Dr. Ahmed Salih Khudhur
BDS, M.Sc., PhD.
Newcastle University/ UK

Oral Ulceration

Recurrent Aphthous Stomatitis (RAS) or Ulceration (RAU)

RAS constitutes the most common oral mucosal disease and affects around 25% of the population at some time in their life. Many cases are mild, and no treatment is required. Generally, RAS characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of any disease.

However, ulcers similar and sometimes identical to RAS can be a feature of other diseases or syndromes. Whether these are truly aphthous stomatitis is unclear. Diseases & syndromes such as Behçet's disease, MAGIC syndrome (mouth and genital ulcers with inflamed cartilage syndrome), PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis "a childhood syndrome")), and HIV infection have been associated with RAS like ulcers. Furthermore, immunologic disorders, hematologic deficiencies, allergic or psychological abnormalities have also been implicated in cases of RAS.

General clinical features:

• Ulcers frequently start in childhood. Recurrences increase in frequency until early adult life or a bit later, then gradually fade.

• If Ulcers start in adults, this may indicate a hematological deficiency.

• RAU are rare in the elderly, particularly the edentulous unless affected by a hematological deficiency.

• Patients of different socioeconomic status are affected, but the majority of them are non-smokers.

• Many patients have prodromal symptoms of pricking or sensitivity and erythema at the site for a few- 24 hours before the ulcer appears.

• The ulcers have a smooth sharply defined margin with an erythematous halo in the enlarging phase. Typically, the center is yellowish-greyish. The surrounding area is usually slightly inflamed/erythematous.

• The erythematous halo or rim reduces once the ulcer reaches its full size, and while it heals, the margin becomes irregular or less well defined.

There are three types of RAS, each of which is defined by its clinical presentation.

1- Minor aphthous ulcers
2- Major aphthous ulcers (other clinical variants Sutton's disease, periadenitis mucosa necrotica recurrens)
3- Herpetiform ulcers

Minor aphthous ulcer: Is the most common type of RAS which usually occurs as one painful ulcer of less than 1 cm in diameter, less common in a group of 2-3 ulcers.

Minor aphthous ulcer recurs at intervals of a few weeks (during its peak). Typically affecting only the non-keratinized mucosa, usually the labial and buccal mucosa, sulcuses, lateral borders of the tongue, or floor of the mouth.

The individual minor aphthae persist for 7–10 days, then heal without scarring. Often all ulcers in a group develop and heal more or less synchronously. Unpredictable, remissions of several months may be noted. In rare and severe cases, ulcers are more numerous, and new groups may develop and heal continuously at different sites, without remission.

Major aphthous ulcer: Other names (Sutton's disease, periadenitis mucosa necrotica recurrens). Mostly a single painful ulcer which is larger than 1 cm in diameter, occasionally 2-3 major ulcers may develop at same time. The ulcer usually develops on the keratinized mucosa (less commonly on the non-keratinized) affecting the palate, fauces (back of the mouth

or oropharynx), buccal mucosa, dorsum and lateral borders of the tongue.

Major aphthous is very painful and interfere with eating. It persists for many weeks and heals with scarring. Ulcer can be designated as major on the basis of either size or duration.

Herpetiform aphthous ulcers also rare and distinct clinical form of RAU which causes crops of many tiny ulcers (1-2 mm across), dozens or hundreds may present at a time. Ulcers may coalesce to form large irregular ulcers. HAUs occur usually on non-keratinized mucosa such as the floor of mouth and ventral surface of the tongue, other parts of the oral mucosa may be affected. The background mucosa is red, giving a resemblance to herpetic ulceration, but viral infection is not the cause.

Etiology of RAU/RAS:

There is no clear explanation for the etiology of RAS; however, different predisposing factors may apply to different individuals or subgroups of patients.

Possible etiologic factors:

• Genetic predisposition: Family history is often positive

• Exaggerated response to trauma

• Immunological abnormalities

• Gastrointestinal disorders: Such as Crohn's disease, ulcerative colitis, and coeliac disease, as well as malabsorption.

• Hematological deficiencies: Deficiencies of vitamin B12, folate or iron have been reported in approximately 20% of patients with RAS (especially if it starts in middle age adults and elderly)

• Hormonal disturbances: RAU might occur in females during the luteal phase of the menstrual cycle. Pregnancy is often associated with remission

• Stress

• HIV infection: RAS is a recognized feature of HIV infection. It's both frequency and severity are related to the degree of immune deficiency

• Non-smoking: Smokers don not have RAS, this might be due to the effects of nicotine on the oral mucosa by increasing its epithelium thickness or keratinization

• Allergy: Though it's less common, allergy to foods such as milk, cheese, wheat, and flour. As well as, allergy to a detergent present in toothpaste, sodium lauryl sulfate (SLS), was suspected as a predisposing etiologic factor in RAS development

Diagnosis of RAU/RAS:

Diagnosis is mostly achieved via detailed history and examination. RAS is essentially diagnosed by exclusion of other diseases. Primarily recurrences of self-healing intraoral ulcers at regular intervals. Almost the only other condition with this history is Behçet's disease.

Usually, increasing frequency of ulcers brings the patient to seek treatment. A detailed history of the ulcer number, shape, size, site, duration, frequency of attacks is required.

Though patients appear well, laboratory investigations should be considered especially when ulcers worsen or begin above the age of 25 years. Hematological investigations are particularly important in older patients and those with recent exacerbations in frequency of crops, ulcer size or pain.

Hence, patients with abnormal hematological values should be referred to a hematologist/ or physician to rule out GIT Diseases or malabsorption syndromes and to initiate proper replacement therapy which control or abolish aphthae.

It is also useful to investigate any food allergy or gluten sensitivity especially in severe cases resistant to other forms of treatment.

Biopsies are only indicated when it is necessary to exclude other diseases, particularly granulomatous diseases such as Crohn's disease or Sarcoidosis. Biopsy might be considered with Major aphthous to exclude malignancy.

HIV infected patients, particularly those with CD4 counts below 100/mm^3, may develop major aphthous, occasionally, such oral ulcers are the presenting sign of AIDS.

Treatment of RAU/RAS:

Apart from the minority with underlying systemic disease, treatment is empirical and palliative only. Despite numerous clinical trials, no medication gives complete cure or relief. Low-potency and topical agents should be tried first. Some patients report that changing toothpastes is helpful.

1. Reassurance and education: Patients need to understand that the ulcers may not be curable but can be made bearable with symptomatic treatment. Reducing the number of attacks is more difficult to address, but some treatments are successful, particularly if attacks are frequent. The condition usually wanes eventually by its own, although after many years.

2. Medications prescribed should relate to the severity of the disease.

* Corticosteroids: Some patients get relief from hydrocortisone pellets or muco-adhesive buccal tablets (2.5 mg hydrocortisone sodium succinate) allowed to dissolve next to the ulcer three times per day. These low-potency corticosteroids adhere to the mucosa to provide a high local concentration of drug and are suitable for use in dental practice. They probably reduce the painful inflammation but do not speed healing much or reduce frequency of attacks. They are best applied in the very early, asymptomatic stages.

Triamcinolone dental paste such as Kenalog in Orabase 0.1% 2-3 times daily.

Composition: 1mg of triamcinolone (medium potency steroid) in orabase (Orabase contains gelatin, pectin, & carboxymethylcellulose sodium in plasticized hydrocarbon gel, a polyethylene and mineral oil gel base).

Angiovag spray (aerosol): Composed of Dequalinium chloride (0.1% w/v), Hydrocortisone acetate (0.06 % w/v), Lidocaine hydrochloride (0.1% w/v), Tyrothricin (0.4% w/v). Initial dose (first 3 days) 1-2 nebulization (spray) every 3 hours, then maintenance dose 1-2 nebulization (if required) every 6 hours.

* Local analgesics: These provide only symptomatic relief. Benzydamine 0.15% w/v mouthwash or oromucosal spray helps some patients. Benzydamine (benzydamine hydrochloride) is a locally acting nonsteroidal anti-inflammatory drug with local anesthetic and analgesic properties for pain relief and anti-inflammatory treatment of inflammatory conditions of the mouth and throat. Topical lidocaine or benzocaine sprays and gels are more effective but can only be used in limited doses and for a short time (mostly before meals).

* Chlorhexidine: A 0.2% solution has also been used as a mouth rinse for aphthae. Used three times daily after meals and held in the mouth for at least 1 minute, it has been claimed to reduce the duration and discomfort of aphthous stomatitis.

* Topical salicylate preparations: Salicylates have an anti-inflammatory action and also have local effects. Preparations of choline salicylate in a gel can be applied to aphthae. These preparations, which are available over the counter, appear to help some patients.

* Tetracycline mouth rinses: Trials in both the UK and USA showed that tetracycline rinses significantly reduced both the frequency and severity of aphthae. Best reserved for herpetiform aphthae. The contents of a tetracycline capsule (250 mg) can be stirred in a cup of water and held in the mouth for 2–3 minutes, three times daily. However, there are few easily soluble tetracycline preparations, and their use carries a risk of super-infection by *Candida albicans*.

* Hyaluronic acid: Recent studies and clinical trials showed that 0.2% hyaluronic acid gel was effective for the treatment of recurrent minor aphthous ulcers.

Note: Low level Diode LASER may also be used for the treatment of some cases of RAUs

Treatment of major aphthae which are so painful, persistent and resistant to conventional treatment. MAUs can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15 to 30 minutes to allow for longer contact of the medication. Intralesional injection of steroids can be used to treat large major RAS lesions. Reportedly effective treatments include pentoxifylline, azathioprine, cyclosporin, colchicine and dapsone, but thalidomide is probably most reliably effective. However, such drugs can only be given under specialist supervision. Thalidomide has been shown to reduce both the incidence and severity of major RAS in both HIV-positive and HIV-negative patients, but this drug must be used with extreme caution in women during childbearing years (not used in pregnancy) owing to the potential for severe life-threatening and deforming birth defects or congenital defects.

Behçet's disease/syndrome

Behçet's disease (BD) was initially described by the Turkish dermatologist Hulusi Behçet as a triad of symptoms including recurring oral ulcers, recurring genital ulcers, and eye involvement.

BD is now known to be a multisystem disorder with many possible manifestations. There is a systemic vasculitis of small blood vessels and affects many more organ systems than suggested by the triad limited definition.

The importance Behçet's diagnosis is indicated by the life-threatening risk of thrombosis, blindness or brain damage.

The highest incidence of BD has been reported in Eastern Asia, the Middle East, and the Eastern Mediterranean, particularly Turkey and Japan, where BD is a leading cause of blindness in young males; however, cases have been reported worldwide, including Europe and North America (especially immigrants). BD is more severe in younger patients and those with eye and GIT involvement.

Clinical manifestation:

Patients are usually young adult males between 20 and 40 years old. Patients suffer one of four patterns of disease:

* Mucocutaneous: Oral aphthae are the most consistent feature, not distinguishable from common aphthous stomatitis and may be of any of the three RAU types. There is often genital ulceration, skin rash/inflammation (erythema nodosum) and vasculitis.

* Arthritic: Joint involvement with or without mucocutaneous involvement. The large weight-bearing joints are most affected. There is pain, but no destructive arthritis and only a few joints are involved. The pain may be relapsing or constant.

* Neurological: This type may occur with or without other features and is usually a late stage. Vasculitis within the brain causes a variety of neurological symptoms including sensory and motor disturbances, confusion and seizures. Thrombosis of vessels causes raised intracranial pressure, blurred vision and headache.

* Ocular: This type may also be solitary or accompanies other types. There may be uveal inflammation or vasculitis and thrombosis of the retinal arteries, either of which can lead rapidly to blindness if not treated.

Etiology:

The etiology is unknown, but the disease has features including circulating immune complexes, high levels of cytokine secretion and activation of lymphocytes and macrophages in the

circulation. These suggest an immune-mediated reaction (disease), and it is presumed that this may be a response to an unknown infectious agent, possibly through immune cross reaction between pathogen and host heat shock proteins.

The racial distribution suggests a strong genetic component and HLA tissue types are linked, most strongly to HLA-B51. This is a common allele and so is not of use in diagnosis but can predict ocular lesions.

Diagnosis:

Oral aphthae are frequently the first manifestation. Behçet's disease should therefore be considered in the differential diagnosis of aphthous stomatitis, particularly in patients from a racial group at risk, and the medical history should be checked for the features of The International Criteria for Behçet's Disease System.

The frequency of other manifestations is highly variable. However, in a dental clinic, aphthous stomatitis in combination with any two of the other major features can be regarded as likely indicators for referral of the patient to a specialist.

Hence, BD diagnosis is mostly history & clinical based.

Pathergy test: It is common for patients with BD to have a cutaneous hyper-reactivity to intra-cutaneous injection or a needlestick

Apart from pathergy test, other tests are not helpful in diagnosis of BD. However, laboratory tests may be used to rule out other diseases, such as connective tissue (e.g., lupus erythematosus) and hematologic diseases causing severe neutropenia.

Pathergy test is positive if there is an exaggerated response to a sterile needle puncture of the skin. However, the test must be interpreted by an experienced clinician and tends to be positive only in Mediterranean patients. Moreover, a positive pathergy test does not correlate with the presence of oral lesions or with the overall severity of the disease and is rarely positive in

patients who are not originally from the Mediterranean basin. It is also not entirely specific for BD.

The International Criteria for Behçet's Disease 2010 together with their overall incidence in all patients*

Sign group	Criteria	Points	Incidence
Oral aphthous stomatitis	Three attacks or more in one year	2	80%†
Genital ulceration	Recurrent ulcers or scarring	2	80%
Ocular lesions	Uveitis or retinal vasculitis	2	50%
Skin lesions	Follicular pustular rash or erythema nodosum	1	75%
CNS involvement	Any involvement	1	10%
Vascular manifestations	Superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, and aneurysm	1	30%
Positive pathergy test (optional to include)		1	5-60%‡

*A score of 4 or more points predicts Behçet's disease with 95% certainty, 98% if the pathergy test is performed. Incidence of features varies between populations.

†100% using older criteria, previously a requirement for diagnosis.

‡The higher figure is for patients from the middle East and central Asia.

Complications include:

* Blindness

* Rupture of a large-vessel, aneurysms, thrombosis and embolism.

In the absence of these significant complications, relapses become less frequent, and the disease may eventually fade.

Treatment:

Treatment of BD depends on the severity and the sites of involvement.

Patients with sight-threatening (eye involvement) or CNS lesions require more aggressive therapy with drugs that have higher potential for serious side effects.

Azathioprine and other immunosuppressive drugs combined with prednisone have been shown to reduce ocular disease as well as oral and genital involvement.

Pentoxifylline, which has fewer side effects than immune-suppressive drugs or systemic steroids, has also been reported to be effective in decreasing disease activity, particularly of oral and genital lesions.

Dapsone, colchicine, and thalidomide have also been used effectively to treat mucosal lesions of BD.

Inflammatory bowel disease (IBD)

IBD is a general classification of inflammatory processes that affect the large and small intestines such as:
Ulcerative colitis
Crohn's disease
Both diseases are of unknown etiology (Idiopathic). They are of interest to the dentists because of their associated oral findings and the impact of their medical management (particularly the use of corticosteroids) on dental management.

Ulcerative colitis:

Diagnosis of ulcerative colitis is made on the basis of:
*History *Clinical examination *Gastrointestinal imaging *Endoscopy, which involves direct visualization of the intestinal mucosa.

Most important is the sigmoidoscopic examination, which usually reveals the characteristic picture of multiple tiny mucosal ulcers covered by blood and pus.

Crohn's disease:

Crohn's disease is an inflammatory disease of the small or large intestine and the inflammation involves all layers of the gut. Gross examination may reveal mucosal ulcers or open sores of the intestines.

Oral lesions:

* Multiple recurrent aphthous ulcers.

* Diffuse swelling of the lips and face.

* Inflammatory hyperplasia of the oral mucosa with a cobblestone pattern.

* Indurated polypoid tag like lesions in the vestibule and retromolar pad area.

* Angular cheilitis and glossitis (oral manifestations of anemia)

* Persistent deep linear ulcerations with hyperplastic margins.

* Localized mucocele formation.

* Oral lesions may precede the radiologic changes of the disease by up to 1 year.

In conclusion: Patients with IBD complain of pain associated with ulcerative lesions in the oral cavity.

Palliative rinses, ointment, and topical steroids may be helpful. The treatment of the IBD is carried out by a specialist physician or GIT surgeon.

Note: There appears to be an increased risk of dental caries that is probably related to dietary changes in patients with IBD. The causes of the dental caries and increased incidence of bacterial and fungal infections are multifactorial but appear to be related to either the patient's altered immune status (due to therapy) or diet.

Cyclic neutropenia:

Cyclic neutropenia is a rare hematologic disorder that occurs secondary to a periodic failure of the stem cells in the bone marrow to form neutrophils.

It is characterized by transient severe neutropenia that occurs approximately every 21 days (3-4 weeks). The neutrophil count lasts 3 to 7 days and is occasionally associated with elevations in monocytes.
One/third of cases are inherited as an autosomal dominant trait, and two/thirds arise spontaneously during the first few years of life.

The disease is frequently present during infancy or childhood, although there is an adult-onset form of the disease, and both sexes appear to be equally affected.

The patient looks healthy between neutropenic episodes, but at regular intervals the absolute neutrophil count falls quickly below 500/µl, and in some patients the neutrophil count falls to 0.

Normal count 1500-8000/µL

Mild neutropenia 1000-1500/µL

Moderate neutropenia 500- 1000/µL

Severe neutropenia < 500/µL

Note: Increased number of neutrophils or Neutrophilia >8000/µL

Clinical manifestations:
The major signs and symptoms of cyclic neutropenia attributed to infections occurring during neutropenic episodes.
The most common signs are:
1. Fever
2. Stomatitis (oral ulceration) and periodontal diseases
3. Pharyngitis
4. Skin abscesses
The severity of the infections is related to the severity of the neutropenia.

However, some patients with severe periodic neutropenia experience few infections owing to a compensatory increase in monocytes, which act as phagocytes to prevent the spread of bacterial infection. Less frequently, patients experience lung and urinary tract infections and rectal and vaginal ulcers.

Life expectancy is good for patients who receive careful monitoring.

Oral manifestations:
Oral lesions are common in cyclic neutropenia and might be the major clinical manifestation of the disease.
The two most common oral manifestations are oral ulcers and periodontal diseases.
* The oral ulcers recur with each new bout (cycle) of neutropenia and resemble the large deep scarring ulcers seen in major aphthous stomatitis.
* The periodontal manifestations range from marginal gingivitis to rapidly advancing destructive periodontitis.

Diagnosis:
Thorough history and clinical examination of patients with major RAUs or generalized rapidly advancing progressive periodontitis that cannot be explained by local factors alone, cyclic neutropenia should be ruled out as a possible cause.

Suspicion of cyclic neutropenia should be particularly high when either of these oral diseases is seen in children. Diagnostic

evaluation entails serial measurement of circulating neutrophils. The diagnosis may be established by demonstrating at least two cycles of neutropenia.

Treatment:

* Refer to Hematologist for treatment and monitoring of the disease.

* Dental management: Patients with known cyclic neutropenia require frequent dental treatment visits to minimize advancing periodontal disease.

Routine treatment should be confined to the periods when the absolute neutrophil count is above 2,000/µL.

WBC count should be taken on the day of any dental procedure is a wise precaution because the neutrophil count can change rapidly.

Oral hygiene must be carefully maintained, and patients should be recalled for oral hygiene maintenance every 2 to 3 months. Treating the disease itself, has reduced oral ulcers and periodontal disease in these patients.

Erythema multiforme:

Erythema multiforme (EM) is an acute, inflammatory muco-cutaneous disease which affects the skin and oral mucosa, other mucosal surfaces, such as the genitalia, may also be involved.

In patients presenting to dentists, oral lesions may be the only sign.

EM is one of the few causes of recurrent oral ulceration and also produces blisters.

It represents a hypersensitivity reaction to infectious agents (majority of cases) or medications.

In general, EM is classified into:

EM minor if there is less than 10% of skin involvement and there is minimal to no mucous membrane involvement

EM major has more extensive but still characteristic skin involvement, with the oral mucosa and other mucous membranes affected

However, there is a subset of EM that affects the oral mucosa only without skin involvement

Other forms of EM known as Stevens–Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) (Lyell disease, Lyell syndrome, Lyell's syndrome). However, recent studies consider them both as different entities.

Etiology:

Though the mechanism is unclear, erythema multiforme appears to be a cell-mediated hypersensitivity reaction.

EM is a hypersensitivity reaction, and the most common inciting factors are infections particularly with Herpes Virus HSV (however, infections with mycoplasma and Chlamydia pneumonia have been reported). Drug reactions to Penicillin, NSAIDS, anticonvulsants, or other drugs play a smaller role. Cases of oral EM precipitated by benzoic acid, a food preservative, have been reported.

Studies show that recurrent EM is associated with HSV infection in 65%–70% of cases, both by history of HSV infection one to three weeks before onset of EM, and sero-positivity for HSV antibodies or identification of HSV antigens.

Clinical manifestations:

Most patients are aged between 20 and 40 years, with a slight male predominance.

In the minor form, only skin is involved and this is a relatively mild self-limiting condition.

In the major form there are florid lesions on skin and oral, nasal and genital mucosae.

There is acute onset, sometimes preceded by vague arthralgia or slight fever for a day in the major form.

Then the characteristic 'target' "Iris" "Bulls' Eye" lesions appear, initially on arms and legs and spreading centrally.

Each lesion is a well-defined red macule about a cm or more in diameter.

During a period of a few hours to days, the center becomes raised, with a bluish cyanotic center.

In severe cases, skin lesions blister and ulcerate centrally.

New crops of lesions develop during a period of approximately 10 days.

Oral and lip lesions appear a few days into the attack, most commonly anteriorly in the mouth on the buccal and labial mucosa and tongue. Target lesions are not seen intra-orally

The oral lesions are inflamed patches with irregular blistering and broad, shallow irregular ulcers.

On the lips, fibrin oozes continually and forms hemorrhagic crusts.

There is severe pain.

Diagnosis:

Diagnosis relies on the typical presentation, history of previous recurrent episodes and a trigger, if present. When only the mouth is involved, a biopsy may be required; however, as the appearances are very variable excluding alternative causes might aid in the diagnosis.

Treatment:

The attack usually lasts for 3 or 4 weeks and is self-limiting without treatment in the minor form. However, oral lesions are painful, interfere with eating and fluid intake must be maintained. Mild oral EM can be managed with systemic or topical analgesics for pain and supportive care since the disease is self-limiting and resolves within a few weeks.

Unless already resolving, lesions might benefit from treatment with corticosteroids. A short reducing dose of prednisolone starting at around 60 mg/day for 3 days, then tapering off over a week, is frequently given.

Chlorhexidine will prevent secondary oral mucosal infection and maintain gingival health while tooth brushing is impossible.

If present, Eye lesions require specialist treatment.

More severe cases are usually managed with systemic corticosteroids. Topical steroids also help to resolve oral and cutaneous lesions.

Recurrences, usually at intervals of several months, for a year or two are characteristic and are sometimes increasingly severe. Hence, attempts should be made to identify the trigger.

Recurrent HSV infections trigger most of cases, therefore, suspected HSV-associated EM should be treated with antiviral medications. Treatment with acyclovir at the first sign of the disease in recurrent EM, suppresses the trigger and controls EM in approximately half of patients.

Other treatment modalities include dapsone, hydroxychloroquin, mycophenolate mofetil, azathioprine, colchicine, methotrexate, and intravenous immunoglobulin.

In patients who have persistent oral lesions, mycoplasmal infection should be suspected and suppressed.

Dr. Ahmed Salih Khudhur
BDS, M.Sc., PhD.
Newcastle University/ UK

Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis

Severe hypersensitivity reaction which has many features in common with EM but is now considered a separate entity on the basis of its severity, extent and causes.

Toxic epidermal necrolysis is its most severe presentation.

The mouth is always involved in SJS & TEN.

SJS & TEN are more severe than EM and tend to arise on the chest rather than the extremities as erythematous and purpuric macules, lesions known as “atypical targets”.

Unlike EM, SJS/TEN trigger is mainly a drug* and sometimes mycoplasmal infection. Many drugs are implicated, but the most frequent causes are antibacterial sulfonamides* & penicillin, other drugs such as anticonvulsants, and NSAIDs in children. Same drugs in addition to allopurinol, and oxicams (NSAIDs cox-2 inhibitors) in adults.

Some genetic predispositions are known for individual drugs (as in Han Chinese).

Histopathology indicates that primary cytokine involved in these hypersensitivity reactions is tumor necrosis factor (TNF)-α.

The mucosal surfaces of the eye, genitalia, and mouth are almost always severely affected by SJS/TEN, always with skin involvement.

The typical oral manifestation is extensive oral ulceration with hemorrhagic crusts on the lips vermilion, oral and other mucosal surfaces.

Treatment:

* First of all, cessation of causative drugs.

* Because of the severity of this condition, treatment is generally with intensive supportive care because of loss of skin barrier (and alternative antibiotics to control skin infection), intravenous immunoglobulin, immunosuppressants (systemic steroids,

cyclosporine, cyclophosphamide, and TNF-α inhibitor) and plasmapheresis.

There is a high risk of death when the area of skin involved in toxic epidermal necrolysis is extensive.

Other miscellaneous oral ulcers

Other types of ulcers might present in the oral cavity associated with/or as the main manifestation of local (oral) or systemic diseases

Such as:

Pemphigus & Mucous Membrane Pemphigoid

Oral cancer

Ulcers associated with: Oral mucositis, Xerostomia & Sjögren's syndrome, Diabetes Mellitus, Renal failure and Others

The basic principles for the management of oral ulcers in general:

1. **Early diagnosis (might be life-saving)**
2. **Relief pain**
3. **Remove the cause if possible / Treat the underlaying cause: Direct cause (sharp edge of broken tooth or restoration, trauma from dental appliance), infection (viral, bacterial, fungal), and underlying cause (anemia, malnutrition, immune disturbance, systemic disease)**
4. **Isolate the ulcer from any unwanted effect (such as further trauma), and prevent super-infection.**
5. **Reduce inflammation and promote healing.**
6. **Cure if possible.**