS): herpetiform ulceration

From: Scully C, Flint S, Porter SR, et al. Oral and Maxillofacial diseases. London UK; 2004. Used with permission

- Rarer than major and minor aphthous ulcers
- Multiple (5-100) pinhead-sized discrete ulcers that can increase in size and coalesce to leave large areas of ulceration
- Mimics herpes simplex stomatitis, but are not preceded by vesicles or blistering, and are not communicable
- Often extremely painful
- Involve any oral site, including the keratinized mucosa (palate and dorsum of tongue)
- Heal in 10 days or longer
- Recur so frequently that ulceration may seem continuous
- Occur in a slightly older age group than the other forms of RAS and mainly in women.

Case history

Case history #1

A 17-year-old male student presents with recurrent mouth ulceration since his early schooldays. He has no respiratory, anogenital, gastrointestinal, eye, or skin lesions. His mother had a similar history as

a teenager. The social history includes no tobacco use and virtually no alcohol consumption. He has no history of recent drug or medication ingestion. Extraoral exam reveals no significant abnormalities and specifically no pyrexia; no cervical lymph node enlargement; nor cranial nerve, salivary, or temporomandibular joint abnormalities. Oral exam reveals a well-restored dentition and there is no clinical evidence of periodontal-attachment loss or pocketing. He has five 4 mm round ulcers with inflammatory haloes in his buccal mucosae.

Other presentations

The ulcer pattern is an important aspect of diagnosis of any recurrent oral ulceration. Recurrent ulcers starting from childhood are usually aphthous ulcers (aphthae) but they may be aggravated in adult life on smoking cessation or if there is systemic disease. If similar ulcers start later or are associated with fever or systemic disease, they may be aphthous-like ulcers.

Approach

Diagnosis is based on the history and clinical examination. There are no specific laboratory findings. It is important, however, to consider and exclude any possible systemic cause for recurrent ulcers, such as celiac disease, especially in people with systemic symptoms or signs, or adults with no prior history of oral ulceration.[1] [6] Furthermore, a solitary ulcer lasting more than 3 weeks may well represent malignancy and would warrant urgent referral to a specialist.[29] This will require further investigation and may involve incisional biopsy.

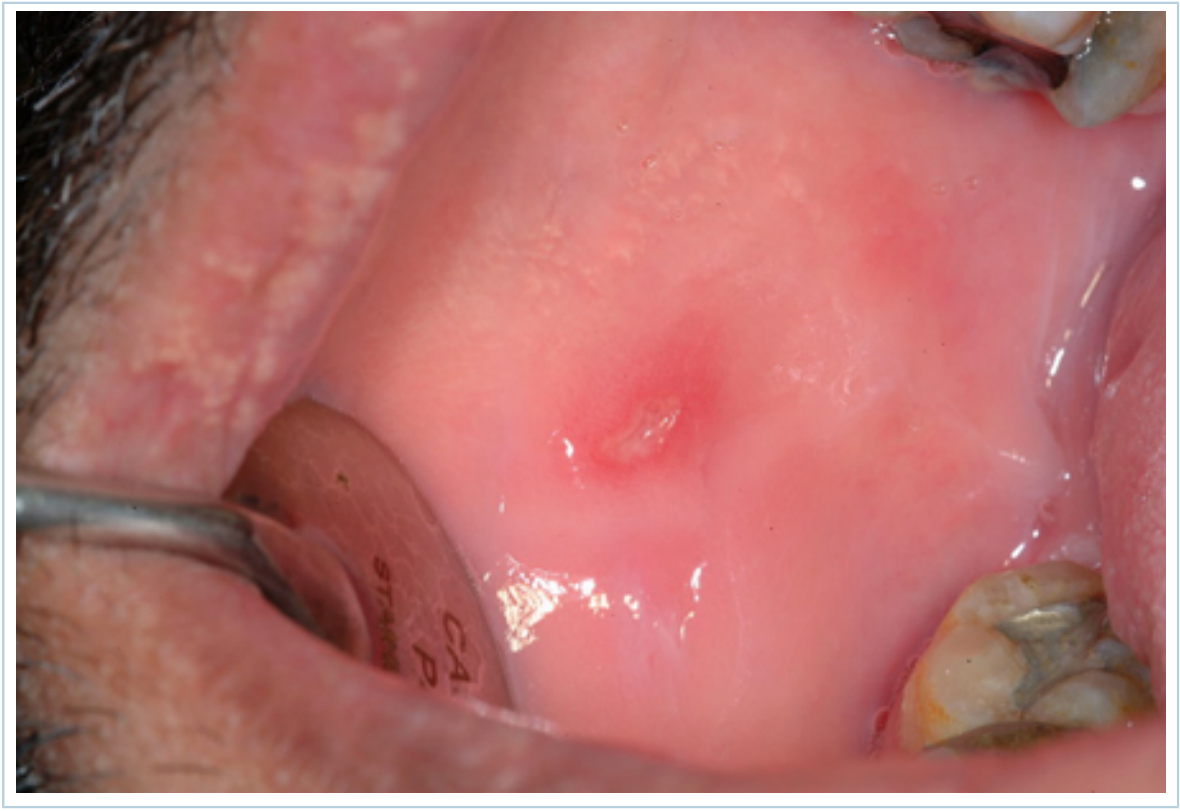
History

The onset of recurrent aphthous stomatitis (RAS) is usually during childhood; in 80% of cases, it develops before 30 years of age. History should include detailing the episodic pattern/cyclic nature of ulceration, number of ulcers, duration, age of onset, and any associated trigger factors. A family history is of value as over 42% of patients have first-degree relatives with RAS.[1] [10] RAS is more severe and starts at an earlier age in patients with a positive family history.[1] Trigger factors for onset of an episode of active ulceration may include trauma (e.g., following over-vigorous tooth brushing) and certain foods (e.g., chocolate, peanuts, coffee, and gluten products).[3] In some patients, ulcers coincide with the luteal phase of the menstrual cycle and often remit with oral contraceptives or during pregnancy.[6]

Clinical examination

Ulcers typically occur on the nonkeratinized oral mucosa: the buccal and labial mucosae, floor of the mouth, or ventrum of the tongue. There are three clinical presentations of RAS.[1] [2] [6]

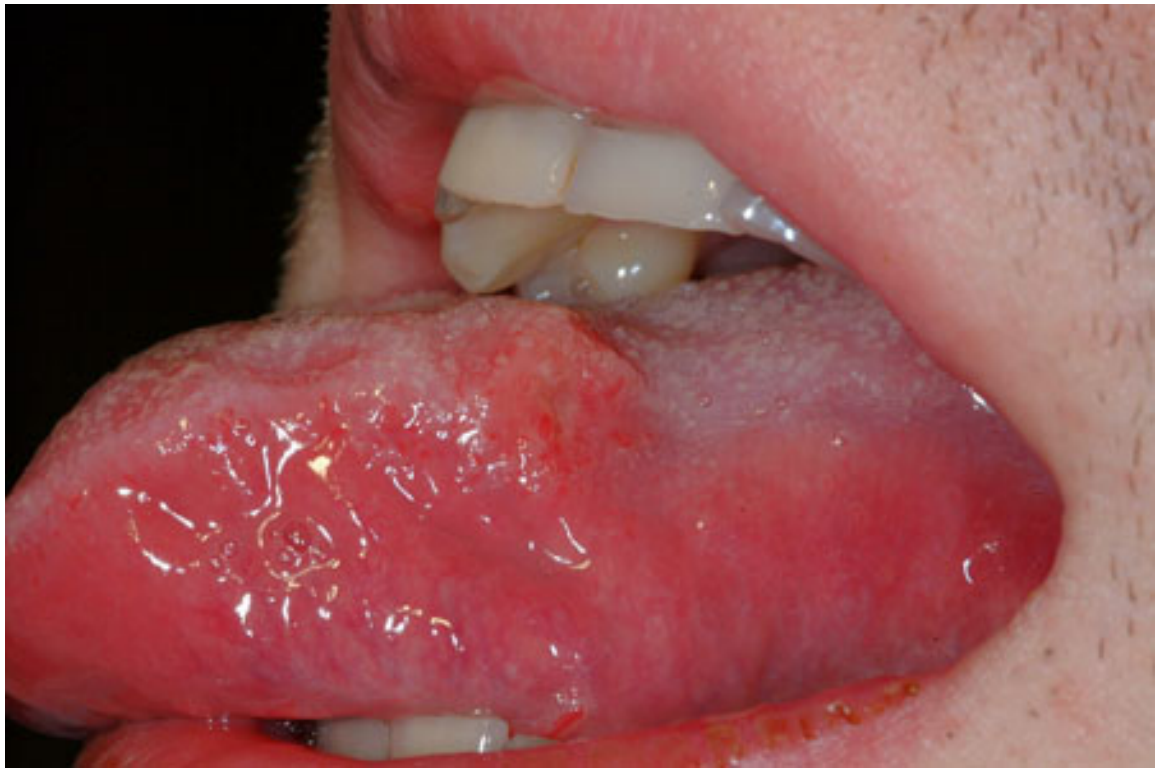
- Minor aphthous ulcers account for 75% to 85% of all RAS cases. These are less than 10 mm in diameter and tend to heal within 7-10 days without scarring. They are found mainly on the nonkeratinized mucosa of the lips, cheeks, floor of the mouth, sulci, or ventrum of the tongue.



Recurrent aphthous stomatitis (RAS): minor aphthae

From the personal collection of Crispian Scully, MD, PhD, FDSRCS, FRCPath

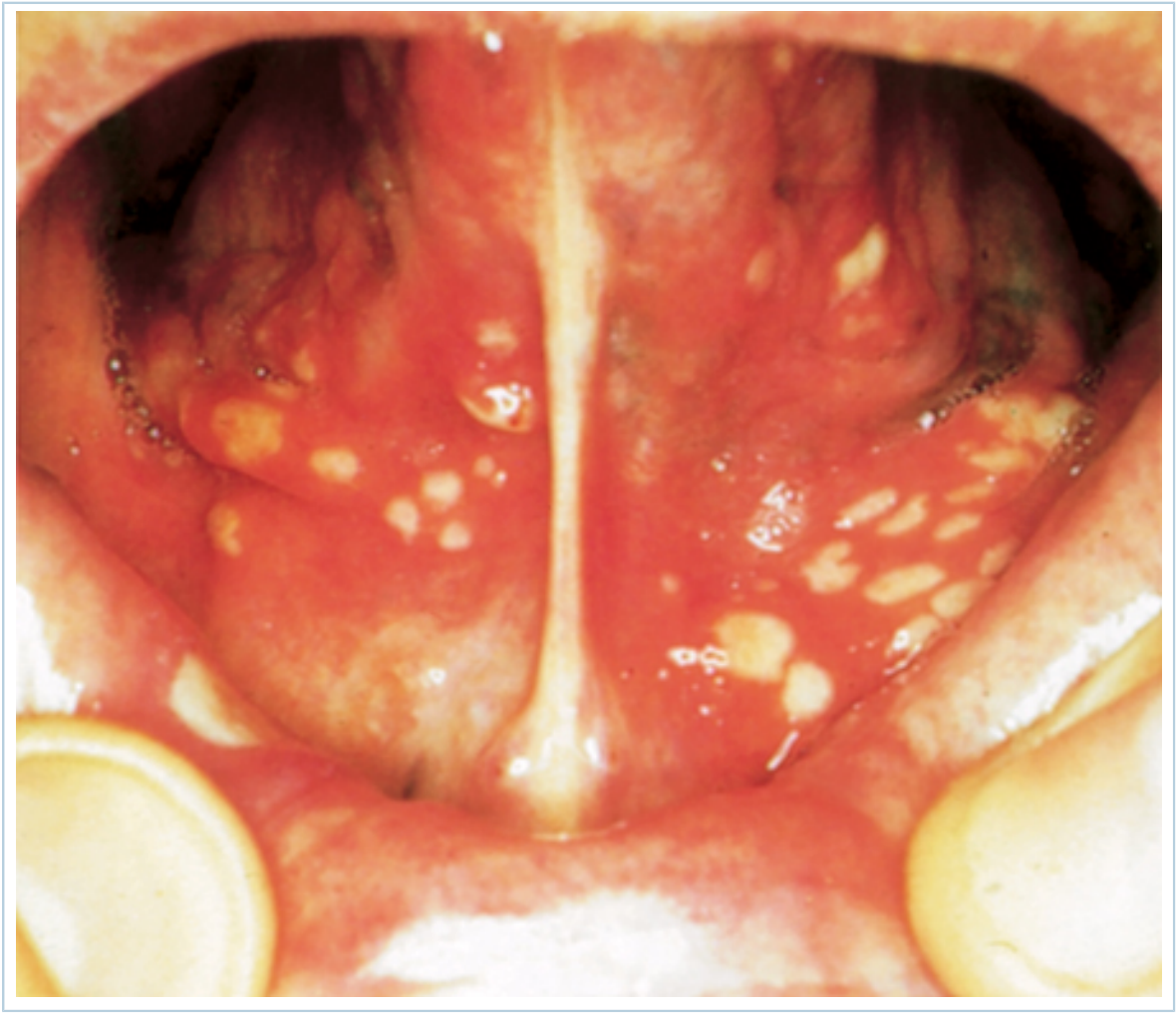
- Major aphthous ulcers (10% to 15% of all RAS cases) are round or ovoid and are greater than 10 mm in diameter. They are often more painful and persistent than minor aphthae. They involve any oral site, including the keratinized mucosa (palate and dorsum of tongue). They occur in groups of 1 to 6 at a time. They heal slowly over 10-40 days, or occasionally longer, recur frequently, and may heal with scarring.



Recurrent aphthous stomatitis (RAS): major aphthae

From the personal collection of Crispian Scully, MD, PhD, FDSRCS, FRCPath

- Herpetiform aphthous ulcers are rarer than major and minor aphthous ulcers and typically present as multiple (5-100) pinhead-sized discrete ulcers that can increase in size and coalesce to leave large areas of ulceration. They mimic herpes simplex stomatitis, but are not preceded by vesicles or blistering, and are not communicable. They are often extremely painful. They can involve any oral site, including the keratinized mucosa (palate and dorsum of tongue). They heal in 10 days or longer and recur so frequently that ulceration may seem continuous. They occur in a slightly older age group than the other forms of RAS and mainly in women.



Recurrent aphthous stomatitis (RAS): herpetiform ulceration
From: Scully C, Flint S, Porter SR, et al. Oral and Maxillofacial diseases. London UK; 2004. Used with permission

Oral ulceration similar in clinical appearance to RAS (aphthous-like ulceration [ALU]) can present as a manifestation of a number of systemic disorders.

- ALU may occur in immunodeficiency states including HIV infection or neutrophil dysfunction (e.g., as a component of cyclic neutropenia).[6] [30]
- ALU may occur in Behcet syndrome. These patients may present with, or have a history of, aphthous-like ulcers occurring on genital or other mucosae; erythema nodosum or other skin lesions; uveitis; joint involvement; or central nervous system manifestations.[1] [31] In MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome, a variant of Behcet syndrome, a generalized chondritis may be present along with major aphthae.[32]
- Other autoinflammatory states in which ALU may present include periodic fever with aphthae, pharyngitis, and adenitis (PFAPA syndrome), and tumor necrosis factor receptor-associated periodic syndrome.[33] [34] In these patients, fever is characteristic; cutaneous and other lesions may also be present, such as cervical lymphadenopathy.
- Hematinic (iron, folic acid, or vitamin B12) deficiencies may also present with ALU as a component of the underlying anemia, or in pre-anemia, often with angular stomatitis and/or sore tongue. Pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise may result from anemia per se and should be ascertained from the history. Assessment of other signs of iron

deficiency (e.g., glossitis, angular stomatitis, and spooning of the nails) should be made. In patients with B12 deficiency, a wide range of other signs and symptoms may be present. A history of diet poor in sources of folate and phenytoin or heavy alcohol use may suggest folate deficiency.

- ALU can also be a feature of inflammatory bowel disease, both of Crohn disease and less commonly of ulcerative colitis and celiac disease. In these patients, the ulceration probably often reflects the associated hematinic deficiencies.[6] [35]
- A full medication history should be taken. ALU has been reported in patients taking nonsteroidal anti-inflammatory drugs, beta-blockers, nicorandil (a potassium channel blocker), ACE inhibitors, antibiotics, anticonvulsants, anticoagulants, and methotrexate.[1] [36]

Laboratory investigations

Although there are no specific laboratory findings in RAS, in some patients - for example, where history and exam suggest a nutritional deficiency or a hematologic disorder - complete blood count and hematinic estimation (serum ferritin, serum/red cell folate, and serum B12) is indicated to exclude iron and vitamin deficiencies.[1] In patients of all age groups with suspected celiac disease, a serum immunoglobulin A-tissue transglutaminase may be an appropriate initial investigation. Testing for HIV infection should be considered in patients with a history of HIV-associated infections (candidiasis, hairy leukoplakia) or neoplasms (Kaposi sarcoma, lymphoma), or other clinical evidence of, or risk factors for, HIV infection.[1] An elevated plasma viscosity or erythrocyte sedimentation rate may be found in autoinflammatory states. In patients with abnormal results, a diagnosis of ALU is more likely than RAS. In these patients, definitive diagnosis will depend on subsequent investigations as appropriate. Symptoms of autoimmune disorder (e.g., skin lesions) alongside ulcers may warrant an antinuclear antibody test in order to rule out autoimmune disease.

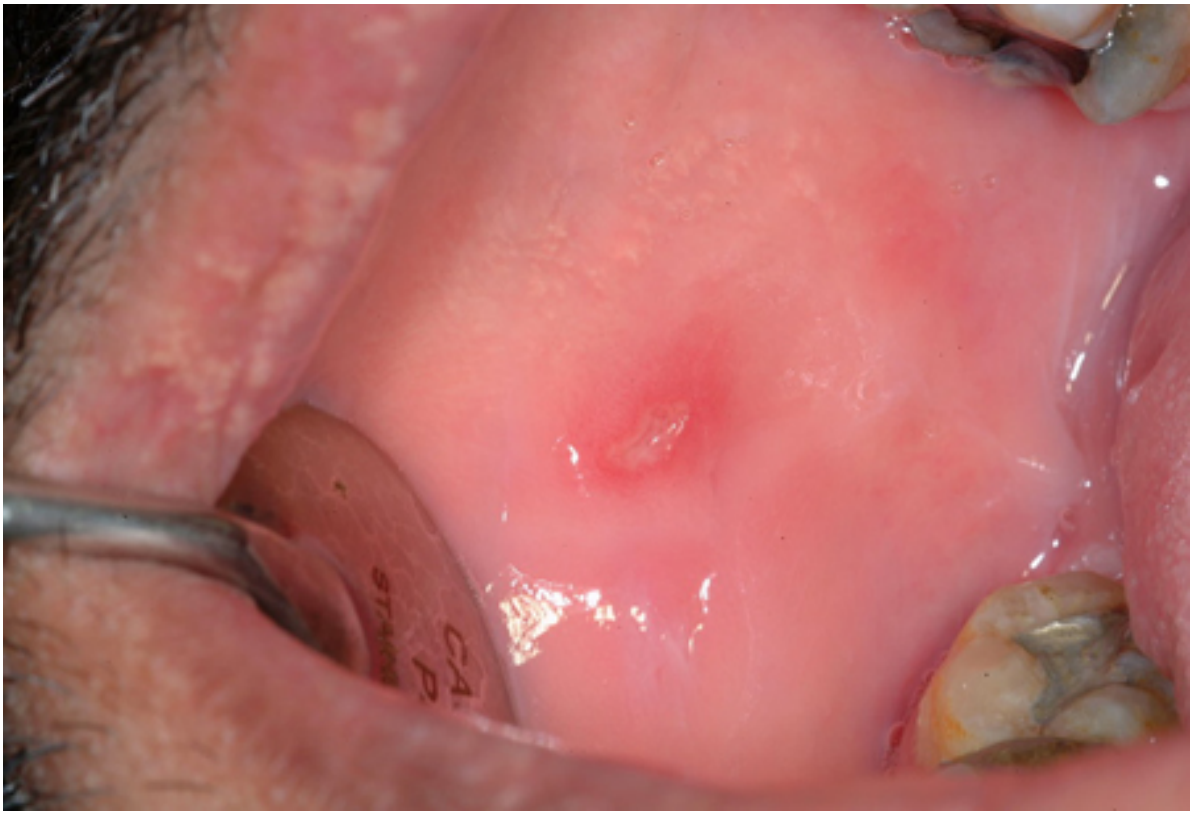
A solitary ulcer lasting more than 3 weeks may well represent malignancy and would warrant urgent referral to a specialist.[29] This will require further investigation and may involve incisional biopsy.

History and exam

Key diagnostic factors

oral ulcers (common)

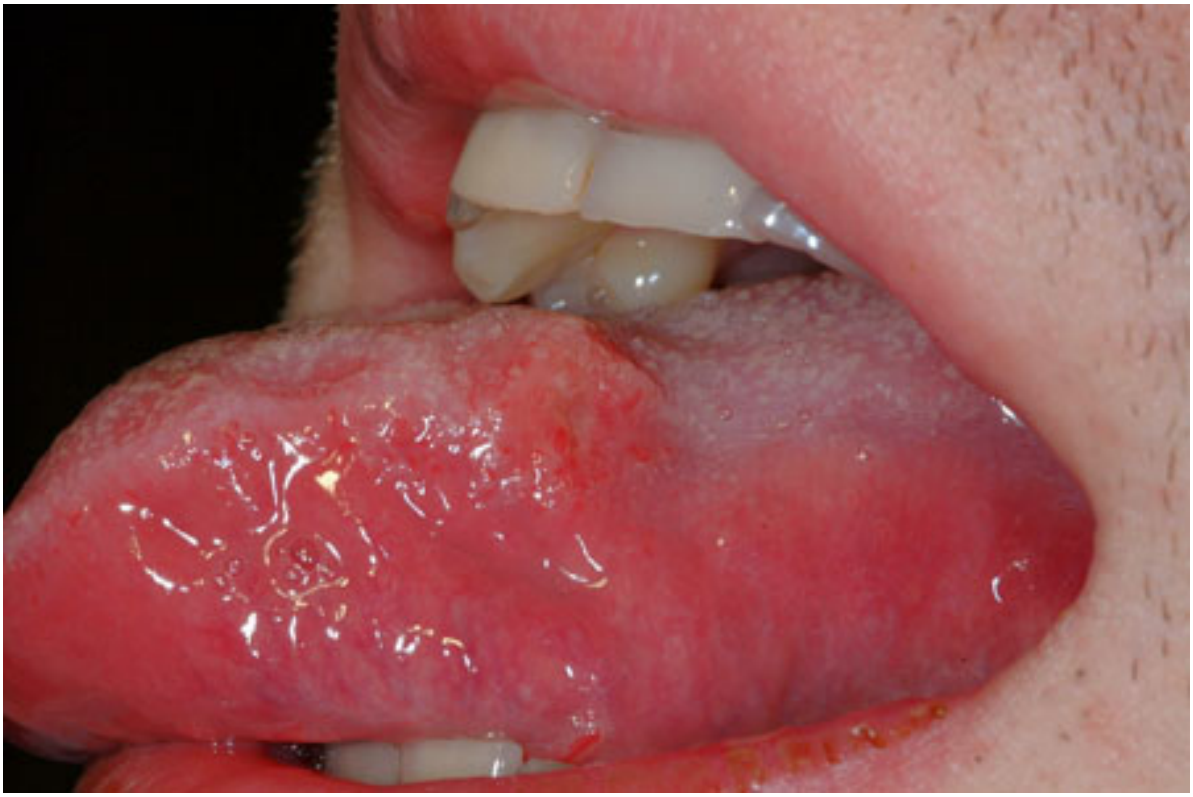
- Minor aphthae are found mainly on the nonkeratinized mucosa of the lips, cheeks, floor of the mouth, sulci, or ventrum of the tongue. They are less than 10 mm in diameter, occur in groups of 1 to 6 at a time, and tend to heal within 7-10 days without scarring.[1] [2] [6]



Recurrent aphthous stomatitis (RAS): minor aphthae

From the personal collection of Crispian Scully, MD, PhD, FDSRCS, FRCPath

- Major aphthae involve any oral site, including the keratinized mucosa (palate and dorsum of tongue). They are round or ovoid ulcers greater than 10 mm in diameter, and occur in groups of 1 to 6 at a time. They are often more painful and persistent than minor aphthae and heal slowly, over 10-40 days, or occasionally longer.[1] [2] [6]



Recurrent aphthous stomatitis (RAS): major aphthae

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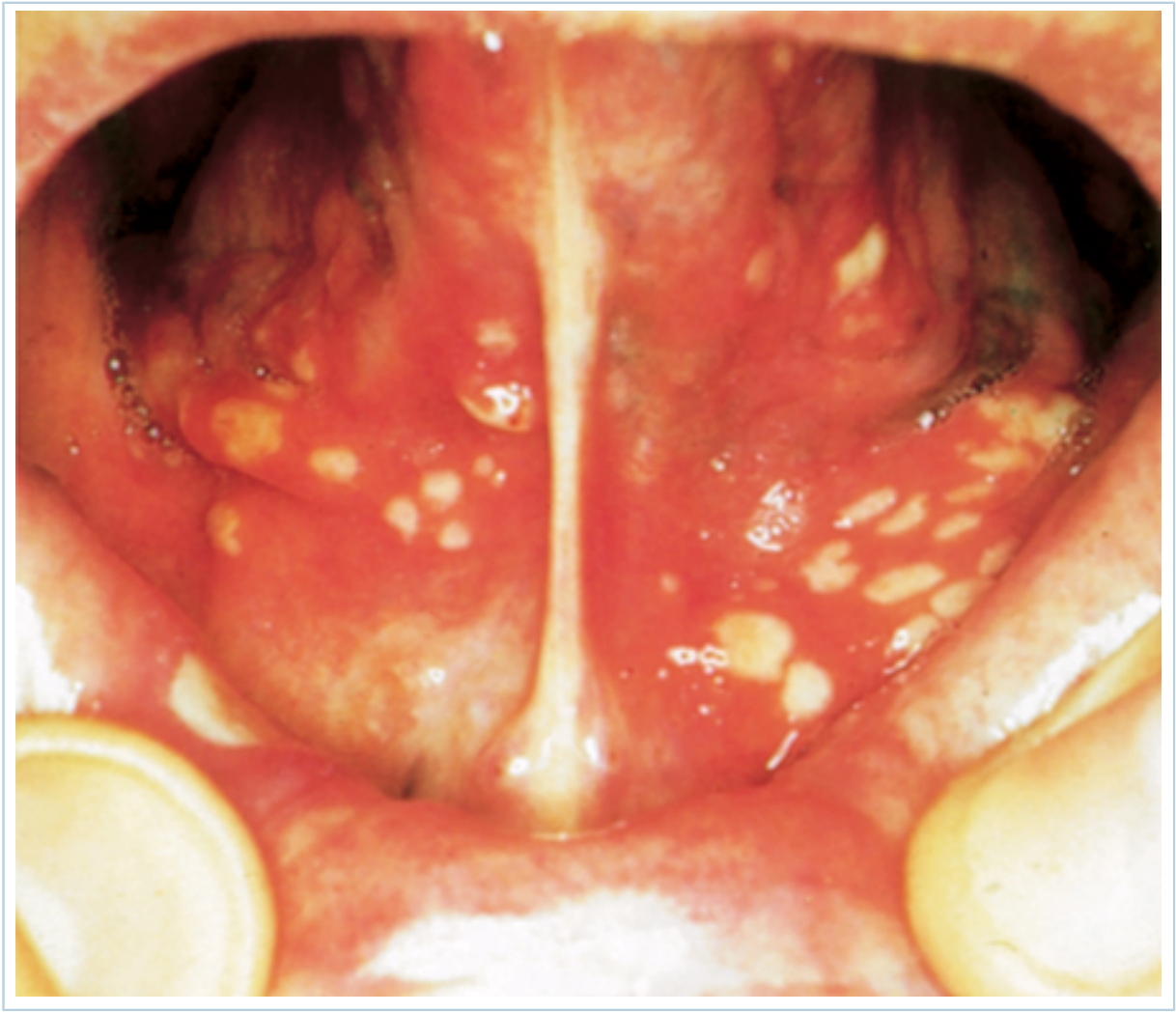
- Herpetiform aphthous ulcers are rarer than major and minor aphthous ulcers and typically present as multiple (5-100) pinhead-sized discrete ulcers that can increase in size and coalesce to leave large areas of ulceration. They mimic herpes simplex stomatitis, but are not preceded by vesicles or blistering, and are not communicable. They are often extremely painful. They can involve any oral site, including the keratinized mucosa (palate and dorsum of tongue). They heal in 10 days or longer and recur so frequently that ulceration may seem continuous. They occur in a slightly older age group than the other forms of recurrent aphthous stomatitis and mainly in women.[1] [2] [6]



Recurrent aphthous stomatitis (RAS): herpetiform ulceration

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afebrile (common)

- Periodic/recurrent fevers suggest an alternate systemic condition (e.g., cyclic neutropenia, periodic fever with aphthae, pharyngitis, and adenitis [PFAPA syndrome], or tumor necrosis factor receptor-associated periodic syndrome).

absence of genital or ocular ulceration (common)

- Patients with aphthous-like ulcers occurring on genital or other mucosae or uveitis suggest aphthous-like ulceration as a component of a systemic process (e.g., Behcet syndrome).[1] [6]

no history of immunodeficiency (common)

- Immunodeficiency (including HIV infection) suggests aphthous-like ulceration rather than recurrent aphthous stomatitis.[6]

absence of pallor (common)

- Anemia leading to pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise may result from an underlying hematinic deficiency.
- Pallor may also suggest iron deficiency anemia as a cause of aphthous-like ulceration if accompanied by glossitis, angular stomatitis, and spooning of the nails.

Risk factors

Strong

positive family history

- Over 42% of recurrent aphthous stomatitis (RAS) patients have first-degree relatives with RAS.[1] [10]
- The likelihood of childhood-onset RAS is 90% when both parents are affected but only 20% when neither parent has RAS.
- RAS is more severe and starts at an earlier age in patients with a positive family history.[1]

nonsmoker or cessation of smoking

- Patients with recurrent aphthous stomatitis are usually nonsmokers and there is a lower prevalence and severity of ulcers in heavy compared with moderate smokers.[15] [16]
- Some patients report an onset of ulcers parallel to smoking cessation, whereas others report control on reinitiation 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 aphthae.[6]

trauma

- Local trauma may trigger ulcers in susceptible people.[1] [6] [19]

age <30 years

- The onset of recurrent aphthous stomatitis (RAS) is usually during childhood; in 80% of cases, RAS develops before 30 years of age.[1] [10]

Weak

cows' milk-fed children

- Recurrent aphthous stomatitis (RAS) may be more prevalent in cows' milk-fed children.[20] There is still no conclusive evidence to support environmental allergens or food hypersensitivities as a major cause of RAS.

female sex

- Studies suggest that recurrent aphthous stomatitis is more common in women.[1] [2]

high stress levels

- Symptoms of recurrent aphthous stomatitis (RAS) have been shown to have a high correlation with anxiety, depression, and psychological stress.[6] [11] [28]

food intolerance

- Certain foods (e.g., chocolate, peanuts, coffee, and gluten products) have been reported to trigger episodes of recurrent aphthous stomatitis.[3]

hormonal imbalance

- There are patients whose ulcers coincide with the luteal phase of the menstrual cycle and often remit with oral contraceptives or during pregnancy.[6]

use of sodium lauryl sulfate-containing toothpaste

- An increased frequency of recurrent aphthous stomatitis (RAS) related to sodium lauryl sulfate (SLS)-containing dentifrice has been reported, although other studies found no such association.[21]
- Because SLS dentifrices are in widespread use, it seems unlikely that this agent truly predisposes to, or causes, most RAS.[6]

Investigations

Other tests to consider

Test	Result
CBC • Anemia may indicate an alternate or coexisting cause (e.g., iron, B12, or folate deficiency, or leukemia). • Hematinic (iron, folic acid, or vitamin B12) deficiencies may be twice as common in some groups of patients with recurrent aphthous stomatitis as in healthy control subjects.[1] [6] [17] [18]	**variable; usually normal**
serum ferritin • Consider in order to rule out iron deficiency as a cause of aphthous-like ulceration.[37]	**usually normal**
serum folate • Consider in order to rule out folate deficiency as a cause of aphthous-like ulceration.[37]	**usually normal**
serum vitamin B12 • Consider in order to rule out B12 deficiency as a cause of aphthous-like ulceration.[37]	**usually normal**
serum IgA-tTG • Consider an immunoglobulin A-tissue transglutaminase (IgA-tTG) test in any case of suspected celiac disease in patients of all age groups. • If celiac serology is positive or celiac disease is suspected, it should be confirmed with small-bowel endoscopy and biopsy.[38]	**negative**
viral serology (e.g. HIV or Epstein-Barr virus) • Consider in order to rule out HIV or Epstein-Barr virus infection as a cause of aphthous-like ulceration.	**negative**
erythrocyte sedimentation rate and CRP • Consider in order to rule out systemic inflammatory disease (e.g. Behcet syndrome or other autoinflammatory states) as a cause of aphthous-like ulceration.	**normal**
biopsy • Order if a malignant ulcer or immunobullous disease is suspected. • Multiple ulcers are unlikely to represent an oral malignancy, but a single ulcer lasting more than 3 weeks may represent malignancy and would warrant urgent referral to a specialist.[29] This will require further investigation and may involve incisional biopsy.[1] [6]	**inflammatory infiltrate with no evidence of malignancy**
antinuclear antibody test • Symptoms of autoimmune disorder (e.g., skin lesions) alongside ulcers may warrant an antinuclear antibody (ANA) test in order to rule out autoimmune disease.	**negative**
serum HIV test • Considered if other symptoms of immunodeficiency (e.g., oral candidiasis) are present. Staff should be trained to do the rapid test. Should be ordered when HIV testing is indicated (e.g., presence of widespread oral candidiasis and weight loss). False negatives may occur during window period immediately after infection,	**positive**

Test	Result
before antibodies to HIV have occurred. A positive result should be confirmed with a second rapid test.	

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Behcet syndrome	• Patients may present with aphthous-like ulcers occurring on genital or other mucosae; erythema nodosum, acneiform pustular lesions, or other skin lesions; uveitis; joint involvement; or central nervous system manifestations.[1] [31] • Seen most commonly in the Middle East, the Far East, and around the Mediterranean.[39]	• Diagnosis is based on history and clinical features. • Pathergy test is positive in up to 60% of patients, with highest frequency in those of Middle Eastern origin. • May be HLA-B51 genotype, although this association varies with ethnicity.
Malignant ulcer	• Persistent, nonhealing ulcers are typical of malignant disease (e.g., oral squamous cell carcinoma); however, red or white lesions or lumps may be present in malignant cases. • Lesion may be indurated and painless; cervical lymphadenopathy may be present. • A solitary ulcer lasting more than 3 weeks may well represent malignancy and would warrant urgent referral to a specialist.[29]	• Incisional biopsy will show malignant disease (most commonly squamous cell carcinoma).
Folate deficiency	• History of a diet poor in sources of folate, or of heavy alcohol use. • Pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise may result from the anemia.	• Anemia is macrocytic (mean corpuscular volume [MCV] >100 femtoliters); serum folate low (<2.5 nanograms/mL); red blood cell folate level <140 nanograms/mL.
Iron deficiency anemia	• May present with glossitis, angular stomatitis, and spooning of the nails. • Pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise may result.	• Ferritin is typically low (<50 nanograms/mL) in iron deficiency; a ferritin level of <15 nanograms/mL strongly suggests iron deficiency.
Vitamin B12 deficiency	• May present with evidence of peripheral neuropathy	• Anemia is typically macrocytic (mean corpuscular volume [MCV]

Condition	Differentiating signs / symptoms	Differentiating tests
	or posterior column degeneration (e.g., ataxia). • Pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise may result.	>100 femtoliters); serum B12 is low (<200 picograms/mL).
HIV/AIDS	• HIV-associated infections (candidiasis, hairy leukoplakia) or neoplasms (Kaposi sarcoma, lymphoma); other clinical evidence of, or risk factors for, HIV infection. • In HIV infection, aphthous-like ulceration may be seen independent of the necrotizing ulceration of HIV infection.[40]	• Diagnosis is based on history and clinical features. • HIV serology will be positive.
Crohn disease	• Crohn disease can affect any part of the gastrointestinal tract and symptoms may be extremely variable. • Features may include: bloody diarrhea; weight loss; labial or facial swelling; perioral erythema; cobblestoning of the oral mucosa; and, occasionally, joint manifestations.	• Colonoscopy will show mucosal inflammation and discrete deep ulcers located transversely and longitudinally, creating a cobblestone appearance. • Full-thickness bowel biopsies demonstrate transmural involvement with noncaseating granulomas present. Oral biopsy may show noncaseating granulomas and lymphangiectasis (dilation of lymph structures reflecting edematous swelling).
Ulcerative colitis	• Ulcerative colitis typically presents with features of colitis including left-sided abdominal pain and bloody diarrhea. In addition to oral ulcers, superficial pus-filled blisters (pyostomatitis vegetans) may be present.	• Colonoscopy will show rectal and continuous uniform involvement, loss of vascular marking, diffuse erythema, mucosal granularity, rare fistulas, and normal terminal ileum (or mild "backwash" ileitis in pancolitis). • Bowel biopsies will show mucin depletion, basal plasmacytosis, and diffuse mucosal atrophy.
Celiac disease	• Patients typically present with unexplained gastrointestinal symptoms, chronic diarrhea,	• Diagnosis is suggested by a positive immunoglobulin A-tissue transglutaminase test.

Condition	Differentiating signs / symptoms	Differentiating tests
	unexplained iron deficiency anemia, or a skin rash consistent with dermatitis herpetiformis.	• Duodenal endoscopy will show atrophy and scalloping of mucosal folds, nodularity, and mosaic pattern of mucosa; histology will show presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia.
MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome	• Thought to potentially be a variant of Behcet syndrome. • A generalized chondritis may be present.[32]	• Diagnosis is based on history and clinical features.
Cyclic or other neutropenia	• Patients may present with recurrent fevers and recurrent infections.[30]	• Diagnosis is based on history and clinical features. • CBC may show leukopenia.
PFAPA (periodic fever with aphthae, pharyngitis, and adenitis) syndrome	• Comprises periodic fever, aphthae, pharyngitis, and cervical adenitis. • Although rare, it tends to occur in young children.[33]	• Diagnosis is based on history and clinical features. • CBC may show leukopenia.
TRAPS (tumor necrosis factor receptor-associated periodic syndrome)	• Comprises periodic fever and aphthae.[34]	• Diagnosis is based on history and clinical features. • CBC may show raised erythrocyte sedimentation rate.
Sweet syndrome	• Patients have ulceration similar to recurrent aphthous stomatitis but with sudden onset of fever, and well-demarcated plum-colored skin lesions.[41] • There is an associated malignancy (e.g., acute myeloid leukemia) in 50% of patients.	• Diagnosis is based on history and clinical features. • CBC may show leukocytosis.
Pemphigus	• This is a blistering disease. The early phases of oral pemphigus may be characterized by recurring oral ulcers.[1] [42]	• Incisional biopsy and histopathology may show characteristic findings of pemphigus: epithelial acantholysis with suprabasal blistering. • Direct immunofluorescence will show staining for IgG, C3, or both, as a thin linear band on the surface of keratinocytes in the suprabasal epithelium.
Syphilis	• Primary syphilis: oral chancre presents as	• Serum treponemal enzyme immunoassay: positive.

Condition	Differentiating signs / symptoms	Differentiating tests
	solitary painless indurated ulceration at the site of inoculation, persisting 3-7 weeks and healing without scarring; most likely sites of involvement are lips, tongue, commissures, gingiva, palate, and tonsils; lymphadenopathy is common. • Secondary syphilis: mucous patches presenting as shallow, irregularly shaped plaques or ulcerations with erythematous borders; gray-white necrotic membrane covering may be present; snail track appearance; concurrent cutaneous rash; genital lesions. • Tertiary syphilis: locally destructive granulomas (gummas) or glossitis may be present with mucosal atrophy.	
Tuberculosis	• Painful granulomatous ulceration; lymphadenopathy may be present; lesions may be locally destructive and mimic squamous cell carcinoma; common sites of occurrence are tongue, palate, buccal mucosa, or lips.	• Sputum smear: positive for acid-fast bacilli.
Mycoses (e.g., histoplasmosis, paracoccidiomycosis)	• Granulomatous ulceration may mimic neoplasm.	• Diagnosis is based on history (e.g., recent foreign travel to endemic areas) and clinical features (e.g., HIV/AIDS). • Positive microbiology or nucleic acid test for fungal infection.
Herpangina	• Cervical lymphadenopathy is present, and ulcers are also seen on the soft palate.	• Diagnosis is clinical.
Hand-foot-and-mouth disease	• Most commonly affects children, and causes a low-grade fever and general malaise. Rash is typically present on the palms and/or soles, and may last for up to 10 days.	• Diagnosis is typically clinical. • CBC will show raised WBC count; viral culture will allow isolation of non-polio enterovirus 71 if this is the causative virus.

Condition	Differentiating signs / symptoms	Differentiating tests
	• Oropharynx is inflamed, with scattered papules, macules, vesicles, or superficial ulcers on an erythematous base on the tongue, pharynx, buccal mucosa, gingiva, and occasionally the lips; may be only yellowish ulcerations, as vesicles tend to rupture quickly. Typically heal within 1 week. Occasional serious neurologic complications.	
Epstein-Barr virus (EBV) infection (infectious mononucleosis)	• Small superficial ulcers of the oral mucosa may be a feature of EBV infection. • Features of infectious mononucleosis are often present.	• CBC may show lymphocytosis and atypical lymphocytosis in EBV infection. • Serology will be positive for EBV-specific antibodies: viral capsid antigen (VCA)-IgM, VCA-IgG, early antigen, Epstein-Barr nuclear antigen.
Intra-oral herpes (Herpes simplex)	• Herpes simplex virus infection of the oral cavity can usually be differentiated from other causes of recurrent oral ulcerations on the basis of its clinical appearance and distribution.[43]	• Diagnosis is clinical.

Approach

The main goals are to exclude serious and/or systemic disease, and to provide therapy to achieve pain relief, reduction of ulcer duration, and reduction in frequency of episodes.[44]

Initial treatment consists of simple options, including changing the patient's toothpaste to a sodium lauryl sulfate-free formulation, antibacterial mouthwash (e.g., chlorhexidine), and symptom relief (e.g., topical lidocaine). Patients should be instructed to avoid recognized trigger foods, and acidic foods and drinks.[1]

If simple measures alone do not work to reduce the symptoms, topical corticosteroids are still the mainstay of treatment, with adjunctive topical antimicrobials, which may reduce the inflammatory component. However, if recurrent aphthous stomatitis (RAS) fails to respond to topical therapies, systemic therapies may be required.[3] [45]

For all patients, the possibility of local trauma (e.g., from sharp and/or broken teeth, dentures and orthodontic appliances, and biting during chewing) should be assessed and appropriate dental treatment undertaken.[3] There is some evidence of benefit from vitamin B12, even in the absence of any deficiency; supplementation with oral vitamin B12 (cyanocobalamin) has been shown to be effective in studies, irrespective of serum B12 levels.[46] [47] [48]

Consider iron supplements if iron deficiency anemia occurs.[37] [49] However, it is important to consider the cause of iron deficiency before treating it because this can often be the first sign of malabsorption or occult blood loss. Iron supplementation in adults and children may be necessary to prevent ulcers that are a result of iron deficiency anemia. Initial treatment is daily oral iron replacement therapy.[49]

Topical therapies

Topical corticosteroids are the mainstay of treatment when simple measures alone do not work to improve the symptoms. A variety of different agents can be used, including a corticosteroid paste (a combination of a potent topical corticosteroid such as triamcinolone and dental paste), hydrocortisone buccal tablets, and betamethasone soluble tablets.[50] However, these specific formulations of hydrocortisone and betamethasone are not available in the US and corticosteroid mouth rinses may need to be specially compounded. More potent topical corticosteroids (such as betamethasone dipropionate, clobetasol, or fluocinonide) may also be used.[3] Treatment duration is case-dependent but there is no evidence of adrenal suppression with low-potency corticosteroids.

Topical therapies for symptom relief may be of benefit. These include topical anesthetics (e.g., lidocaine) and topical anti-inflammatory agents. Adjunctive antimicrobial agents may also be of some value, in part by reducing secondary infection. These may reduce the severity and pain of ulceration. For example, randomized controlled trials have shown that chlorhexidine oral solution may reduce the duration of RAS and increase the number of ulcer-free days.[51] [52] [53] [54] Topical tetracyclines used as rinses may also be effective.[55] [56] However, they must be compounded, and they should be avoided in children less than 8 years of age as they may cause tooth discoloration.[57]

Systemic therapies

If RAS fails to respond to topical therapies, systemic therapies may be required. However, studies are lacking to assess their efficacy (or their adverse effects).[58] For patients with severe RAS, a short course of systemic corticosteroids, systemic immunomodulators, or anti-inflammatory agents, such as colchicine, azathioprine, or thalidomide, may be necessary.[1] [3] [45] [59] [60]

Oral prednisone as a 1-week course tapered over a second week is one suggested regimen.[3]

The first-line systemic immunomodulator used in RAS and the mucocutaneous manifestations of Behcet syndrome is colchicine.[61] There is weak evidence to support the use of azathioprine.

Thalidomide is rarely used; great caution is required for its use, and specialist referral and prescription is recommended.[1] [3] However, the use of thalidomide in RAS is supported by data in both RAS and in patients with aphthous-like ulceration in HIV infection.[62] [63] In these patient groups, open and double-blind studies have shown that thalidomide is an effective agent available for the management of severe, refractory RAS.[6] [59] Thalidomide would never be commenced in primary care - there is tight legislation around prescribing of it. For example, in the UK its use is approved only on case-by-case discussion with various health boards/trusts.

Results with other immunomodulatory agents used to treat severe or refractory RAS, such as levamisole or pentoxifylline, have shown either poor clinical response or a significant incidence of treatment-related adverse effects.[6]

Management of children under the age of 12 years

As with adults, the first-line treatment in children is the introduction of simple measures (i.e., change of toothpaste, avoidance of triggers, or assessment for trauma). In addition to this, there are a number of over-the-counter anti-inflammatory treatments available for the relief of symptoms. A suitable formulation that is licensed for use in children should be selected.[64]

There are a limited number of topical corticosteroids that are licensed for oral use in children. If topical corticosteroids are needed, they can be used off-label, but only in children who can follow instructions with regards to spitting out the medication. This means that they usually cannot be used in children under 6 years of age. These treatments should only be started under specialist care after the child has been assessed and other causes of oral ulcers have been excluded. Oral asthma inhalers have been used off-label as a topical application for this indication.[64]

Systemic treatments for RAS are rarely used in children under the age of 12 years, and are only commenced under specialist care.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute		(summary)
all patients		
	1st	change toothpaste and avoid triggers
	plus	symptom relief
	adjunct	antibacterial mouthwash
	adjunct	oral vitamin B12
	adjunct	oral iron
	2nd	topical corticosteroid
	plus	symptom relief
	adjunct	antibacterial mouthwash
	adjunct	oral vitamin B12
	adjunct	oral iron
	3rd	systemic corticosteroid or colchicine
	plus	symptom relief
	adjunct	antibacterial mouthwash
	adjunct	oral vitamin B12
	adjunct	oral iron
	4th	specialist referral

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

all patients

1st **change toothpaste and avoid triggers**

» Patients should be advised to change their toothpaste to a sodium lauryl sulfate (SLS)-free formulation. An increased frequency of recurrent aphthous stomatitis (RAS) related to SLS-containing dentifrice has been reported, although other studies found no such association.[21] However, because SLS dentifrices are in widespread use, it seems unlikely that this agent truly predisposes to, or causes, most RAS.[6]

» Patients should also be instructed to avoid recognized trigger foods, and acidic foods and drinks.[1]

» For all patients, the possibility of local trauma (e.g., from sharp and/or broken teeth, dentures and orthodontic appliances, and biting during chewing) should be assessed, and appropriate dental treatment undertaken.[3]

plus **symptom relief**

Treatment recommended for ALL patients in selected patient group

Primary options

» lidocaine oropharyngeal viscous solution: (2%) children: 1.25 mL every 3 hours when required (swish around in mouth and spit out), maximum 4 doses/12 hours; adults: 15 mL every 3 hours when required (swish around in mouth and spit out), maximum 8 doses/day

» Topical therapies for symptom relief may be of benefit. These include topical anesthetics (e.g., lidocaine) and over-the-counter topical anti-inflammatory agents.[65]

adjunct **antibacterial mouthwash**

Treatment recommended for SOME patients in selected patient group

Primary options

» chlorhexidine oropharyngeal: (0.12%) children and adults: 10-15 mL as a mouthwash twice daily

Acute

» Adjunctive antimicrobial agents may also be of some value, in part by reducing secondary infection. These may reduce the severity and pain of ulceration.[3]

» Randomized controlled trials have shown that chlorhexidine oral solution can reduce the duration of recurrent aphthous stomatitis and increase the number of ulcer-free days.[51] [52] [53] [54]

» Topical tetracyclines used as rinses may also be effective.[55] [56] These formulations need to be specially compounded. They may provide relief and reduce ulcer duration. Should be avoided in children less than 8 years of age as they may cause tooth discoloration and tooth staining. Patients should be advised to thoroughly brush teeth before use (as it stains the plaque on the teeth), and that it is not for regular long-term use.

adjunct **oral vitamin B12**

Treatment recommended for SOME patients in selected patient group

Primary options

» cyanocobalamin (vitamin B12): children: consult specialist for guidance on dose; adults: 1000 micrograms orally once daily
If available, sublingual tablets may be used; they should be dissolved under the tongue and swallowed.

» There is some evidence of benefit from vitamin B12, even in the absence of any deficiency; supplementation with oral vitamin B12 (cyanocobalamin) has been shown to be effective in studies, irrespective of serum B12 levels.[46] [47] [48]

adjunct **oral iron**

Treatment recommended for SOME patients in selected patient group

Primary options

» ferrous sulfate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily
Dose expressed as elemental iron.
Alternative dose regimens may be available.

OR

MANAGEMENT

Acute

» ferrous gluconate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily

Dose expressed as elemental iron.

Alternative dose regimens may be available.

OR

» ferrous fumarate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily

Dose expressed as elemental iron.

Alternative dose regimens may be available.

OR

» ferric maltol: adults: 30 mg orally twice daily

» Iron supplementation in adults and children may be necessary to prevent ulcers that are a result of iron deficiency anemia. Initial treatment is daily oral iron replacement therapy.[49]

2nd **topical corticosteroid**

Primary options

» triamcinolone topical: (0.1% paste) children: consult specialist for guidance on dose; adults: apply to the affected area(s) two to three times daily

» Topical corticosteroids are the mainstay of treatment if simple measures alone do not work.

» A variety of different agents can be used, including a corticosteroid paste (a combination of a potent topical corticosteroid, such as triamcinolone, and dental paste), hydrocortisone buccal tablets, and betamethasone soluble tablets.[3] However, these specific formulations of hydrocortisone and betamethasone are not available in the US and corticosteroid mouth rinses may need to be specially compounded.

» A more potent topical corticosteroid, such as betamethasone dipropionate, clobetasol, or fluocinonide, may also be used.[3] However, these drugs may need to be specially compounded in dental paste if they are not commercially available.

» Treatment duration is case-dependent but there is no evidence of adrenal suppression with low-potency corticosteroids.

Acute

» There are a limited number of topical corticosteroids that are licensed for oral use in children. If topical corticosteroids are needed, they can be used off-label, but only in children who can follow instructions with regards to spitting out the medication. This means that they usually cannot be used in children under 6 years of age. These treatments should only be started under specialist care after the child has been assessed and other causes of oral ulcers have been excluded.[64]

plus **symptom relief**

Treatment recommended for ALL patients in selected patient group

Primary options

» lidocaine oropharyngeal viscous solution: (2%) children: 1.25 mL every 3 hours when required (swish around in mouth and spit out), maximum 4 doses/12 hours; adults: 15 mL every 3 hours when required (swish around in mouth and spit out), maximum 8 doses/day

» Topical therapies for symptom relief may be of benefit. These include topical anesthetics (e.g., lidocaine) and over-the-counter topical anti-inflammatory agents.[65]

adjunct **antibacterial mouthwash**

Treatment recommended for SOME patients in selected patient group

Primary options

» chlorhexidine oropharyngeal: (0.12%) children and adults: 10-15 mL as a mouthwash twice daily

» Adjunctive antimicrobial agents may also be of some value, in part by reducing secondary infection. These may reduce the severity and pain of ulceration.[3]

» Randomized controlled trials have shown that chlorhexidine oral solution can reduce the duration of recurrent aphthous stomatitis and increase the number of ulcer-free days.[51] [52] [53] [54]

» Topical tetracyclines used as rinses may also be effective.[55] [56] These formulations need to be specially compounded. They may provide relief and reduce ulcer duration. Should be avoided in children less than 8 years of age as they may cause tooth discoloration.

Acute

adjunct **oral vitamin B12**

Treatment recommended for SOME patients in selected patient group

Primary options

» cyanocobalamin (vitamin B12): children: consult specialist for guidance on dose; adults: 1000 micrograms orally once daily
If available, sublingual tablets may be used; they should be dissolved under the tongue and swallowed.

» There is some evidence of benefit from vitamin B12, even in the absence of any deficiency; supplementation with oral vitamin B12 (cyanocobalamin) has been shown to be effective in studies, irrespective of serum B12 levels.[46] [47] [48]

adjunct **oral iron**

Treatment recommended for SOME patients in selected patient group

Primary options

» ferrous sulfate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily
Dose expressed as elemental iron.
Alternative dose regimens may be available.

OR

» ferrous gluconate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily
Dose expressed as elemental iron.
Alternative dose regimens may be available.

OR

» ferrous fumarate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily
Dose expressed as elemental iron.
Alternative dose regimens may be available.

OR

» ferric maltol: adults: 30 mg orally twice daily

» Iron supplementation in adults and children may be necessary to prevent ulcers that are a

Acute

result of iron deficiency anemia. Initial treatment is daily oral iron replacement therapy.[49]

3rd **systemic corticosteroid or colchicine**

Primary options

» prednisone: children: 0.5 to 1 mg/kg/day orally for 7 days, then taper over 7 days; adults: 30-60 mg orally once daily for 7 days, then taper over 7 days

Secondary options

» colchicine: adults: 0.5 mg orally two to three times daily

» If recurrent aphthous stomatitis (RAS) fails to respond to topical therapies, systemic therapies may be required.

» Oral prednisone as a 1-week course tapered over a second week is one suggested regimen.[3]

» The first-line systemic immunomodulator used in RAS and the mucocutaneous manifestations of Behcet syndrome is colchicine.[61]

» Systemic treatments for RAS are rarely used in children under the age of 12 years, and are only commenced under specialist care. Colchicine is rarely used in children.

plus **symptom relief**

Treatment recommended for ALL patients in selected patient group

Primary options

» lidocaine oropharyngeal viscous solution: (2%) children: 1.25 mL every 3 hours when required (swish around in mouth and spit out), maximum 4 doses/12 hours; adults: 15 mL every 3 hours when required (swish around in mouth and spit out), maximum 8 doses/day

» Topical therapies for symptom relief may be of benefit. These include topical anesthetics (e.g., lidocaine) and over-the-counter topical anti-inflammatory agents.[65]

adjunct **antibacterial mouthwash**

Treatment recommended for SOME patients in selected patient group

Primary options

Acute

» chlorhexidine oropharyngeal: (0.12%) children and adults: 10-15 mL as a mouthwash twice daily

» Adjunctive antimicrobial agents may also be of some value, in part by reducing secondary infection. These may reduce the severity and pain of ulceration.[3]

» Randomized controlled trials have shown that chlorhexidine oral solution can reduce the duration of recurrent aphthous stomatitis and increase the number of ulcer-free days.[51] [52] [53] [54]

» Topical tetracyclines used as rinses may also be effective.[55] [56] These formulations need to be specially compounded. They may provide relief and reduce ulcer duration. Should be avoided in children less than 8 years of age as they may cause tooth discoloration.

adjunct **oral vitamin B12**

Treatment recommended for SOME patients in selected patient group

Primary options

» cyanocobalamin (vitamin B12): children: consult specialist for guidance on dose; adults: 1000 micrograms orally once daily
If available, sublingual tablets may be used; they should be dissolved under the tongue and swallowed.

» There is some evidence of benefit from vitamin B12, even in the absence of any deficiency; supplementation with oral vitamin B12 (cyanocobalamin) has been shown to be effective in studies, irrespective of serum B12 levels.[46] [47] [48]

adjunct **oral iron**

Treatment recommended for SOME patients in selected patient group

Primary options

» ferrous sulfate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily
Dose expressed as elemental iron.
Alternative dose regimens may be available.

OR

Acute

» ferrous gluconate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily

Dose expressed as elemental iron.

Alternative dose regimens may be available.

OR

» ferrous fumarate: children: 3 mg/kg orally once daily; adults: 65-130 mg orally once daily

Dose expressed as elemental iron.

Alternative dose regimens may be available.

OR

» ferric maltol: adults: 30 mg orally twice daily

» Iron supplementation in adults and children may be necessary to prevent ulcers that are a result of iron deficiency anemia. Initial treatment is daily oral iron replacement therapy.[49]

4th **specialist referral**

» The use of additional agents above systemic corticosteroids and colchicine are typically provided under specialist supervision. For example, the use of systemic immunomodulators or anti-inflammatory agents, such as azathioprine or thalidomide, may be considered following referral.[1] [3] [45] [59] [60] There is weak evidence to support the use of azathioprine.

» Thalidomide is rarely used, only prescribed by specialists with experience in its use, and would never be commenced in primary care - there may be tight legislation around the prescribing of it.

» The use of thalidomide in RAS is supported by data both in RAS and in patients with aphthous-like ulceration in HIV infection.[62] [63] In these patient groups, open and double-blind studies have shown that thalidomide is the most reliably effective agent available for the management of severe, refractory RAS.[6] However, great caution is required for its use in patients with RAS and specialist referral is recommended.[1] [3] Men and women require effective contraception during treatment and for 1 month before and 1 month after use of thalidomide.

Acute

» Thalidomide is not used in children unless in exceptional circumstances and would only ever be instigated by a specialist team.

Emerging

Immunomodulators

Newer biologic therapies using monoclonal antibodies that target particular steps in the immunologic/inflammatory processes have been used in patients with aphthous ulceration.[66] [67] These include tumor necrosis factor alpha antagonists, such as etanercept and adalimumab.[68] [69] However, data are limited as to their efficacy in recurrent aphthous stomatitis (RAS) and caution as to their use in oral ulceration is necessary.[70] [71] Furthermore, adverse effects of these agents are recognized increasingly: most notably, the development of progressive multifocal leukoencephalopathy with efalizumab.[72] Therefore, their use cannot be recommended for patients with RAS, at this time.

Primary prevention

Patients should be instructed to avoid oral trauma, recognized trigger foods, and the use of acidic foods and drinks.[1]

Secondary prevention

Daily multivitamins do not appear to prevent recurrent aphthous stomatitis (RAS). Supplementation with the recommended daily intake of essential vitamins failed to reduce the number or duration of recurrent episodes in a randomized, double-blind, placebo-controlled study.[73]

Patient discussions

Patients should be instructed to avoid:[1]

- Oral trauma (e.g., from sharp and/or broken teeth, dentures and orthodontic appliances, and biting during chewing), and seek assessment and appropriate dental treatment
- Recognized trigger foods
- Acidic foods and drinks.

Corticosteroid use and oral candidiasis

Prolonged use of topical corticosteroids can encourage overgrowth of candidiasis. All topical corticosteroids should be used for as short a term as possible. Other factors for opportunistic fungal infections should be addressed (e.g., diabetes, smoking, dentures, asthma inhalers).

Teeth staining with prolonged use of chlorhexidine and pain on rinsing

Pain on rinsing with chlorhexidine would warrant dilution 50/50 with water.

To prevent staining, make sure teeth (or dentures) are thoroughly brushed before chlorhexidine is used.

Monitoring

Monitoring

Most patients require no specific monitoring.

Patients receiving systemic therapy must be monitored according to which drug is used.

Patients treated with biologic agents require monitoring mainly for infections.[66] [67]

Complications

Complications	Timeframe	Likelihood
scarring	**long term**	**low**
Scarring may complicate recurrent aphthous stomatitis, most commonly in patients with major aphthae.		

Prognosis

For many patients with recurrent aphthous stomatitis (RAS), avoidance of trigger factors may reduce the frequency of episodes. Most patients will benefit from topical therapy during episodes of active ulceration. A small proportion of patients with severe RAS may require aggressive immunomodulatory treatment tailored to the individual patient.

For most patients with RAS, disease activity and frequency of episodes of active ulceration tends to decrease with time.

Diagnostic guidelines

International

The diagnosis and management of recurrent aphthous stomatitis: a consensus approach (https://pubmed.ncbi.nlm.nih.gov/12636124) [3]

Published by: American Academy of Oral Medicine; European Association of Oral Medicine; British Society for Oral Medicine

Last published: 2003

Treatment guidelines

International

The diagnosis and management of recurrent aphthous stomatitis: a consensus approach (https://pubmed.ncbi.nlm.nih.gov/12636124) [3]

Published by: American Academy of Oral Medicine; European Association of Oral Medicine; British Society for Oral Medicine

Last published: 2003

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Images

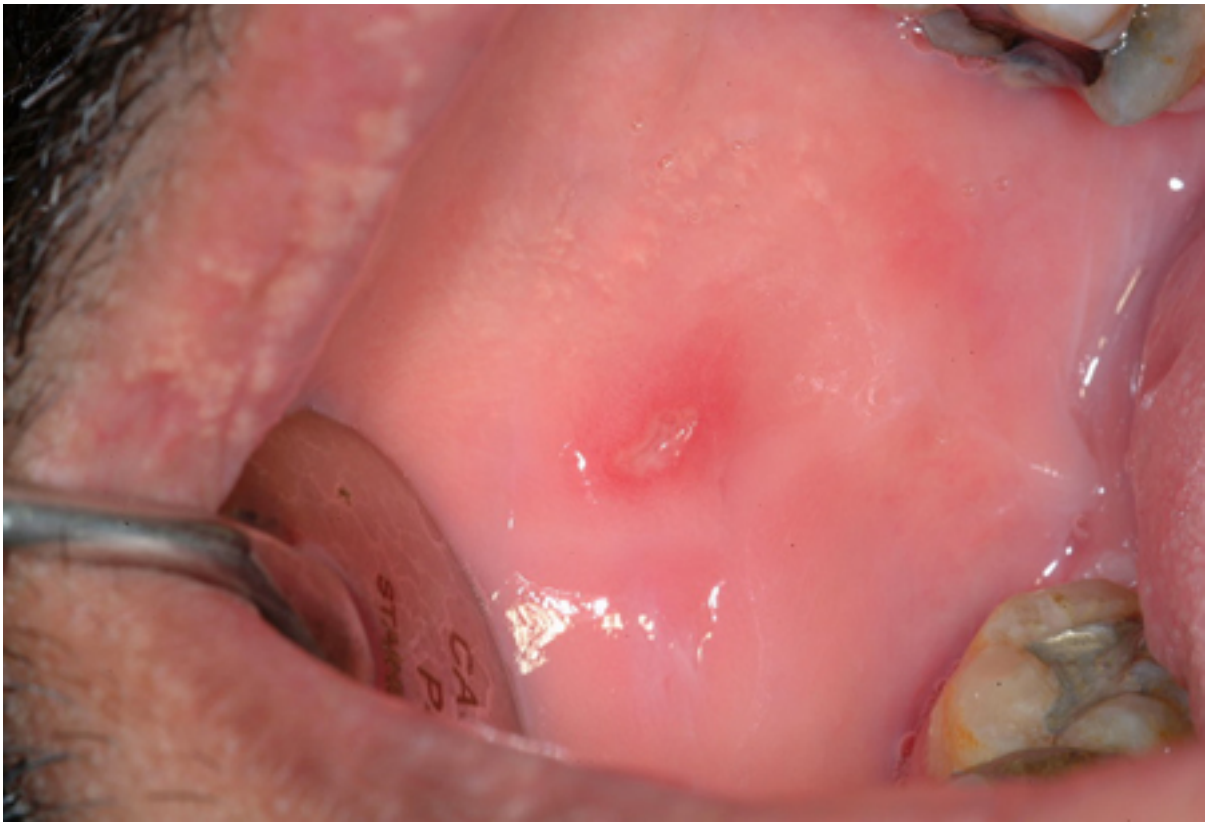

Figure 1: Recurrent aphthous stomatitis (RAS): minor aphthae

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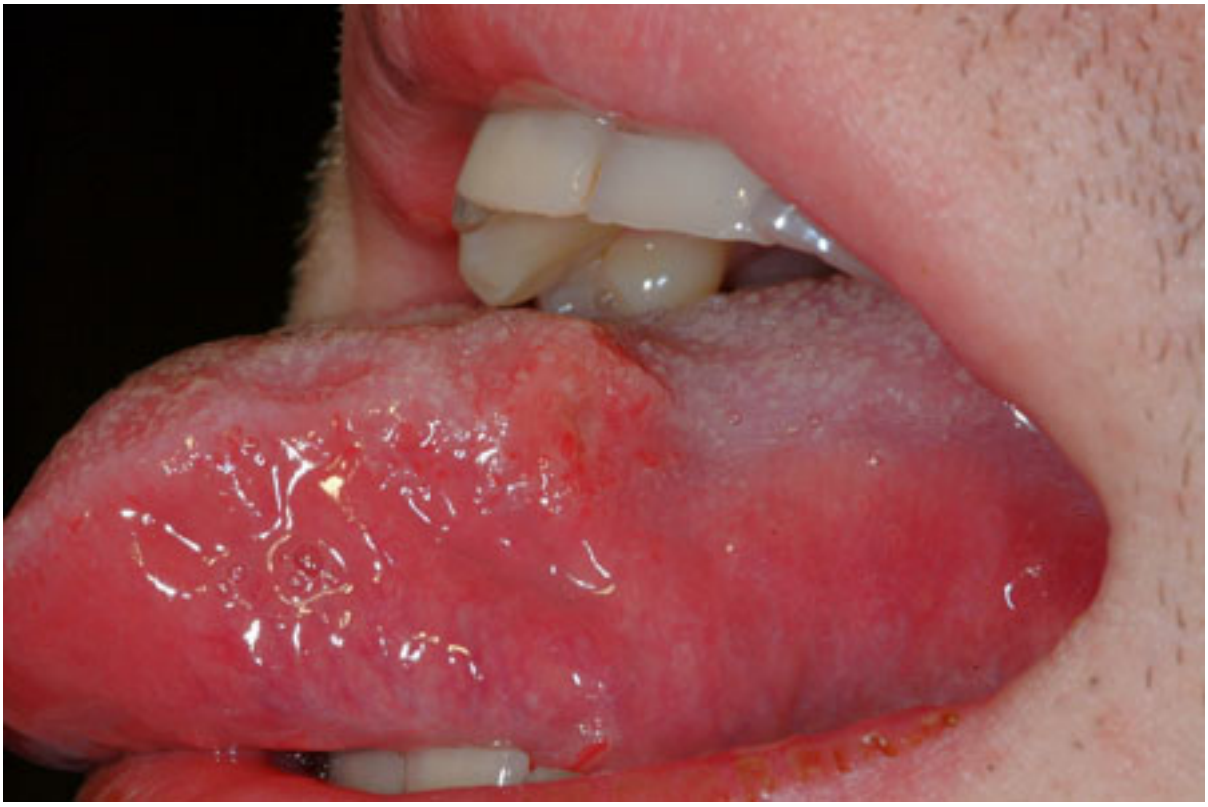

Figure 2: Recurrent aphthous stomatitis (RAS): major aphthae

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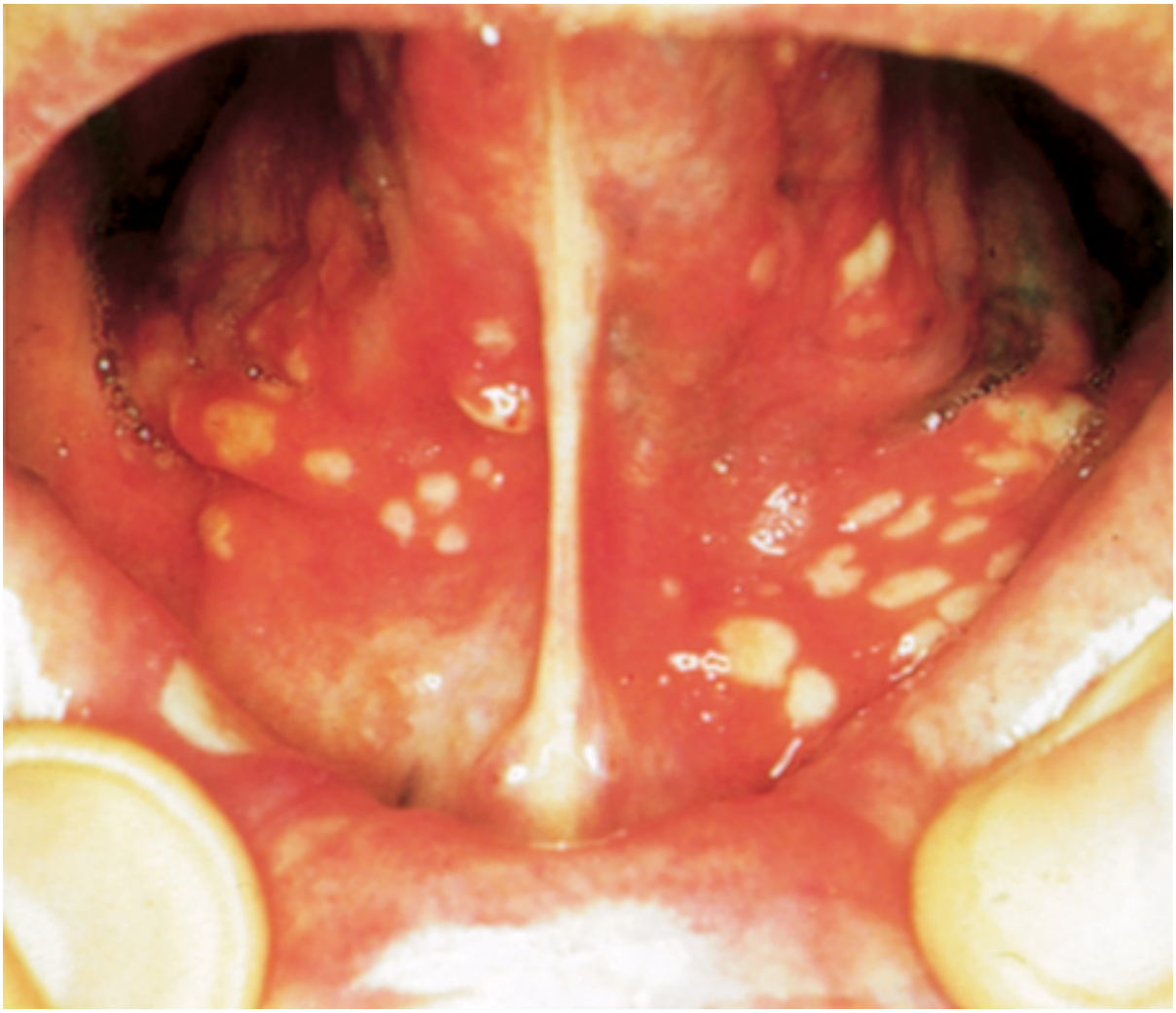

Figure 3: Recurrent aphthous stomatitis (RAS): herpetiform ulceration

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Figure 1 – BMJ Best Practice Numeral Style

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