

Review article

Decision tree analysis for the management of vesiculobullous lesionsK.V. Swathi¹, G. Maragathavalli²¹Department of Oral Medicine and Radiology, SRM Dental College, Ramapuram, Chennai, 600089, Tamil Nadu, India²Department of Oral Medicine and Radiology, Saveetha Dental College, Chennai, 600077, Tamil Nadu, India

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ABSTRACT

A mucocutaneous condition known as a vesiculobullous lesion is characterized by the presence of fluid-filled vesicles and bullae. Bullae and vesicles typically have different sizes. Bullae have a diameter greater than 5–10 mm, whereas vesicles have a diameter of less than 5–10 mm. Infectious etiologies such herpes simplex, varicella zoster infection, hand, foot, and mouth disease, herpangina, and measles can cause vesiculobullous lesions. Additionally, immunobullous conditions including pemphigus vulgaris, pemphigoid, dermatitis herpetiformis, linear IgA disease, or inherited conditions like epidermolysis bullosa may be to blame. The management of common vesiculobullous disorders is reviewed using a decision tree analysis based on etiopathogenesis, clinical characteristics, and diagnostic criteria. A decision tree has been formulated based on predominantly vesicular and predominantly bullous lesions with specific lesions in each category based on recent scientific evidence. This decision tree will guide the clinicians for effective management of the vesiculobullous lesions in the dental office. The timely recognition and management of these lesions is very essential as they can compromise the quality of life due to their chronicity and frequent recurrence in nature.

Keywords: Vesiculobullous; mucocutaneous; infectious; immunobullous; genetic.**INTRODUCTION**

Vesiculobullous diseases are distinct group of mucocutaneous disorders characterised by the presence of vesicles, bullae and can be attributed due to infectious, immunobullous or genetic diseases. Mostly these lesions rupture due to constant irritation and based on nature of the oral mucosa it may cause erosions, ulcerations on the surface of the oral mucosa (1).

Classification of vesiculobullous lesion

These lesions can be divided into two categories: acute vesiculobullous lesions, which can be caused by an allergy, burns, viruses, or autoimmune diseases like pemphigus, bullous pemphigoid, cicatricial pemphigoid, bullous lichen planus, chronic herpes simplex, and linear IgA disease; and chronic vesiculobullous lesions. According to how they present clinically, they can be divided into two groups: those that are predominantly bullous, such as pemphigus vulgaris, bullous impetigo, epidermolysis bullosa, and linear IgA disease, and those that are predominantly vesicular, such as herpes simplex virus infection, varicella infection, hand, foot, and mouth disease, herpangina, dermatitis herpetiformis and linear IgA disease. The classification of vesiculobullous lesions depends on whether they are infectious or non-infectious. Infectious vesiculobullous lesions include herpes simplex infections, varicella infections, herpangina, hand, foot, and mouth disease, while non-infectious vesiculobullous lesions include pemphigus, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, erythema multiforme,

dermatitis herpetiformis, epidermolysis bullosa acquisita and linear IgA disease. (2)

MATERIALS AND METHODS

Based on the recent scientific evidence, a decision tree analysis has been done and depicted in the form of flow diagrams for the management of vesiculobullous lesions. The decision tree has been done as two main categories which includes common entities within respective categories. It is as follows:

Predominantly vesicular lesions: These types of lesions mainly include Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) infections.

Predominantly bullous lesions: These types of lesions mainly include Pemphigus, Bullous Pemphigoid, Mucous Membrane/Cicatricial Pemphigoid and Erythema multiforme

RESULTS**Predominantly vesicular type of lesions****Herpes simplex virus (HSV) infections**

Two DNA viruses, Herpes Simplex Virus (HSV)-1 and Herpes Simplex Virus (HSV)-2, are the main causes of herpes simplex virus infection. While HSV-2 infections are found below the waist, HSV-1 infections are found above the waist. The incubation period lasts for two to three weeks. A few of the various manifestations of HSV-1 infection include orolabial herpes, herpetic sycosis, herpes gladiatorum, herpetic whitlow, ocular HSV infection, herpes encephalitis, Kaposi varicelliform eruption (eczema herpeticum), and severe or chronic HSV infection. HSV-1 is a nuclear replicating enveloped

virus that is spread through saliva or other bodily fluids that have been contaminated. (3) HSV-1 is the virus that causes primary herpetic gingivostomatitis, which typically affects children under the age of six. Even though the majority of the time it will be an asymptomatic presentation, children with symptoms are identified based on the clinical look of erythematous gingiva, mucosal hemorrhages, and clusters of small erupted vesicles throughout the mouth. (4) Infections spread through sexual contact, such as HSV-2, are very common. Herpes genitalis is a prevalent ailment in HIV-positive people. HSV-2

sheds more frequently and in greater quantities in HIV-infected individuals with lower CD4+ levels. (5) Additional specific HSV diseases include herpetic whitlow, herpetic gladiatorum, herpetic meningoencephalitis, herpetic conjunctivitis, herpetic eczema (Kaposi's varicelliform eruption), and diffuse herpes simplex of the newborn. The following decision tree analysis has been developed in relation to the treatment of primary HSV infection (Fig. 1). It compares the management of immunocompetent versus immunocompromised individuals (Fig. 3).

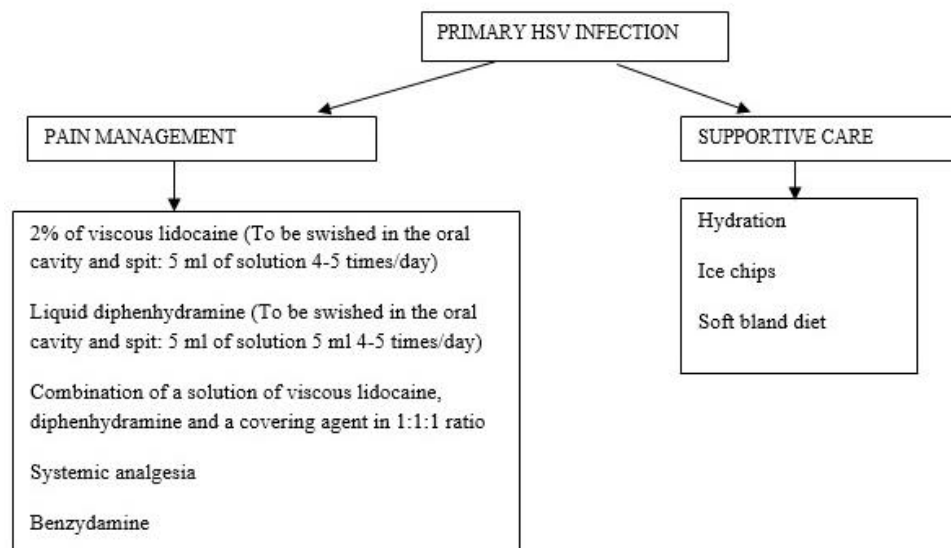


Fig. 1: Management of primary HSV infection

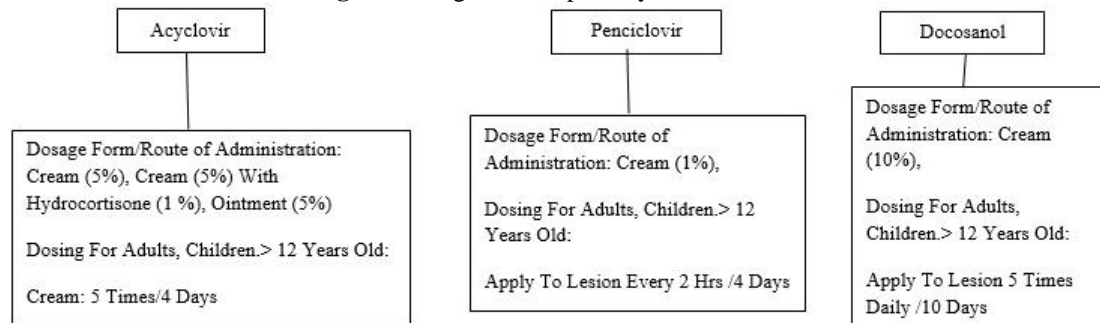


Fig. 2: Antiviral regimen in HSV infection

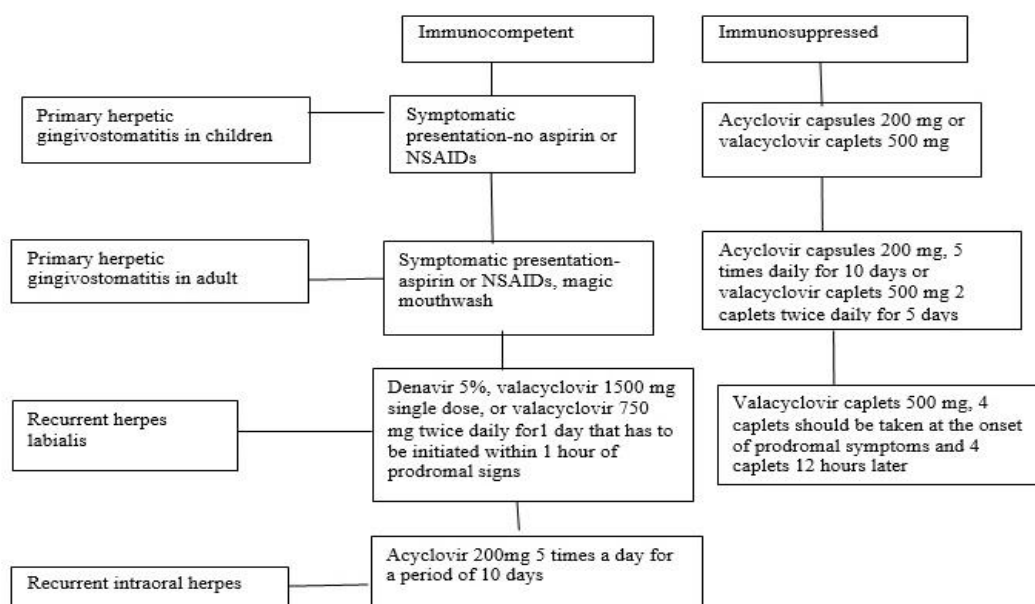


Fig. 3: Antiviral regimen in HSV infection for immunocompetent versus immunosuppressed individual

Varicella Zoster (VZV) infections

Herpes zoster is brought on by the reactivation of VZV, whereas chicken pox is the main infection of VZV infection. (6) Children who contract varicella typically have fever, chills, lethargy, headache, and a brief rash. The pruritic rash could not even be secondary infection. The trunk, face, and extremities are typical areas of involvement. The secondary infection of VZV, popularly known as shingles, is herpes zoster. Adults with a compromised immune system and stress often develop it. One of the trigeminal nerve's branches is usually involved, and it always manifests unilaterally. The development of

post herpetic neuralgia, where the pain manifests as a severe or searing sensation, is the most significant side effect of herpes zoster. Encephalitis, peripheral nerve palsies, and myelitis are additional somewhat unusual consequences. (7)

One of the uncommon herpes zoster presentations where the geniculate ganglion is implicated is the Ramsay Hunt syndrome. Face paralysis, pain, and vesicles in the pinna of the ear, oral cavity, and external auditory canal are its defining features. (8) The following are the various VZV infection therapies (Fig. 4)

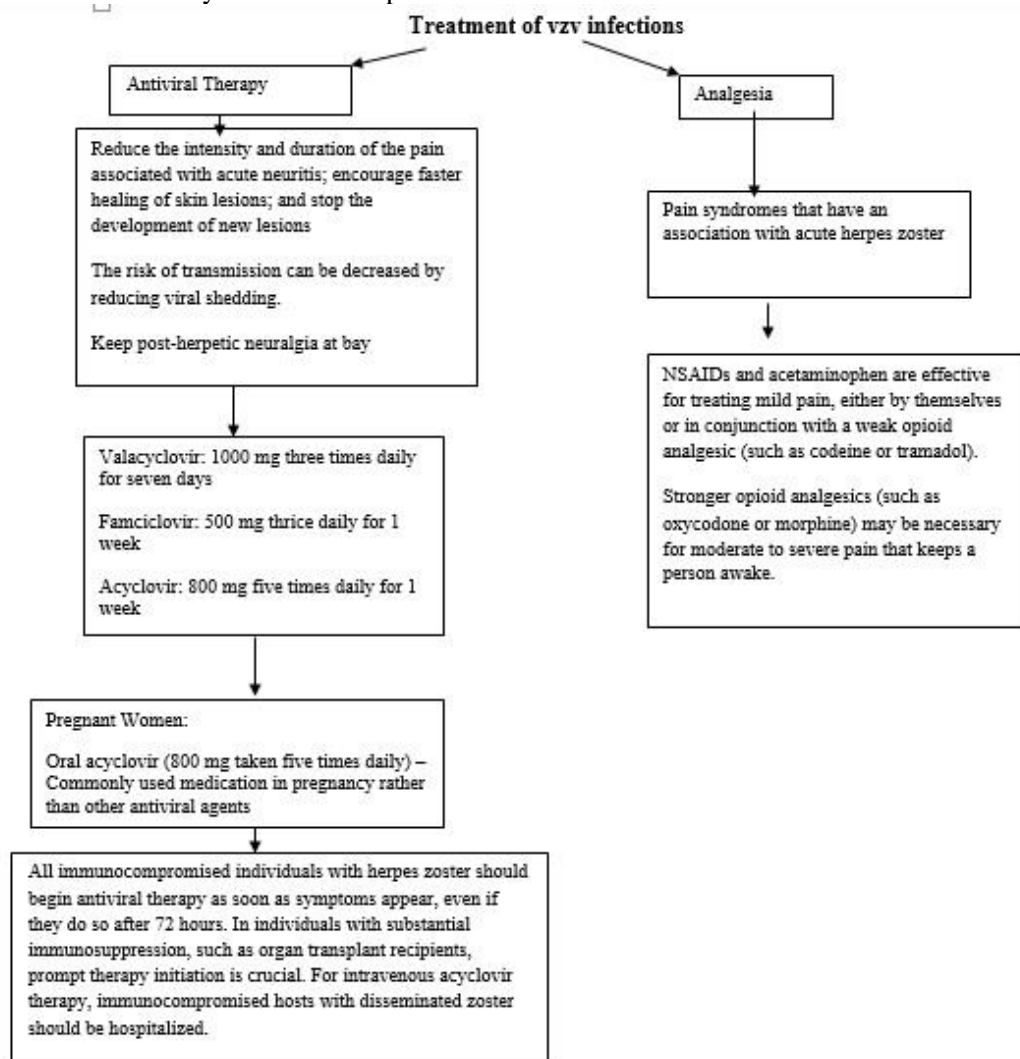


Fig. 4: Management of VZV infections

Predominantly bullous lesions

Pemphigus

A set of autoimmune illnesses that affect the skin and mucosal surfaces are referred to as pemphigus. The subtypes of pemphigus include paraneoplastic pemphigus, pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. The main feature of it is acantholysis, which results in the loss of cellular adhesions. Desmoglein 1, 3, which are cell-to-cell adhesion molecules present in desmosomes, are the target of IgG autoantibodies (9).

Autoantibodies, in particular desmoglein 3 (Dsg 3), are directed towards desmosomes in pemphigus vulgaris. In pemphigus vulgaris, the lack of coherence among keratinocyte layering is the primary cutaneous, mucosal alteration (10).

The primary line of defense in the management of pemphigus vulgaris has traditionally been corticosteroids. Short-term pulsed corticosteroids have also been employed in pemphigus vulgaris instances that were resistant to treatment. Second-line treatment for PV is prednisolone combined with azathioprine or mycophenolate mofetil (MMF),

whereas third-line treatment for PV is prednisolone combined with rituximab, intravenous immunoglobulin (IVIg), immunoadsorption, cyclophosphamide, dapsone, or methotrexate (11).

According to the literature, systemic corticosteroids continue to be the most effective treatment for pemphigus vulgaris. The first line of steroid-sparing medications for the management of pemphigus vulgaris includes azathioprine and mycophenolate mofetil. According to the scientific literature, mycophenolate mofetil is proven to reduce the relapse rate in case of pemphigus when the patient is on the tapering regimen of corticosteroids. (12) Rituximab, a human chimeric anti-CD20 monoclonal

antibody, has been used to treat pemphigus that is resistant to other treatments. (13) Prednisolone is tapered by 25% every two weeks following the consolidation phase and by 5 mg every four weeks until the dose is down to under 20 mg, according to the European Dermatology Forum. In the event of a relapse, the dosage of the steroids is increased to the prior level and an immunosuppressant medication is added. If steroid monotherapy is employed, or if the patient is already receiving combination therapy, it is recommended to switch out one first-line immunosuppressant for another (14) The topical and systemic management for pemphigus is depicted below (Fig. 5).

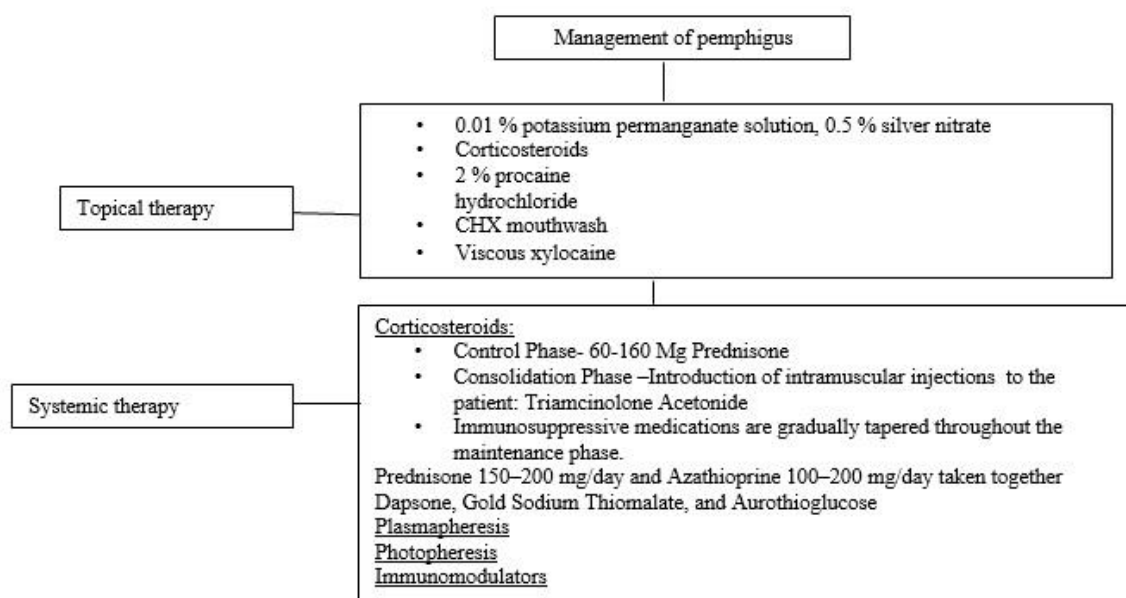


Fig. 5: Management of pemphigus

Bullous pemphigoid

An autoimmune disease known as bullous pemphigoid causes subepidermal blistering, which causes big, tight bullae to form on the skin and, in rare cases, the mucous membrane. The hemidesmosomal proteins at the dermal-epidermal junction are BP 180 and BP 230 which are the target of the autoantibodies. (15) The earliest lesions begin

as urticarial eruptions and develop over weeks or months into bullae. Bullae are filled with clear fluid or hemorrhagic material. Large, tight blisters with immunopathological evidence of linear C3 and IgG deposits at the basement membrane zone are its defining features. (16) The management of bullous pemphigoid is as follows which mainly depends on the nature of severity of the disease (Fig. 6).

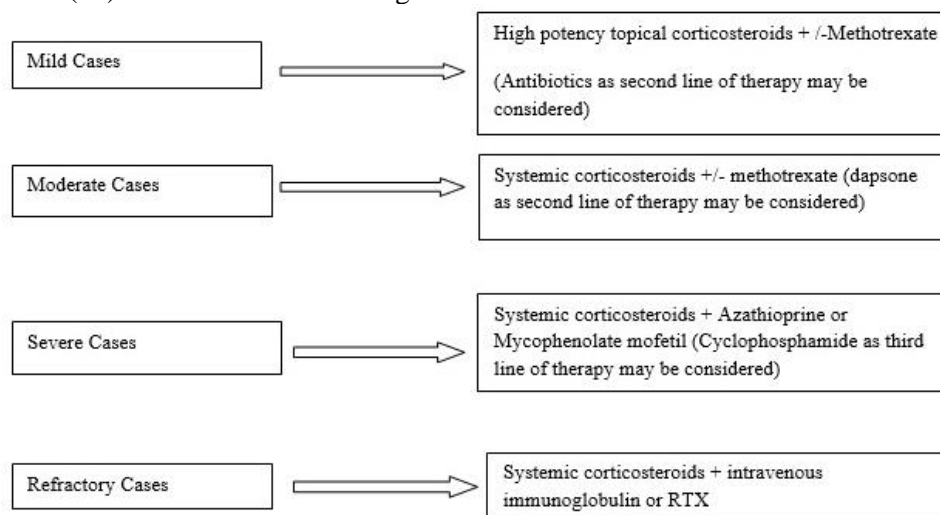


Fig. 6: Management approaches of bullous pemphigoid depending on the case severity

Mucous membrane pemphigoid/ Cicatricial pemphigoid

This autoimmune chronic inflammatory illness, also known as cicatricial pemphigoid (which refers to the scarring of the conjunctival mucosa), is characterized by subepithelial blistering. The mucosa of the skin, mouth, and eyes are all affected. This lesion is distinguished by vesicles that become scarred as they recover. Erosions on gingiva and non-keratinized mucosa are characteristics of oral lesions. Vesicles that are whole are uncommon. Desquamative gingivitis may manifest as variable degrees of erythematous gingiva, either locally or more broadly. (17) Blindness may result from scarring beneath the

conjunctiva. Initial lesions are seen in upper tarsal conjunctiva, it is also characterised by symblepharon formation where fibrous tracts may fuse the scleral and palpebral conjunctiva. (18) Immunofluorescence experiments reveal that IgG, IgA, or C3 are linearly deposited along the epithelial basement membrane. BPAg2 antibodies cause subepidermal blisters by inducing an inflammatory response. After that, immunologic processes take place that result in the production of inflammatory mediators that trigger the migration of mast cells, eosinophils, neutrophils, and lymphocytes to the basement membrane zone. (19) The available MMP therapies are described here. (Fig. 7).

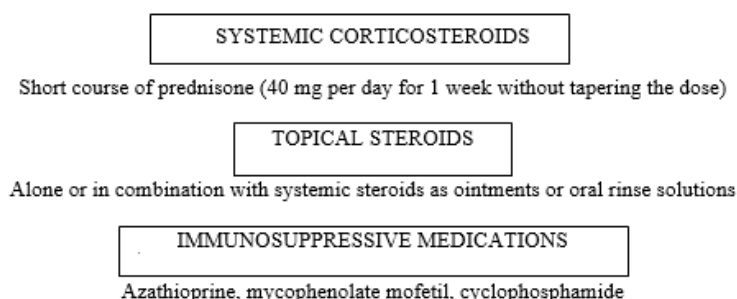


Fig. 7: Management of MMP

Erythema multiforme

Erythema multiforme is an acute, self-limiting, and recurrent mucocutaneous illness characterized by skin and mucous membrane blistering and ulceration. There are three main degrees of severity for erythema multiforme, commonly known as Steven Johnson Syndrome, toxic epidermal necrolysis, or Lyell's disease. (20) Erythema multiforme could be a side effect of a drug or a herpes-related condition. EM has been associated with the use of NSAIDs, penicillin, phenothiazines, sulphonamides, barbiturates, hydantoins, ciprofloxacin, protease inhibitors, and other drugs. (21) The remote skin regions where the

herpes-related erythema multiforme first appears are reached by viral DNA fragments carried by peripheral blood mononuclear cells. HSV-specific CD4+ T Helper cells are attracted to the location where HSV genes in DNA fragments are expressed on keratinocytes. The illness may start with vague prodromal symptoms like fever, malaise and headache. (22) Three concentric zones — a center dark zone, a ring of pale oedema, and a periphery of red rim — define these lesions (23). According on how severe the erythema multiforme is, the following therapy recommendations are suggested (Fig. 8).

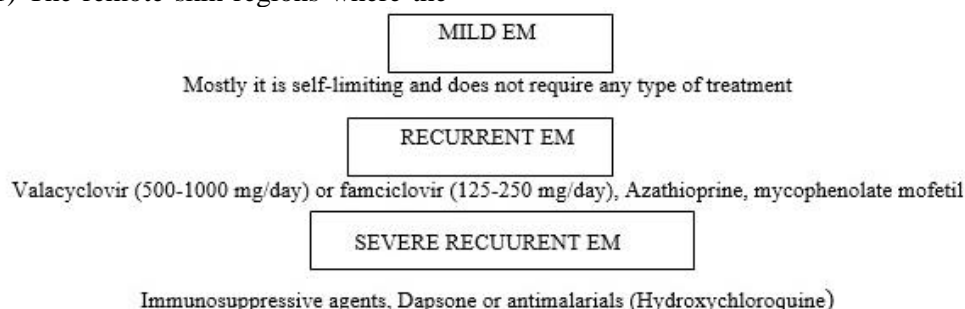


Fig. 8: Treatment of EM based on its severity

DISCUSSION

A series of mucocutaneous illnesses known as vesiculobullous lesions are characterized by the presence of vesicles or bullae, which are fluid-filled blisters that typically develop into ulcerative or erosive lesions when they burst. According to reports, the majority of vesicular lesions are caused by infections and come with constitutional symptoms including fever and malaise. Immunobullous lesions

are ones that are immune mediated in origin and make up the majority of lesions. VBLs include infectious lesions, most of which are viral, like varicella zoster infection, hand, foot, and mouth disease, herpangina, and herpes simplex virus infections. Epidermolysis bullosa, pemphigus vulgaris, pemphigoid, dermatitis herpetiformis, linear IgA disease, and pemphigus vulgaris are among the immunobullous lesions. The early stages of VBL can

be diagnosed by simple chair side assessment signs like the Nikolsky's sign, which is performed by applying lateral pressure on the skin causes the peripheral extension of the blister; the Sable Hansen sign or Bulla spread sign, which is performed by applying pressure on top of the bulla, which is a type of indirect Nikolsky's sign, which causes the blister to extend to the unaffected skin. A biopsy, followed by a histological analysis and immunofluorescence investigations, are used to confirm the diagnosis of VBL. The epithelium will be cleft or separated from the lamina propria histopathologically, along with sub epithelial bullae. The immunofluorescence method employs fluorescently tagged antibodies to detect the bound autoantibodies to the surface of the keratinocytes or basement membrane zone in these lesions. VBL can also be identified by the Tzanck test, an exfoliating cytological approach, as well as molecular methods like immunoprecipitation, western blotting, and enzyme-linked immunosorbent assays (ELISA). Corticosteroids, namely glucocorticoids, have long been the cornerstone of treatment for these lesions. Because of the long-term side effects of steroids, immunomodulators and steroid-sparing medications have recently become more popular. It is typically advised to diagnose the lesions at an early stage and utilize the best treatment options to improve the overall quality of life of these patients due to the long-term chronicity and recurrent nature of the majority of these lesions.

CONCLUSION

Vesiculobullous lesions can be predominantly vesicular, predominantly bullous lesions. They can also present with an infectious or non-infectious etiology. Histopathologically they can be intraepithelial or subepithelial blistering lesions. These lesions apart from causing physical complications, they can also compromise the quality of life if they are chronic and recurrent in nature. Steroids are the most common medication used for these lesions and long-term use can cause potential side effects. As a clinician, a thorough knowledge on the etiopathogenesis, clinical features and awareness of recent updates regarding newer medications, modes of treatment is essential for the successful management of these lesions in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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