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Recurrent aphthous stomatitis

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Abstract Recurrent aphthous stomatitis (RAS) is the most common acute oral ulcerative condition in North America. RAS is divided into a mild, common form, simple aphthosis, and a severe, less common form, complex aphthosis. Aphthosis is a reactive condition. The lesions of RAS can represent the mucosal manifestation of a variety of conditions. These include conditions with oral and genital aphthae such as ulcus vulvae acutum, reactive nonsexually related acute genital ulcers, and Behçet disease. The mouth is the beginning of the gastrointestinal (GI) tract, and the lesions of RAS can be a manifestation of GI diseases such as gluten-sensitive enteropathy, ulcerative colitis, and Crohn disease. Complex aphthosis may also have correctable causes. The clinician should seek these in a careful evaluation. Successful management of both simple and complex aphthosis depends on accurate diagnosis, proper classification, recognition of provocative factors, and the identification of associated diseases. The outlook for patients with both simple and complex aphthosis is positive.
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Introduction

Recurrent aphthous stomatitis (RAS) is also known as canker sores to patients and health care providers. *Aphthous* comes from the Greek word *aphtha,* referring to an ulcer of the mucosal surface. *Stomatitis* refers to an inflammation of the oral mucosa. Other synonyms are simple aphthosis, complex aphthosis, recurrent oral ulcers (ROU), and recurrent aphthous ulcers (RAU). Many patients confuse RAS with recurrent herpes labialis (fever blisters, cold sores), because both are common in young individuals; however, each is a distinct entity. RAS is the most common recurrent acute oral ulcerative condition in North America.[1–4] The lesions of RAS are painful and disabling to many patients, prompting them to seek evaluation and treatment from health care providers.

Recurrent acute oral ulcers are a common problem in clinical practice.[3] The main causes of recurrent acute oral ulcers to be considered are trauma, RAS, recurrent intraoral herpes simplex virus stomatitis, and cyclic neutropenia. Of these four, RAS is the most common cause of recurrent acute oral ulcers. The practical approach to acute oral ulcers is discussed elsewhere in this issue.[5]

The lesions of RAS develop over several days into the typical aphthous ulcer (Table 1).[6] Initially, the patient will note paresthesia before development of a clinical lesion. A macule develops, which evolves into a papule that subsequently becomes necrotic and ulcerates. The typical lesion of RAS is a round to oval ulcer covered by a yellow-white fibromembranous slough, surrounded by a peripheral halo of erythema. Pain, which reaches its zenith before the ulcerative process, diminishes in the healing phase. Smaller aphthae heal in 4 to 7 days. Larger lesions—major aphthous ulcers—require longer to heal. Smaller lesions heal without scarring, but larger ones may scar.

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Table 1 Stages of recurrent aphthous stomatitis

Stage	Time
Premonitory	Hours to 1 day
Preulcerative	1-2 days
Ulcerative	Several days
Healing	Days to weeks

The lesions of RAS characteristically afflict the nonmasticatory, soft oral mucosal surfaces of the cheeks, lips, lateral and ventral tongue, upper and lower nonattached gingivae and sulci, and occasionally the soft palate and fauces. In contradistinction, lesions of recurrent intraoral herpes simplex virus stomatitis afflict the masticatory mucosa of the hard palate and attached gingivae and recur uncommonly in the healthy individual. The lesions of recurrent herpes labialis more characteristically afflict the cutaneous and vermilion lip and spare the intraoral mucosal surfaces. The lesions of cyclic neutropenia may affect both the masticatory and nonmasticatory mucosa but have very specific cyclic periodicity as a differentiating feature, making the distribution of the lesions a key to differential diagnosis.

The lesions of RAS are self-limited, resolving in 1 to 2 weeks in most patients and recurring 3 to 6 times in a year after periods of remission[1] (simple aphthosis). Some patients have almost continuous oral ulcerations, some lesions healing as others develop, with occasional genital aphthae (complex aphthosis).[7]

The lesions of RAS are characteristically noted in childhood and adolescence and recur with decreasing frequency and severity as the patient ages. It is uncommon for an adult older than age 40 to have RAS. The incidence rate varies with the population studied, ranging from 5-60%,[4] with the highest in women student nurses and medical and dental school students and the lowest in men who are hospitalized. In general, younger persons, women, and those of higher socioeconomic classes are more likely to suffer from RAS.

Classification

In terms of clinical presentation, RAS is divided into two categories based on severity—mild and severe. The milder type is called simple aphthosis.[1] The more severe, and fortunately less common type, is called complex aphthosis (Table 2).[7] The vast majority of patients have simple aphthosis; however, those with complex aphthosis may have one or more associated conditions, such as anemia, hematinic or mineral deficiencies, inflammatory bowel disease, gluten-sensitive enteropathy, or other conditions in which lesions of RAS are a component (Table 3).[1,2,4,7–13]

Table 2 Types of recurrent aphthous stomatitis

Simple aphthosis	Complex aphthosis
Common	Uncommon
Episodic	Episodic or continuous
Prompt healing	Slow healing
Few ulcers	Few to many ulcers
3-6 episodes per year	Frequent or continuous ulceration
Minimal pain	Marked pain
Little disability	Major disability
Limited to oral cavity	May have genital aphthae

Table 3 Associated systemic disorders

Ulcus vulvae acutum
Reactive nonsexually related acute genital ulcers
Behçet disease
MAGIC syndrome
Cyclic neutropenia
PFAPA syndrome
Aphthous-like ulcerations of HIV disease
Hematinic deficiencies
Celiac disease (sprue, gluten-sensitive enteropathy)
Inflammatory bowel disease (ulcerative colitis, Crohn disease)
Helicobacter pylori disease
Systemic lupus erythematosus

MAGIC, mouth and genital ulcers with inflamed cartilage; *PFAPA,* periodic fever, aphthous stomatitis, pharyngitis, and adenitis.

Another helpful classification of the lesions of RAS is based on morphology (Table 4).[1,2,14,15] Minor aphthous ulcers (MiAU) are small and few in number, occur on the anterior oral mucosa, and are the typical canker sores known to most patients and health care providers (Figure 1). MiAU heal quickly. Major aphthous ulcers (MjAU) are large, few in number, and occur both anteriorly and posteriorly with risk of scarring (Figure 2). MjAU, also known as Sutton ulcers or periadenitis mucosa necrotica recurrens,[16] are the most painful type and heal more slowly due to the larger size. The third subtype is herpetiform ulcer, which is the least common type of RAS. Herpetiform ulcer lesions present as grouped 1- to 2-mm papulovesicles, which coalesce into larger lesions (Figure 3). The term *herpetiform* was selected[17] to describe the grouped morphology (*herpetiform* means grouped). The term is confusing to patients and health care providers, because *herpetiform* is commonly associated with herpes simplex virus infections, which are also characterized by grouped lesions.

Etiology, pathogenesis, and predisposing factors

There are likely multiple immunologically mediated mechanisms that drive the pathogenesis of RAS. Lymphocytic cells

Table 4 Classification of recurrent aphthous stomatitis

Type	Size (mm)	Number	Location	Prevalence (%)
MiAU	<10	Few	Anterior	85%
MjAU	>10	Few	Anterior > posterior	10%
HU	1-2	Many	Both	5%

HU, herpetiform ulcers; *MiAU,* minor aphthous ulcers; *MjAU,* major aphthous ulcers.

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