British Journal of Pharmaceutical and Medical Research Vol.04, Issue 04, Pg.1946-1951, July-August 2019

Available Online at http://www.bjpmr.org

BRITISH JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

Cross Ref DOI : https://doi.org/10.24942/bjpmr.2019.550 Volume 04, Issue 04 July-August 2019

ISSN:2456-9836
ICV: 60.37

Review Article

"Recurrent Apthous Stomatitis: A Review With Evidence Based Management"

Dr. Pranay Patel, Dr. Ruchita Peter

Senior Lecturer, Department of Oral Medicine & Radiology,
College of Dental Science & Hospital, Amargadh.

ARTICLE INFO

Article History:
Received on 17th July, 2019
Peer Reviewed on 29th July, 2019
Revised on 12th August, 2019
Published on 28th August, 2019

Keywords:
Aphthous, RAS, Herpetiform, HIV

ABSTRACT

Recurrent Apthous stomatitis (RAS) is a common disease of the oral cavity, affecting about 20% of the world's population, women are more affected than men, and in the most cases it starts around the first decade of life. The clinical features and characteristics of this disease are easily defined still the etiology and the pathophysiology remain unclear. Clinically, RAS is seen in three forms minor RAS, major RAS, herpetiform RAS, and in HIV patients, the fourth form is seen. There are many treatment modalities present for RAS including first & second line of treatment. The existing article provides a detailed review of the current perceptions and knowledge of the etiology, pathogenesis, and management of RAS.

Corresponding Author: *Dr. Pranay Patel, Senior Lecturer, Department of Oral Medicine & Radiology, College of Dental Science & Hospital, Amargadh.*

INTRODUCTION:

An ulcer is a well circumscribed sometimes depressed lesion with an epithelial defect that is covered by a fibrin clot, resulting in yellow-white appearance. [5] The term "aphthous" is derived from a Greek word "aphtha" which means ulceration. Recurrent aphthous stomatitis (RAS) is one of the most common painful oral mucosal conditions seen among patients. RAS have weighed down mankind all the way through recorded history and it was first mentioned by Hippocrates who utilized the term 'aphthai' to illustrate disorders of the mouth. [4] Later it has been described by Miculizc and Kummel as "Miculizc's aphthae.[5] These present as recurrent, multiple, small, round, or ovoid ulcers, with circumscribed margins, having yellow or sometimes grayish white flooring and they are bounded by red radiance, present first in middle of childhood or teenage years. It is one of the most common oral complaints seen in the primary Dental care setting. Despite its commonness, its causes remain largely mystifying. The day to life style & activities of current age group affect the occurrence of such kind of ulcers. According to the literature RAS occurrence was superior in male(48.3%) in comparison to female(57.2%) individuals.[4] RAS is mainly diagnosed based on the patient Clinical history and oral expression. There is no specific diagnostic test, though it is essential to discard possible underlying systemic causes .[2] Although, the etiology is unclear, treatments are primarily empiric and aimed at symptom diminution rather than prevention or cure. However, there are quite a lot of methods, both topical and systemic, that can be easily and affordably utilized in the primary care settings.

ETIO-PATHOGENESIS:

RAS is having multifactorial causative agents & conditions as shown in Table no. 1. RAS remains a common oral mucosal disorder in most communities of the world, its precise etiology remains unclear. There is no one way trigger has ever been verified, and there is no convincing evidence for a genetic predisposition to RAS in most patients. Currently, RAS is recognized as an immunologically mediated, inflammatory oral condition rather than an infectious disease. [1]

Table no. 1: Etiological factors of RAS

Cause	Particulars
Local	Trauma, Allergy to foods, Smoking, Altered Salivary Secretion
Systemic	Behcet's disease, Magic Syndrome, Crohn's Disease, Ulcerative colitis, HIV infection, Cyclic neutropenia, Anxiety, Stress, psychologic imbalance, menstrual cycle, PFAPA or Marshall's syndrome, Reiter's syndrome, Sweet's syndrome
Genetics	Associations with HLA antigens, alteration in CD4:CD8 lymphocyte ratio, and dysfunction of the mucocutaneous cytokine network
Nutritional Deficiency	Iron, folic acid, zinc, and vitamins B1, B2, B6, B12
Microbial	Bacterial: Streptococci, Viral infection like: Varicella Zoster, Cytomegalovirus
Harmful Oral Habits	Tobacco: It reduces production of tumor necrosis factor alpha and interleukins 1 and 6.
Drugs	Angiotensin converting enzyme inhibitor captopril, gold salts, nicorandil, phenindione, phenobarbital, and sodium hypochloride.

CLINICAL MANIFESTATIONS:

RAS is clinically divided into three different variants, according to the classification of Stanley (1972), Cooke (1969) and Lehner (1968) based on clinical manifestation – minor RAS, major RAS, and herpetiform RAS & HIV associated RAS are

considered as fourth type,[8,2,3]

- Minor RAS (Mickuliz's aphthae or mild aphthous ulcers)
- Major RAS (periadenitis mucosa necrotica recurrent or Sutton's disease)
- Herpetiform - ulceration is characterized by recurrent crops of multiple ulcers; may be up to 100 in number. [5,6]

On clinical examination, these ulcers are mild-moderate or severely painful, having clear distinction with an oval or round shallow necrotic hub roofed by a yellow or greyish white artificial pseudo membrane & bounded by elevated margins and red halo.

Table no. 2: Clinical features of RAS

Features	Apthous Minor	Apthous Major	Herpetiform Ulcers
Peak Age Of Onset	Second	First- second	Third
Gender	F>M	F>M	F>M
Number Of Ulcers	1-5	1-3	5-20 (up to 100)
size of ulcers (mm)	< 10	> 10	1-2
Duration	7-14 days	2 weeks to 3 months	7-14 days
Healing With Scaring	No	Yes	No
Site	Non-keratinized mucosa especially labial/buccal mucosa. Dorsum and lateral borders of tongue	Keratinized plus non-keratinized mucosa particularly soft palate	Non-keratinized mucosa, but particularly floor of mouth and ventral surface of tongue

The stages of natural evolution of lesions of RAS have been synthesized by Stanley [8] which divides the natural history into following four stages that is;

1. Premonitory [first 24 hrs]
2. Pre-Ulcerative [3 days]
3. Ulcerative [1-16 days]
4. Healing [4- 35 days]

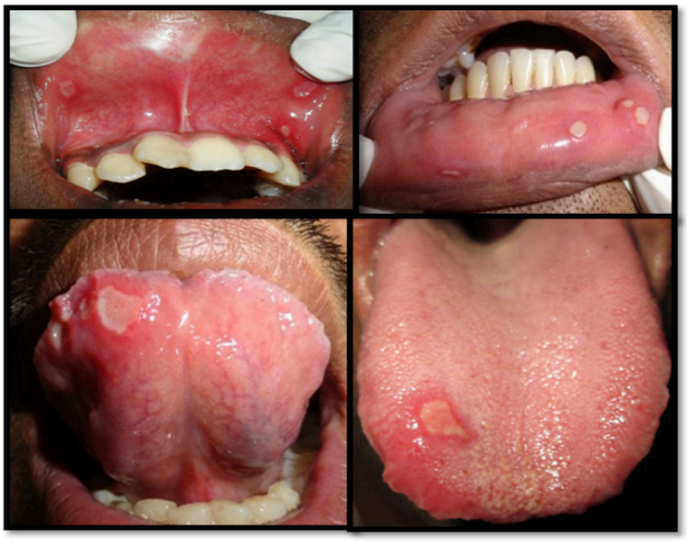

Figure 1: Different Types Of Ras

Syndrome Associated With RAS [4]:

- Behcet's Disease – Characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis and skin lesions. Genetic component - HLA-B51
- Magic syndrome - Mouth and Genital ulcers with Inflamed Cartilage
- Reiter's syndrome - characterized by recurrent oral aphthous ulcers, urethritis, polyarthritis and ocular lesions.
- Sweet's syndrome - Acute Fever, increase in PMN in peripheral neutrophilic blood, Skin lesions: Erythematous dermatosis plaques, nodules, vesicles, pustules dense dermal neutrophilic infiltrate Circulating autoantibodies, cytokines, dermal dendrocytes, HLA serotypes, immune complexes and leukotactic mechanisms have been suggested as factors that contribute to the pathogenesis of this syndrome.
- PFAPA: Periodic fever, aphthosis, pharyngitis, and adenitis.

DIAGNOSIS:

The diagnosis is made from the clinical presentation & from exclusion of other diseases that produces ulcerations that closely resembles RAS. Apart from that the other diagnostic procedures include; Routine Hematological test-Serological tests (Complete blood count, HB%, serum iron & ferretin level), Histopathological &. Histo-pathologic appearance of RAS is characteristic but not pathognomonic.[6] Early lesions show a central zone of ulceration, which is covered by fibrinopurulent membrane & connective tissue shows increased vascularity & inflammatory cell infiltrate.

MANAGEMENT:

Main Goals of treatment of RAS are as follows:

1. Reduce the painful symptoms.
2. Reduce the severity of the condition.
3. Reduce the duration of the lesions
4. Reduce the size of the lesions
5. Increase the time interval between recurrences.
6. Use the medications that have the fewest adverse effects.

Various treatment modalities for RAS are as follows:

- Treat the underlying disease & do necessary Behavioral management
- Symptomatic treatment - topical drugs[2,3].
- When food sensitivity is demonstrated from patch testing, avoidance of the allergen can improve oral symptoms. A gluten-free diet has been suggested for patients with RAS and gluten sensitive enteropathy. [10,11]
- Pharmacological therapies:
  - Topical analgesics - Lignocaine (2.5%,5% gel), Benzocaine (10%,15%,205 gel), Diphenhydramine mouth rinse (12.5mg/5cc rinse), Capsaicin (0.025%,0.075% cream). [11,12]
  - Topical steroids – fluocinonide (0.05% ointment, 0.05%cream), bethamethasone (0.1%cream, 0.05%gel), clobetasol (0.05%cream).
  - Intralesional steroids - Triamcinolone (10mg/ml-inject 0.1cc/cm of lesion), Dexamethasone (4mg.ml-inject 0.1cc/cm of lesion). [2,13]
  - Immunomodulators - Dapsone (100mg/day), Thalidomide (100 – 300 mg), Colchicine (200mg/day – 4 weeks). [12,14]
- Physical Therapy – Surgical removal, LASER ablation, Chemical cautery, low dense Ultrasound

Table no. 3 : Treatment Modalities Of RAS [11,13,14].

Type Of Treatment	Treatment Modalities	Evidence
Supportive Care	Multivitamin supplements- folic acid	II c
	Vitamin B12 – 1000 mcg daily for 6 months	II c
First Line Of Treatment	25% Benzydamine – Tantum Mouthwash	II b
	Triamcinolone Acetonide- TESS	I a
	Topical Dexamethasone: Mouthwash, Gel	II c
Second Line Of Treatment	Tab Pentoxifylline 400 mg 3 times daily for 60 days	I a
	Tab Levamisole 150 mg per day for three consecutive days	II b

CONCLUSION:

Quality of life is relatively new perception in the measurement of health. It broadens the evaluation of the impact of disease to include physical, psychological & communal functioning. Recurrent Apthous stomatitis (RAS) is such kind of disease that causes much suffering in affected patients due to recurring painful attacks. RAS remains a poorly understood entity, regardless of having obvious clinical features in clinical practice. Hence further Evidence based research should be conducted on RAS to establish a standard Treatment protocol.

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How To Cite This Article:
Pranay Patel, Ruchita Peter *Recurrent Apthous Stomatitis: A Review With Evidence Based Management* Br J Pharm Med Res , Vol.04, Issue 04, Pg.1946 -1951, July - August 2019. ISSN:2456-9836 Cross Ref DOI : https://doi.org/10.24942/bjpmr.2019.550

Source of Support: Nil **Conflict of Interest:** None declared