Recurrent aphthous stomatitis (RAS) and recurrent intraoral herpes (RIH) are the two most commonly present oral lesions in the dental setting. It is critical that the oral health professional be able to accurately discriminate between these disorders. To facilitate the differential diagnosis between RAS and RIH, important components of assessment are discussed. These include: prodromal signs and symptoms, lesion location, and appearance of the initial and mature lesion. The comparative etiology, prevalence, pathogenesis, and treatment considerations for these lesions are presented. A familial case report is provided.

**Keywords:** Herpes, lesion, primary herpetic gingivostomatitis, aphthous stomatitis, RIH, RAS, recurrent intraoral herpes, recurrent aphthous stomatitis, ulcer, canker sore, cold sore, fever blister.

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Introduction

Recurrent aphthous stomatitis (RAS) and recurrent intraoral herpetic (RIH) lesions are common oral disorders that are often mistaken for one another. The confusion associated with developing an accurate diagnosis is somewhat understandable since these two very different lesions share some common characteristics. However, since they do differ in a variety of parameters, the well-informed clinician should be able to differentiate between these distinctly separate conditions.

The patient history, the physical examination, and the results of any indicated tests are important to the diagnostic process. A complete and accurate patient history is a critical component of developing a working diagnosis. Information regarding initiating factors, frequency of lesions, relieving factors (including any previously prescribed or over-the-counter medications), and aggravating factors provides historically important data. It has often been said that if you listen to the patient, he or she will give you the diagnosis.

If the patient history is accurate and the physical examination allows the clinician to see the lesion(s), other tests may not be necessary. In most cases, the clinician should be able to differentiate herpetic lesions from aphthous ulcers.

Lesion Identification: How Accurate Are You?

Review the following images of mucosal lesions to assess your skills at differentiating between aphthous ulcers and RIH lesions. (Figures 1 A-D)
The high prevalence and often-painful presentation of these lesions suggests that patients will frequently seek out the oral health professional for diagnosis and treatment. Since the lesions are almost always self-limiting, one might question the importance of being able to distinguish one from the other. What then is the rationale for the differential diagnosis?

Table 1 summarizes some of the features of RIH and RAS.

Rationale for Differential Diagnosis
Developing an accurate diagnosis for herpes and aphthous is critical to the treatment plan because the recommended treatment approaches are very different for herpetic lesions and aphthous ulcerations. Treating a herpetic lesion with topical steroids (as appropriate for an aphthous ulcer) can have serious sequelae. Telling a patient with an active herpes infection that he or she has an aphthous ulcer and that it is not potentially contagious is simply bad healthcare. Additionally, the accompanying peace of mind that occurs with providing a name and treatment for what may have been a long-standing condition can have psychological advantages for the patient.

Prodromal Symptomology
Both herpetic and aphthous lesions often present with prodromal symptoms which can provide important clues to the development of a diagnosis. However, the indications of an impending herpetic lesion are generally more descriptive than for a developing aphthous ulcer.

Awareness of the initiation of the aphthous lesion is generally indicated by local discomfort at the lesion site. The degree of pain can vary from slight to severe and is frequently described as out of proportion to the size of the lesion.

The prodromal symptomology for herpes may seem confounding to the patient at initial occurrence, but for those experiencing frequent outbreaks of herpetic lesions, the symptoms are often recognizable. The first indication of a

Table 1: Comparison between recurrent intraoral herpes (RIH) and recurrent aphthous stomatitis (RAS).

<table>
<thead>
<tr>
<th>Feature</th>
<th>RIH</th>
<th>RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of primary lesion</td>
<td>vesicle</td>
<td>ulcer</td>
</tr>
<tr>
<td>Appearance of mature lesion</td>
<td>shallow, punctate ulcers</td>
<td>ulcer (with erythematous halo)</td>
</tr>
<tr>
<td>Common location</td>
<td>attached gingiva, hard palate, vermilion border</td>
<td>buccal mucosa, floor of mouth, oropharynx, vestibule, tongue</td>
</tr>
<tr>
<td>Number</td>
<td>few to several</td>
<td>one to few</td>
</tr>
<tr>
<td>Lesion duration</td>
<td>1-3 weeks</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>Etiology</td>
<td>Viral</td>
<td>Unclear, immunologically mediated</td>
</tr>
<tr>
<td>Prevalence (by adulthood)</td>
<td>70-80% (HSV-1)</td>
<td>Possibly up to 86%</td>
</tr>
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recurrent herpetic outbreak may be an unusual sensation of the affected tissue that may manifest as a lack of tactile or sensory perception. This may progress to a tingling, burning, or throbbing sensation. The development of vesicles (small blisters) within 24-48 hours will help to validate the occurrence of a recurrent herpes outbreak.

**Lesion Location**

The site of the initial lesion can provide important clues concerning the presenting condition. Recurrent aphthous ulcerations are usually described as occurring on non-keratinized, or gland-bearing tissues. Common sites for recurrent aphthous ulcers include labial and buccal mucosa, floor of the mouth, oropharynx, vestibule, and lateral tongue. With the exception of sites of frequent trauma, there appears to be no predilection for aphthous ulcers to recur at a previous location.

In contrast, RIH generally appears on keratinized tissues such as the vermillion borders of the lips, hard palate, attached gingiva, and alveolar ridges. The initial lesion can be at any of these locations with subsequent outbreaks often manifesting at or very near the original site.

**Appearance of Lesions**

The clinician is not always able to view a lesion at the initial stage when most easily diagnosed. Therefore, eliciting a detailed description of the course of the eruption becomes essential. In most cases the combination of the history of the lesion and viewing the current stage can allow for a working (presumptive) diagnosis.

The aphthous ulcer does not transition through specific discernable stages as does the herpetic lesion. It may, however, increase in size from first detection to maturity. Aphthous ulcers are usually divided into two general categories: aphthous major and minor. A more uncommon form, herpetiform aphthous stomatitis, mimics herpetic lesions in appearance but is found in the same areas as the other forms of aphthous stomatitis.

In the aphthous minor form of aphthous stomatitis, the ulcer is shallow and 0.5-2 cm in size. It usually appears as a single lesion, although 1-5 ulcers may be present. The initial lesion may begin as an erythematous macule, but it quickly progresses to an ulcer characterized by a white to yellow or gray center of necrosis surrounded by a smooth, symmetrical, round or elliptically shaped erythematous perimeter often described as a "red halo." Within 10-14 days of the initial presentation, the aphthous ulcer should usually be fully healed.

Major aphthae typically are larger, last longer than aphthous minor, and may heal with scarring. Clinicians should remember that HIV/AIDS patients can present with ulcers demonstrating a clinical appearance similar to or indistinguishable from major aphthae due to their immunocompromised health status.

Following the characteristic prodromal stage previously described, the herpetic lesion manifests as a cluster of small grey to white vesicles that rupture to form small punctate ulcers that are usually 1 mm or less in diameter. These ulcers may coalesce into one larger ulcer up to 1.5 cm in size. A red halo effect may be visible, but will appear scalloped in contrast to the smooth halo seen in aphthous ulceration. The next stage is 'crusting,' which precedes the healing process. From prodrome to crusting takes up to 96 hours with pain resolution over 96-120 hours and complete healing by 8-10 days. Since "crusting" does not occur intraorally, this feature is noted primarily in labial or cutaneous lesions.

Comparing the two lesions, it is apparent that both become ulcerative, but the progression to the ulcer stage differs widely, as does the appearance of the mature lesions associated with herpes and aphthous. Thus, the history, location, and appearance of the lesions should allow the knowledgeable clinician to establish a presumptive diagnosis. Regarding transmissibility, it is important to note that while the aphthous ulcer is not contagious, the herpetic lesion is transmissible to a susceptible host. Herpes is communicable throughout the course of the outbreak, particularly during the vesicle and ulceration phases.
Etiology, Prevalence, and Pathogenesis

Aphthous Stomatitis
The term 'aphthous' originated with Hippocrates as far back as 460-370 BC in reference to disorders of the mouth. In general usage, the word 'aphthae' refers to the presence of an otherwise undefined ulcer. Despite the fact that aphthous stomatitis is the most common human oral mucosal disease, the cause is poorly understood. Although symptomatic treatment is available, aphthous is not preventable. Since the etiology of aphthous ulcers is indeterminate, research has focused upon a variety of potentiating factors. Until the etiology is clarified, the focus has shifted toward the notion of 'precipitating factors.' Studies of these are not conclusive, but precipitating factors that have been identified include: stress, nutritional deficiencies, trauma, hormonal changes, diet, and immunologic disorders. Other contributors that have received attention are: foods, allergies, progesterone levels, psychologic factors, and a familial history. Despite extensive research, no conclusive etiology has been determined. For some time it was thought that aphthous ulcerations were due to an L-form of Streptococcus since this organism was often isolated from the lesions. A more common belief is that the lesions may become secondarily infected with streptococci. Since the lesions are often suppressed by steroid therapy, which affects the immune response, it is more likely that the lesions are a manifestation of the immune response, perhaps a hypersensitivity to streptococci or another oral phenomenon. RAS is currently characterized as an idiopathic disorder whose fundamental etiology is unclear. It is, however, widely recognized as immunologically mediated.

RAS is a common oral disorder. The prevalence among differing populations has been documented as 5-66% and 50%. World-wide, approximately 15-20% are afflicted with RAS. It is especially common in North America. RAS also occurs in association with some systemic disorders that are associated with chronic gastrointestinal malabsorption disturbances such as Crohn's disease and celiac disease. Another systemic disorder associated with aphthous ulceration is Behcet syndrome that is characterized by recurrent attacks of genital and oral ulcers.

Aphthous stomatitis is divided into three clinical presentations. It is unclear whether these presentations are manifestations of one disease or represent other oral disorders characterized by recurrent ulcers. The three designations are aphthous minor, aphthous major and herpetiform ulcers.

Etiology, Prevalence, and Pathogenesis
Aphthous minor is the most common variety accounting for 80% to 95% of all RAS lesions. The lay term for this lesion is canker sore.

During an attack of minor aphthous, lesions may occur singly or up to five or more concurrent ulcers. Each lesion typically lasts 10-14 days. Lesions may continually appear and heal spontaneously during a 3-4 week period.

Precipitating Factors

- Stress
- Nutrition
- Trauma
- Hormonal
- Diet
- Immunologic
Aphthous major, which accounts for about 10% of cases of aphthous stomatitis, is characterized by large lesions which vary from 5-20 mm or more in size. Usually only 1-2 lesions occur at a time and primarily in two locations, lip mucosa and posterior palate/anterior fauces area.

The lesions are much more severe than that of minor aphthae and are associated with severe pain. The lesions are crateriform and deep, involving much tissue necrosis, often resulting in scarring upon healing. Aphthous major can last 6 weeks or more and can become secondarily infected with bacterial and fungal organisms. Lesions of aphthous major can become intractable in those with immunodeficiency disorders such as HIV and AIDS, resulting in weight loss due to painful deglutition.

Herpetiform aphthous is the least common variety comprising about 10% of occurrences. The name is misleading since it suggests a herpetic infection. Rather it is the similar appearance of the ulcers that can mimic the appearance of primary herpetic gingivostomatitis. Additionally, although most commonly occurring on non-keratinized surfaces, herpetiform aphthae can infrequently appear on keratinized mucosa as can primary herpetic gingivostomatitis.

Herpetiform aphthous is characterized by multiple recurrent crops of 10 or more small crateriform ulcers of variable size. The episodes may last several weeks or months with individual ulcers healing after 1-2 weeks. The lesions are shallow, like aphthous minor, and heal without scarring.

The age of onset of herpetiform aphthous is later than with the other types, with the initial episode usually presenting in the second or third decade of life.

**Treatment**

Once a diagnosis of aphthous is reached, the clinician must decide whether to provide more than palliative care. As part of informed consent, the patient should receive instruction about the condition, treatment options, and the expected outcome from each of the various treatment plans offered. Patients with frequent or severe outbreaks of aphthae should be counseled regarding the advisability of a medical screening for diabetes, various forms of anemia, gastrointestinal disease, food "allergies," and other diseases potentially affecting the immune system. It may also be wise to rule out Behcet's disease through questioning about the presence of lesions of the genital mucosa. Suggested supportive care includes rest, increased fluid intake, adequate nutritional intake, multi-vitamin and mineral therapy, and reassurance that aphthae are not communicable.

When conservative, palliative care such as eliminating trauma (where possible), avoiding exposure to identified causative factors, and stress reduction are not enough, steroids of various types can be utilized. Aphthae that are localized or in small numbers can often be effectively treated with a topical steroid. For single (or few) shallow lesions, a mild steroid ointment or gel is usually adequate. Kenalog (triamcinolone acetonide 0.1%) in Orabase can be used on many mild aphthae cases. Larger lesions, when accessible, can be treated with a more potent steroid like Lidex (0.05%) or Temovate (0.05%) gels or ointments. When the lesions are more diffuse, difficult to access (i.e., oropharynx), or in larger numbers, a steroid rinse is more helpful than a topical ointment or gel. Decadron (dexamethasone) elixir 0.5 mg/5 ml can be considered when treating these lesions. If the lesion(s) are large and accessible, combining dexamethasone with a topical ointment or gel can reduce the signs and symptoms.

Although topical steroids used appropriately on a limited basis rarely cause untoward effects, patients should be counseled regarding the potential for candidal overgrowth when steroid rinses are used for extended periods. The more potent steroids (i.e., Temovate) when applied more than twice per day for more than two weeks can lead to mucosal thinning and erosions.

Aphthae are expected to respond quickly to steroid therapy. It must be emphasized that when an intraoral ulcer does not heal after potential causes have been addressed and/or after steroid therapy, the lesion should be re-assessed and biopsied. Oral malignancy and other disease processes should be considered as part of the differential diagnosis for lesions that do not respond to conservative therapy. Other immune-mediated disease may also mimic aphthae and require an accurate diagnosis before an adequate treatment plan can be developed.
Herpes Etiology, Prevalence, Pathogenesis

The herpes infection has a history dating back to ancient Greece. The word ‘herpes’ was used by Hippocrates to describe lesions that ‘creep’ or ‘crawl.’ Although previously well characterized, it was not until 1893 that the transmissibility was recognized.6

The herpes family of viruses currently is thought to consist of herpes simplex 1 (HSV-1), herpes simplex 2 (HSV-2), varicella-zoster, Epstein-Barr, cytomegalovirus, and human herpes virus VI, VII, and VIII.5 All are capable of entering and replicating in epithelial cells, while some of the herpes family is neurotropic and others are lymphotropic. HSV-1 and HSV-2 are neurotropic, infecting sensory nerve fibers and have been demonstrated to reproduce in epithelial cells. HSV-1 and HSV-2 are lytic to human epithelial cells and latent in neural tissue at the site of regional ganglions. Usually the virus initially enters the body through a break in the mucous membrane integrity, although there is evidence that it may penetrate intact skin. In either case, transmission results from mucocutaneous contact with infected secretions and aerosols. When reactivated, the virus travels along the nerve axon to the surface epithelial cells and can cause a recurrent epithelial outbreak.

Often the initial herpes infection goes undetected. However, in a small percentage of cases, the initial oral infection with HSV-1 or HSV-2 is acutely symptomatic causing many signs and symptoms detected by the patient. When the patient demonstrates systemic signs, symptoms, and has perioral and intraoral vesicular lesions, it is referred to as primary herpetic gingivostomatitis. Although the condition most often occurs in children, it can also affect adolescents and adults. Fever and lymphadenopathy may occur, lasting from 2-10 days. Pharyngitis, malaise, myalgia, fiery red gingival, and mucosal tissues associated with painful swallowing are hallmarks of the primary infection. Intraorally, many small punctate ulcers may form on keratinized and nonkeratinized mucosa as well as at the nasopharynx. Perioral tissues can also be affected.

Another manifestation of acute primary herpetic stomatitis is an acute inflammation of the marginal and attached gingiva without accompanying vesicular lesions. It has been reported that only 12% of those with RIH remember an initial infection7,8

After the initial infection, the virus will remain dormant until activated. The frequency of reactivation with clinical recurrence has been reported as occurring in 40%5 and 10-15%4 of those with the latent virus.

Reactivation can occur as a result of several factors that suppress the immune system. These include but are not limited to emotional stress, trauma, cold, sunlight, extreme fatigue, fever, and menstrual cycle.

The recurrent vesicular/ulcerative lesions have become known as ‘cold sores’ or ‘fever blisters’ because people may notice activation following an illness such as upper respiratory infection. Some patients may report an outbreak following an immunosuppressive experience.

The incubation period between infection or reactivation and the appearance of vesicles is about 7-8 days but may range from 1-26 days. During this pre-emergence period and during the vesicular stage, secretions are highly contagious.6 Additionally, there is evidence that those with recurrent HSV-1 shed the virus in the saliva even when asymptomatic. People with genital HSV-2 shed the virus about 10% of the days when they are asymptomatic, although this declines over time.9

HSV-1 and HSV-2 are both different and alike. HSV-1 generally is described as occurring above the waist, with HSV-2 occurring below the waist. In reality, either variety can reside at either location. HSV-1 usually establishes latency in the trigeminal or other ganglion. HSV-2 is usually latent at the sacral ganglion at the base of the spine. Usually at its alternate site, the virus causes milder infection as well as less asymptomatic shedding. It is much more common for HSV-1 to spread genitally than for HSV-2 to occur orally. Overall 80%-90% of the adult human population have been infected with HSV.
Treatment for Recurrent Intraoral Herpes

As with aphthae, an accurate diagnosis of RIH must be developed prior to initiating definitive treatment for the viral lesions. Patients should be informed that there is potential for self-inoculation and transmission of the virus to other susceptible hosts. Patients or their caregivers should be warned about potentially transmitting the virus to the eye, genitals, or hands through direct contact with saliva or vesicular fluid containing the virus.

Topical steroids applied to intraoral herpetic lesions must be avoided as steroid use allows the virus to spread. As with aphthae, adequate hydration and nutrition are essential to the healing process. Palliative rinses combining equal parts by volume of a topical anesthetic (Lidocaine 2% or Dyclonine 1%), an antihistamine (diphenhydramine 12.5 mg/ml), and a coating agent that binds to the lesion's surface (Maalox or Kapectate) can relieve the symptoms associated with the herpetic lesions. Clinicians might consider discussing the mixing of such palliative rinses with a pharmacist. When using a topical anesthetic that can potentially affect the swallowing process, patients should be counseled to use caution when drinking and eating. Depending on the degree of patient discomfort, acetaminophen with or without a narcotic can also be given for relief of pain.

Systemic medications interfering with viral DNA synthesis can be helpful but are not routinely used for mild RIH in the immunocompetent patient. In the less common case of an immunocompromised or immunosuppressed adult patient, antivirals can be prescribed. Sample prescriptions are listed below for three of the more commonly used antivirals. Dosages may need to be adjusted up or down based on the size and systemic health (especially in the presence of renal disease) of the patient.

Rx: Acyclovir (Zovirax) 200 mg capsules
Disp: 50 (fifty) capsules
Sig: Take by mouth one capsule five times per day during the waking hours for ten days.

Rx: Valacyclovir (Valtrex) 500 mg tablets
Disp: 21 (twenty one) tablets
Sig: Take by mouth one tablet three times per day for seven days

Rx: Famciclovir (Famvir) 250 mg tablets
Disp: 21 (twenty one) tablets
Sig: Take by mouth one tablet three times per day for seven days

Case Report

Two days prior to embarking upon a planned out-of-town trip, a 33-year old woman became aware of vague symptoms of illness in her two children, ages 2 and 5. Symptoms included irritability, anorexia, painful deglutition, and pharyngitis. This combination of symptoms did not appear pathognomonic for any particular disorder and were suggestive of a non-descript viral disorder, possibly an upper respiratory infection. The day of departure, upon examining the mouths of the children, a generalized acute inflammation of the gingivae was apparent. This sign combined with the previous signs and symptoms allowed for a presumptive diagnosis of primary herpetic stomatitis.

Once this designation was determined, the self-limiting nature of the disorder allowed for the children to be left with a caretaker and the parents continued with vacation plans. As predicted, the children's illness ran its course within 3-5 days.

Approximately 2-3 weeks later the maternal parent begin to experience similar symptoms. The malaise and discomfort were so severe that she was bedridden for 3 days. With a history of being quite healthy,
she had no prior recollection of being ill enough to ‘stay in bed’. Her gingivae were so severely inflamed and painful that it was impossible to follow her usual oral hygiene regimen. Full recuperation ensued within 5-7 days.

Subsequently, the paternal parent, age 35, developed the same disorder. In his case, the palatal tissue was so affected that it became denuded to the bone. Painful deglutition resulted in a weight loss of 15 pounds over a 7-10 day period of time. Full recuperation ensued. Both parents had experienced primary herpetic gingivostomatitis, presumably infected by the children who may have been exposed in child-care settings.

The oral pathologist who examined the family members commented that it was extremely rare to find 2 adults in the same household who had not previously experienced the primary episode early in life.

At current age 16, the youngest child had not had secondary herpes eruptions, while the older, now 19, has had several episodes of recurrent herpes labialis.

The mother has had recurring bouts of non-vesicular herpetic gingival inflammation, usually associated with precipitating factors of stress and/or fatigue and unrelated to any changes in local factors/oral hygiene regimen. The father has had no recurrences.

**Conclusion**

The oral health professional is viewed as the 'expert' when an individual develops mouth sores. These peri-oral or intraoral lesions can be very disconcerting to the affected individual both due to pain and fear/confusion about the meaning of such lesions.

Along with performing a thorough and skilled intraoral and extraoral examination at every dental visit, the oral health professional must be knowledgeable in differentiating between RIH and RAS.
References


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