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Review Article

A Short Review on Pemphigus Vulgaris

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Abstract: Pemphigus vulgaris (PV) is a rare, chronic autoimmune blistering disorder affecting the skin and mucous membranes. It is characterized by the production of IgG autoantibodies against desmoglein-1 and desmoglein-3, which are essential components of desmosomes responsible for cell-to-cell adhesion in the epidermis. Loss of adhesion between keratinocytes leads to acantholysis and the formation of painful blisters and erosions, commonly beginning in the oral cavity before involving the skin. PV most frequently affects middle-aged individuals and shows higher prevalence among certain ethnic groups, including those of Mediterranean and Ashkenazi Jewish descent. Diagnosis is confirmed by clinical features, histopathology, and direct immunofluorescence studies. Early diagnosis and prompt treatment with systemic corticosteroids and immunosuppressive agents, such as azathioprine or rituximab, significantly reduce morbidity and mortality. Although once associated with high fatality rates, advances in immunotherapy have markedly improved patient prognosis.

Keywords: Pemphigus Vulgaris, Histopathology, Immunosuppressive Agents, Immunotherapy.

INTRODUCTION

Background History

Pemphigus was derived from the Greek word pemphix, which means vesicle or blister. There are many different types of pemphigus, all involving vesicle formation at some stage, but the most common of all of them is pemphigus vulgaris. All types of pemphigus involve acantholysis. Which means the breaking apart of intercellular connections through an autoantibody-mediated response. It was in 1964 that researchers first found that antibodies were responsible for breaking the intercellular connections between keratinocytes leading to this disease. Then, in 1971 through immunofluorescent staining, it was found that the body produces immunoglobulin G (IgG) autoantibodies against the intercellular substance that holds epithelial cells together [1].

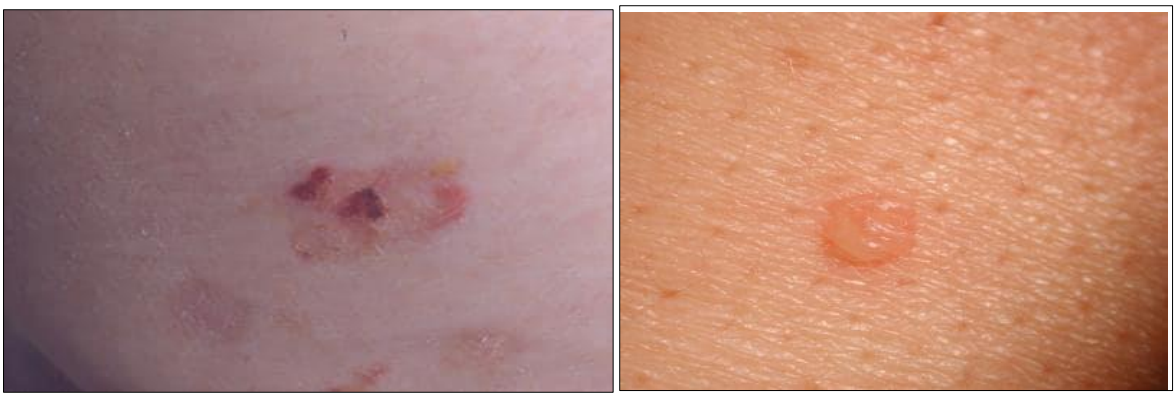


Figure 1: Pemphigus vulgaris [2]

Class: Autoimmune disorder [3].

Definition: Pemphigus vulgaris (PV) is an autoimmune disorder of the skin. It involves Blistering and sores (erosions) of the skin and mucous membranes [3].

Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are immunobullous disorders that are clinically significant because they can lead to high morbidity and mortality. If left untreated. Their diagnosis is often delayed. Because their pathophysiology is driven by an autoimmune process, the autoantibodies are the basis of diagnostic investigations and treatment strategies. The key target antigens, desmoglein (Dsg)1 and Dsg3, are important components of desmosomes, which are the 'rivets' that hold keratinocytes in epithelia together. When these desmosomes fail, the keratinocytes split from one another resulting in blistering. It takes, on average, five doctors 10 months to make a diagnosis of PV. Reasons for this delay include lack of awareness with failure to recognize the clinical features and failure to confirm the diagnosis. In the case of PV, the initial presentation is usually with mucosal ulceration and there is often a delay before the skin is involved. At this stage, patients are likely to see specialists that deal with mucosal pathology such as dentists, oral surgeons, gynaecologists, genitourinary medicine physicians, and ear, nose and throat surgeons, who may have limited awareness of immunobullous diseases, owing to their rarity. In both PV and PF, intact blisters may not be seen, which may mislead even those who are familiar with these diseases [4].

Pemphigus refers to a family of rare acantholytic autoimmune dermatoses of the mucocutaneous membranes in which acantholysis, or the loss of cell-to-cell adhesion, causes potentially lethal bullae and erosion formation. Multiple subtypes of pemphigus disease have been identified based on their distinct clinical features and pathophysiology, including pemphigus vulgaris (PV), pemphigus foliaceus (PF), IgA pemphigus, and paraneoplastic pemphigus (PNP). The significant morbidity and mortality associated with pemphigus disorders warrants a review of their pathogenesis, clinical presentation, and diagnostic work-up. Assessment of standard and new therapies builds further conviction in the evaluation and management of these rare bullous deratoses. Pemphigus occurs worldwide but has a disproportionate geographic and ethnic distribution, with a significantly higher prevalence in patients of Ashkenazi Jewish or Mediterranean descent. Despite its increased prevalence in these populations, pemphigus universally affects all racial and ethnic groups. The prevalence of pemphigus disease in Ashkenazi Jewish populations may be attributed to the increased presence of several distinct HLA class II genes, specifically HLA-DRB1*04 and HLA-A*10 Overall, the epidemiologic trends associated with pemphigus diseases largely vary based on region of the world and the ethno-demographic characteristics of the population being studied. Pemphigus largely affects patients between the ages of 50 and 60, although the mean age at diagnosis can differ significantly based on the country of origin and ethnic background. In some Western Asian nations such as Kuwait, the mean age at diagnosis is 36.5 years, whereas in European nations such as Bulgaria, the mean age at diagnosis is 72.4 years. Importantly, disease onset in the pediatric population has also been described, including in patients as young as 6 years old. Although the diagnosis of pemphigus in younger patient populations has increasingly been identified in recent studies, pemphigus disease is very rare in children overall. The global male-to-female ratio of pemphigus patients is approximately equal. Nonetheless, adolescent girls are more likely to be affected than adolescent boys [18].

Types: There are several forms of pemphigus, depending on which layer of the skin is blistered and where the blistering is located. The blisters always appear on or near the skin surface. The different forms of pemphigus are described in more detail below.

- **Pemphigus Vulgaris:** This is the most common form of pemphigus. The condition usually affects the mouth first and it can be painful. The blisters start to appear on skin and mucous membranes that were previously healthy looking. They form inside the deep layer of the epidermis and the skin becomes so delicate that simply rubbing it with a finger can cause it to fall off. Usually, the blisters heal without

causing any scarring, but some areas of the skin that have become pigmented may stay so for several months.

- **Pemphigus Fliaceus:** Pemphigus foliaceus is another common form of pemphigus. In this type, blisters or crusty sores initially develop on the scalp and face, with other areas of the body such as the chest becoming affected later. The lesions are often itchy, but are not usually as painful as those that develop in pemphigus vulgaris. Areas of the skin may also become moist, loose, and scaly.
- **Pemphigus Vegetans:** This form of the disease causes thick sores to arise under the arms and in the groin area.
- **IgA Pemphigus:** Here, immunoglobulin A (IgA), an antibody different from the antibodies involved in other forms of the condition binds to the epidermis cell surface. The resulting blisters are similar to those that develop in pemphigus foliaceus, although sometimes pus-containing bumps also arise. IgA pemphigus is the least harmful type of pemphigus.
- **Paraneoplastic Pemphigus:** This is a rare condition that is not actually pemphigus, but shares some of the disease characteristics. It develops in people with certain cancers and leads to ulcers forming in the mouth and on the lips. The skin also becomes blistered and the eyelids may become cut and scarred. The antibody that binds to the surface of epidermis cells also targets the membranes of the airways and hence patients with this condition can develop fatal lung problems [5].

Drugs	Containing a Thiol Group	Penicillamine, Captopril, and Cephalosporin
	Containing a Phenol Group	Cephalosporin, Rifampin, and Levodopa
	Other	ACE inhibitors other than captopril, most NSAIDs, biological modifiers of the immune response (vaccine, interferons, imiquimod and other cytokines), chloroquine/hydroxychloroquine, cocaine
Viral İnfections	HSV, HHV8, and EBV	
Physical Agents	Sunburns, ionizing radiation, thermal or electrical burns, and surgical and cosmetic procedures	
Contact Allergens	Chemical exposure in those involved in photography, dry cleaning, industrial solvent work, horticulture, pesticides and intensive agriculture	
Dietary Factors	Although not proven, thiol allyl compounds in garlic, leeks and onions, as well as tannins in black pepper, red pepper, cherry, cranberry, blackberry, red wine and tea are known to cause acantholysis	

Table 1: Trigger factors for pemphigus vulgaris [9]

Etiology: Although the cause of pemphigus vulgaris remains unknown, several potentially relevant factors have been identified, as follows.

1. **Genetic Factors:** Pemphigus is linked to genetic factors. Certain major histocompatibility complex (MHC) class II molecules—in particular, alleles of human leukocyte antigen (HLA) DR4 (DRB1*0402) and HLA DRw6 (DQB1*0503)—are common in patients with pemphigus vulgaris. One study found that the genes FGA (fibrinogen alpha chain), VWF (von Willebrand factor), and ACTG1 (actin gamma 1) were dysregulated in patients with pemphigus vulgaris and suggested that such dysregulation may play a role in the pathogenesis of the disease.
2. **Age:** Peak age of onset is between 50 and 60 years. Infants with neonatal pemphigus remit with clearance of maternal autoantibodies. The disease may develop in children or in older persons.
3. **Disease Association:** Pemphigus occurs in patients with other autoimmune diseases, particularly myasthenia gravis (MG) and thymoma. A study of 110 patients with pemphigus found four patients with autoimmune thyroid disease and three patients with rheumatoid arthritis (RA). In this study, however, autoimmune diseases were no more common in first-degree relatives of patients with pemphigus than in the general population.
4. **Environmental Factors:** A case-control study suggested that the following may be associated with an increased risk of developing pemphigus vulgaris Consumption of foods containing thiol groups (eg, leeks and tomatoes)
5. **High Mental Stress Levels:** Consumption of certain supplements (eg, calcium and multivitamins) Use of chemical cleaning products that contain lime [6].

Risk Factors:

Pemphigus vulgaris isn't contagious and cannot be transmitted from one person to another. It also doesn't appear to be transmitted from parent to child. However, a person's genes can put them at a higher risk for the condition. If your parents or other family members had or have the condition, you're more likely to develop it. Pemphigus vulgaris can affect people of all races, genders, and ages. However, the condition is more common in the following groups: people of Mediterranean descent, eastern European Jews people who live in the rainforests in Brazil middle-aged and older adults [7]. Triggers for autoantibodies' attacks on the skin and mucous membrane cells remains a mystery, but on rare occasions may follow using certain drugs such as angiotensin-converting enzyme inhibitors or penicillamine. The risk of incidence for pemphigus vulgaris is more significant beginning with middle-age and was found to be higher for those of Middle Eastern or Jewish ancestry [8]. PV is a polygenic disease and low titers of disease-associated autoantibodies have been demonstrated in first-degree healthy relatives of patients with pemphigus. For many years, a strong association between Class II Human leukocyte antigen (HLA) polymorphism and pemphigus vulgaris has been known, with the highest incidence seen among Ashkenazi Jews. The interethnic variability in the occurrence of pemphigus vulgaris has been associated with genetic susceptibility. Associated HLA polymorphisms are HLA-DRB1∗ 0402, HLA-DRB1∗14, HLA-DQB1∗ 0503, HLA-DRB1∗ 0302 and HLA-DRB1∗ 08. Of these, HLA-DRB1∗ 0402, HLA-DRB1∗ 14 and HLA-DRB1∗ 08 have a statistically significant relationship with the incidence of pemphigus vulgaris. Pemphigus vulgaris is associated with a variety of diseases, including other autoimmune disorders, psoriasis, neurological and psychiatric disorders and some malignancies. In addition, environmental factors may also be effective in initiating and maintaining the disease process. These causes include medications, viral infections, physical agents, contact allergens, vaccines, diet and psychological factors [8].

Pathophysiology:

Pemphigus vulgaris is an autoimmune intraepithelial blistering disease that affects the skin and mucous membranes and is mediated by circulating autoantibodies directed against keratinocyte cell surfaces. In 1964, autoantibodies against keratinocyte surfaces were described in patients with pemphigus. Clinical and experimental observations indicated that the circulating autoantibodies are pathogenic. An immunogenetic predisposition has been well established. Blisters in pemphigus vulgaris are associated with the binding of immunoglobulin G (IgG) autoantibodies to keratinocyte cell surface molecules. These intercellular or pemphigus vulgaris antibodies bind to keratinocyte desmosomes and to desmosome-free areas of the keratinocyte cell membrane. The binding of autoantibodies results in a loss of cell-to-cell adhesion, a process termed acantholysis. The antibody alone is capable of causing blistering without complement or inflammatory cells.

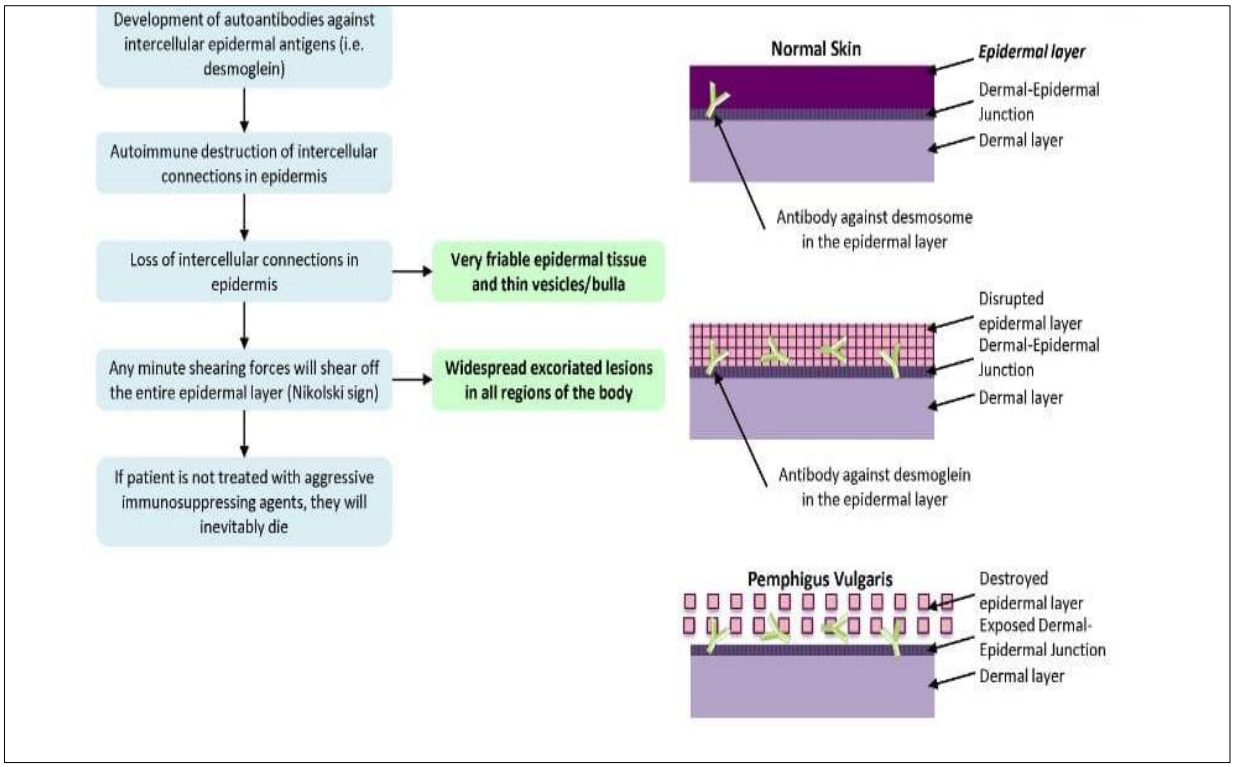


Figure 2: Pathogenesis of pemphigus vulgaris [23]

✓ **Pemphigus Vulgaris Antigen:**

Intercellular adhesion in the epidermis involves several keratinocyte cell surface molecules. Pemphigus antibody binds to the keratinocyte cell surface molecules desmoglein 1 (DSG1) and desmoglein 3 (DSG3). The binding of antibody to DSG may have a direct effect on desmosomal adherence or may trigger a cellular process that results in acantholysis. Antibodies specific for nondesmosomal antigens also have been described in the sera of patients with pemphigus vulgaris; however, the role of these antigens in the pathogenesis of pemphigus vulgaris has not been established.

✓ **Antibodies:**

Patients with the mucocutaneous form of pemphigus vulgaris have pathogenic anti-DSG1 and anti-DSG3 autoantibodies. Patients with the mucosal form of pemphigus vulgaris have only anti-DSG3 autoantibodies. Patients with active disease have circulating and tissue-bound autoantibodies of both IgG1 and IgG4 sub classes. More than 80% of patients with active disease produce autoantibodies to DSG. Disease activity correlates with antibody titers in most patients. In patients with pemphigus vulgaris, the presence of anti-DSG1 autoantibodies, as determined by enzyme-linked immunosorbent assay (ELISA), is more closely correlated with the course of the disease than the presence of anti-DSG3 autoantibodies. Lack of in-vivo antibody binding (reversion to a negative result on direct immunofluorescence [DIF]) is the best indicator of remission and can help predict a lack of flaring when therapy is tapered.

✓ **Complement:**

Pemphigus antibody fixes components of complement to the surface of epidermal cells. Antibody binding may activate complement with the release of inflammatory mediators and recruitment of activated T cells. T cells are clearly required for the production of the autoantibodies, but their role in the pathogenesis of pemphigus vulgaris remains poorly understood. Interleukin (IL)-2 is the main activator of T lymphocytes, and increased soluble receptors have been detected in patients with active pemphigus vulgaris [6].

PV is one of the best-described autoimmune diseases; its pathophysiology seems to result from the deleterious actions of circulating auto-Abs, which are directed against desmosomal components, primarily desmoglein (Dsg3 and Dsg1), and lead to the loss of keratinocyte cell-cell adhesion within the epidermis, a phenomenon known as acantholysis. In addition, blister formation in PV was suggested to result from increased secretion of pro-inflammatory mediators or other mechanisms, such as activation of specific muscarinic receptors expressed by keratinocytes, abnormalities in intercellular signaling or activation of apoptosis. Recent studies support the role of genetic factors in pemphigus. PV is a polygenic disease, and an increased prevalence of low titers of disease-associated autoantibodies in healthy first-degree relatives of patients with pemphigus has been reportes the genetic contribution to the pathogenesis of PV is given by the association with other autoimmune diseases and from the ethnic clustering of PV. Pemphigus is linked to autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, and systemic lupus

erythematosus. In addition, the correlation between pemphigus and myasthenia gravis is well know Several HLA alleles have been identified as risk factors, but the correlation between a certain HLA genetic profile and the patient's clinical profile is still uncleas A meta-analysis demonstrated a strong connection between PV and HLA-DRB1_0402 (which is predominant in Ashkenazi Jews), HLA-DRB1_1401, HLA-DRB1_1404 and HLA-DQB1_0503 (which are both prevalent in non-Jewish patients of European and Asian descent).Environmental factors could be required to initiate and perpetuate the disease process. Thus, drugs, viral infections (herpes simplex virus), physical agents, contact allergens, vaccinations, dietary factors, and psychological stressors have been implicated in the diseases. The mechanism by which blisters are formed is related to the lack of adhesion of desmosomes and to specific cell signaling pathways. Other studies have shown that pathogenic anti-Dsg monoclonal antibodies can bind directly to residues that mediate adhesion and that polyclonal antibodies contribute to acantholysis in a different way [10].

Epidemiology:

United States and International Statistics

Pemphigus vulgaris is uncommon in the United States, and the exact incidence and prevalence depend on the population studied. Pemphigus vulgaris has been reported to occur worldwide. The incidence of this condition has been reported to be in the range of 0.5-3.2 cases per 100,000 population. It is higher in patients of Ashkenazi Jewish descent and those of Mediterranean origin. Few familial cases have been reported. As with endemic pemphigus, there is some evidence to suggest clustering near industrial sites.

- **Age, Sex, and Race-Related Demographics:**

Although most cases of pemphigus vulgaris occur between the ages of 50 and 60 years, the range is broad and disease onset in older individuals and in children has been described. Patients are younger at presentation in India than they are in Western countries. The male-to-female ratio is approximately equal. In adolescence, girls are more likely to be affected than boys. Pemphigus vulgaris affects persons of all races and ethnic groups. As noted, it is more prevalent in regions where the Jewish population is predominant and in Mediterranean regions. For example, in Jerusalem, the prevalence of pemphigus vulgaris has been estimated at 1.6 cases per 100,000 population, whereas in Connecticut, the prevalence has been reported as 0.42 cases per 100,000 population. The incidence in the United Kingdom is 0.68 case per 100,000 persons per year. The incidence of pemphigus vulgaris in Tunisia is estimated at 2.5 cases (women, 3.9; men, 1.2) per million population per year, whereas in France, the incidence is 1.3 cases per million population per year (no significant difference between men and women). In Finland, where few people of Jewish or Mediterranean origin live, the prevalence is low, at 0.76 case per million population.

- **Prognosis:**

The severity and natural history of pemphigus vulgaris are variable. Before the advent of steroids, most patients with pemphigus vulgaris died. Treatment with systemic steroids has reduced the mortality dramatically, to approximately 5-15%. If not properly treated, pemphigus vulgaris still is often fatal because of the susceptibility to infection fluid and electrolyte disturbances. Mortality in patients with pemphigus vulgaris is three times higher than that in the general population. Most deaths occur during the first few years of disease; if the patient survives 5 years, the prognosis is good. Early disease probably is easier to control than wide spread disease, and mortality may be higher if therapy is delayed. Complications secondary to the use of high-dose corticosteroids contribute to mortality as well. Morbidity Mortality are related to the extent of disease, the maximum dose of prednisolone required to induce remission, and the presence of other diseases. The outlook is worse in older patients and in patients with extensive disease. Prognosis is usually better in childhood than in adulthood. Pemphigus vulgaris involves mucosa in 50-70% of patients. This may limit oral intake secondary to dysphagia. Blistering and erosions secondary to the rupture of blisters may be painful and may limit the patient's daily activities. Patients with pemphigus vulgaris typically heal without scarring unless the disease is complicated by severe secondary infection. Reversion of DIF to negative can be useful for predicting sustained remission after withdrawal of medication. Plucked hairs are an alternative to skin biopsy in providing a specimen for immunofluorescence; the pilar sheath epithelium of the anagen hair typically demonstrates immunofluorescence comparable to skin. DIF on plucked hairs may be more acceptable to the patient than serial skin biopsies. Relapses may occur in more than 50% of patients with pemphigus (including variants other than pemphigus vulgaris). In one study, the following were found to be risk factors for relapse Extensive body surface area (BSA) involvement. High patient body mass index (BMI) High degree of severity at onset, as determined by the Pemphigus Disease Area Index (PDAI) Delayed provision of treatment High titers of anti-DSG1 and anti-DSG3 after treatment A few rare cases of pemphigus vulgaris transitioning to pemphigus foliaceus have been reported.

- **Patient Education:**

Because of the chronic nature of pemphigus vulgaris, it is important for patients to have a good understanding of the disease and to be educated regarding its management. Patients should be advised to minimize skin trauma because their skin will be more fragile than usual as a result of both the disease itself and the use of topical and systemic steroids to treat it. They should also be educated regarding their medications. If patients are informed about dosages, adverse effects, and symptoms of toxicity, they will be better able to report any adverse effects to the physician. Finally, instructions

regarding appropriate wound care should be provided [6]. Similarly to other autoimmune diseases, PV is more prevalent among women. The male/female ratio ranges from 1:1.5 in Israel and Iran to 1:4 in Tunisia. PV may occur at any age, and disease onset is usually between 40 and 60 years of age. An increased frequency in the elderly and children has been observed. Interestingly, in some countries of the Middle East and Brazil, disease onset is earlier: a Brazilian study estimated that 17.7% of cases occur before the age of 30 years.8-10 [11]. PV has an average age of onset of 40–60 years. It has a prevalence of around 30,000 cases in the USA and an incidence of 1–10 new cases per 1 million people (Pemphigus. Pemphigus Pemphigoid Foundation (IPPF) 2014. It is a rare disease—especially in the pediatric population, but it needs no less study because it does affect patients and also does affect certain groups of people more than others. Ashkenazi Jews and people from India and the Middle East have higher rates of the disease, It is equally distributed among genders [17].

- **Clinical Symptoms**:

Pemphigus vulgaris causes blisters that burst easily and leave very sore patches. Pemphigus vulgaris inside a person's mouth. There are red, sore-looking patches covering the roof of the mouth. The most common area affected is inside the mouth and throat, which can make swallowing painful. Pemphigus vulgaris in someone with dark brown skin. There are several light brown or orange blisters on the tummy and some scabs where blisters have burst. Many people also get blisters on their skin. These usually appear a few months after the mouth is affected. Pemphigus vulgaris in someone with white skin. There are lots of small red patches covering the chest, tummy, shoulders and arms. The blisters and sore areas can cover a large area of the body. Sometimes they can also affect the eyes, genitals or anus [12].

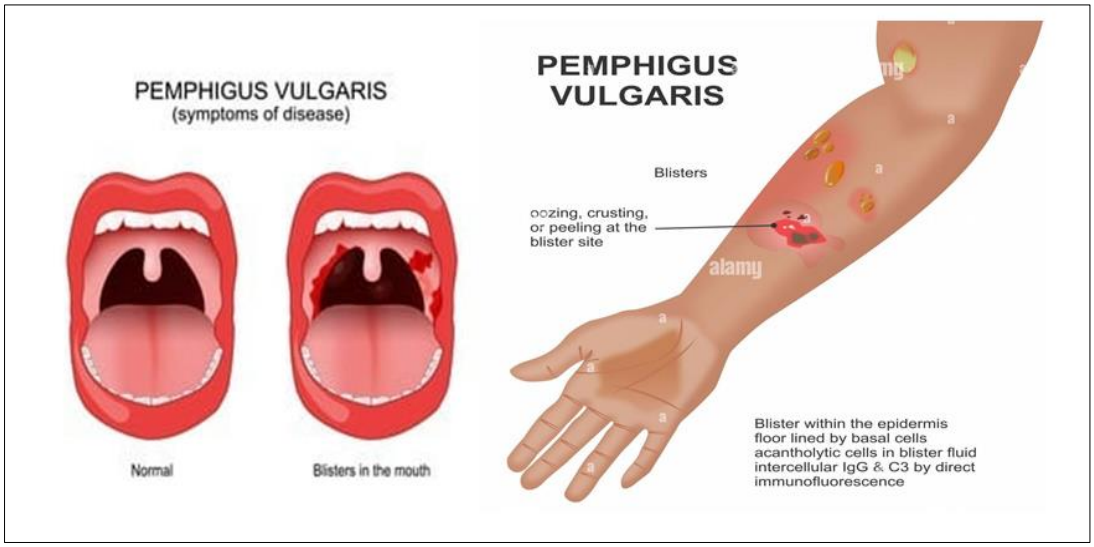


Figure 3: Symptoms of pemphigus vulgaris [19, 20]

Clinical Complications:

Infection of the Skin:

Infection that spreads to your bloodstream, also called sepsis. This type of infection can be life-threatening. Scarring and changes in skin color after the affected skin heals. This is called postinflammatory hyperpigmentation. When the skin darkens and postinflammatory hypopigmentation when the skin loses color. People with brown or Black skin have a higher risk of long-term skin color changes. Malnutrition, because painful mouth sores make it difficult to eat. Side effects from the medicine used to treat pemphigus. Examples are high blood pressure and infection. Death, rarely, if certain types of pemphigus are left untreated [13].

Diagnosis:

The diagnosis of PV is based on a combination of clinical presentation and detection of tissue-bound and/or circulating autoantibodies. The gold standard diagnostic of PV is direct immunofluorescence (DIF) microscopy, which can detect tissue-bound autoantibodies. In pemphigus, DIF microscopy reveals intercellular binding of IgG and/or C3 within the epidermis and/or epithelium. Indirect immunofluorescence (IIF) is frequently used to semi-quantitatively measure circulating antibody levels, using monkey, rabbit or guinea pig esophagus as a substrate. The most frequently used substrates are monkey esophagus and human split skin. Enzyme-linked immunosorbent assays (ELISA) are a more sensitive method for measuring antibodies to desmoglein 1 and desmoglein 3. ELISA reactivity correlates with disease activity; therefore, this test is useful both for diagnosis and for monitoring disease activity in patients with pemphigus. Immunoblot and immunoprecipitation techniques may be used to identify specific autoantibody profiles. These assays use recombinant proteins or extracts of dermis, epidermis or cultured keratinocytes in

addition, confocal laser scanning microscopy is a non-invasive tool for the diagnosis of pemphigus and differentiation of its subtype; it points to the need for further investigation of the patient. It has the advantage of monitoring disease progression and the treatment efficacy [14]. Diagnosis of pemphigus vulgaris generally requires a biopsy of a blister. Diagnosis of pemphigus vulgaris generally requires a biopsy from the skin adjacent to a lesion. Histology typically shows rounded-up and separated keratinocytes (acantholytic cells) just above the basal layer of the epidermis. Suprabasal clefting may be reported. See pathology of pemphigus vulgaris. Pemphigus is confirmed by direct immunofluorescence staining of perilesional skin biopsy sections to reveal immunoglobulin (Ig)G antibodies or complement on the cell surfaces of keratinocytes in most cases, circulating antibodies can be detected by a blood test (indirect immunofluorescence test). The level of antibodies fluctuates and may reflect the effectiveness of treatment. Specific anti-dsg1 and anti-dsg3 antibody titres can also be measured in blood or saliva by enzyme-linked immunosorbent assays (ELISAs). Pemphigus vulgaris may co-exist with or be confused with pemphigus foliaceus, cicatricial pemphigoid and lichen planus [15].

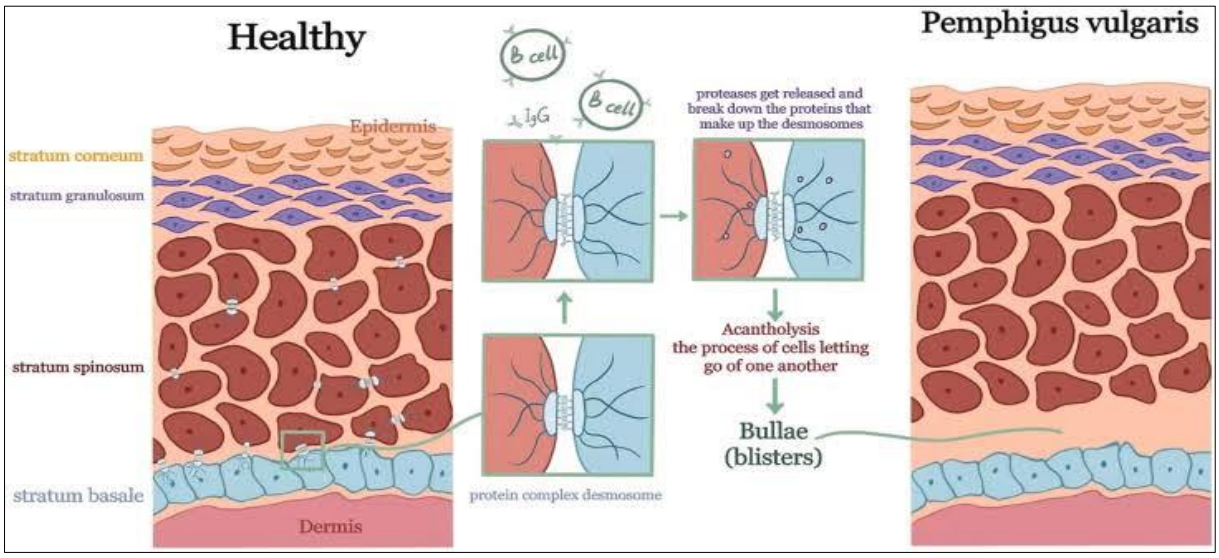


Figure 4: Pemphigum Vulgaris [16]

There are other less common and less severe forms of pemphigus under the pemphigus umbrella, so weaving through the differential diagnosis involves a keen clinical acumen as well as the laboratory. To help confirm the diagnosis, other tests are run. After punch biopsy and histopathologic preparation, PV displays a particular cellular pattern. Because the problem is in between cells and not under the basal aspect of the cell, there is no space between the cell and the basement membrane. This leaves an intact, bottom layer of cells connected to the membrane. There is intraepidermal acantholysis seen. If there was an autoimmune attack against hemidesmosomes on the basal side of the cell, therewould be a loss of connection of the basal keratinocyte to the basement membrane, yielding a different and clinically less severe condition known as bullous pemphigoid. In the case of PV, the new pathologic space is in between the cells; this causes fluid to build up in places with lower intercellular integrity. Because the intercellular connections are lost—like a zipper, where the unzipped part is the damaged intercellular piece—and yet the cells are still intact on the basement membrane, they are said to have a tombstone pattern on histopathology. Shows acantholysis and the "row of tombstones" pattern in PV. An increase in eosinophils can also be seen in the dermis [17]. A summary of the clinical, histopathological, and serological findings of the various pemphigus disorders is outlined. Diagnosis of pemphigus begins with a thorough history and physical exam. During the history, clinicians should ascertain the presence of mucosal involvement, as the presence of mucosal lesions can differentiate subtypes of pemphigus disease. PV and PNP always involve the mucosa, while PF and IgA pemphigus typically do not. Importantly, mucosal involvement in pemphigus disease can be inconspicuous, and mucosal surfaces routinely visible during standard physical exams, such as the eyes and lips, may not be involved. For example, a patient with PV may present with hoarseness and dysphagia secondary to occult mucosal involvement of the posterior oropharynx. Therefore, clinicians should be sure to evaluate for ocular symptoms, hoarseness of voice, dysphagia, and dyspareunia to assess for involvement of all mucosal surfaces. Medications should be reviewed in detail. Clinical presentation and laboratory studies cannot reliably distinguish between idiopathic pemphigus and drug-induced pemphigus. Recent studies have demonstrated that thiol and phenol-based medications are most closely linked to drug-induced pemphigus. Some of the most common triggering medications involved in drug-induced pemphigus include

penicillamine, captopril, tiopronin, aspirin, heroine, rifampin, levodopa, non-steroid anti-inflammatory drugs, and calcium channel blockers. Following a thorough history and physical exam, the laboratory work-up of pemphigus disease includes at least two biopsies with or without serum collection for indirect immunofluorescence (IIF), enzyme-linked immunosorbent assay (ELISA), or immunoblotting. A 4 mm lesional biopsy should be taken from the edge of an early lesion or erosion for hematoxylin and eosin (H&E) staining and routine histopathologic examination. An additional perilesional skin biopsy should be taken from normal-appearing skin, 4 mm from a vesicle or erosion, for direct immunofluorescence (DIF). Biopsies of lesional skin for DIF are more likely to be linked to false negative results as a result of the destruction of immunoreactants involved in the inflammatory process of the underlying pemphigus disease. Clinicians should also be sure to avoid placing DIF biopsies in formalin and instead utilize Michel medium, or Zeus medium, for adequate preservation. Serum is collected for ELISA and/or IIF to identify serologic evidence of pathogenic antibodies. The distinctive findings on histopathology, IIF, and ELISA/immunoblotting for each pemphigus disorder are depicted [18].

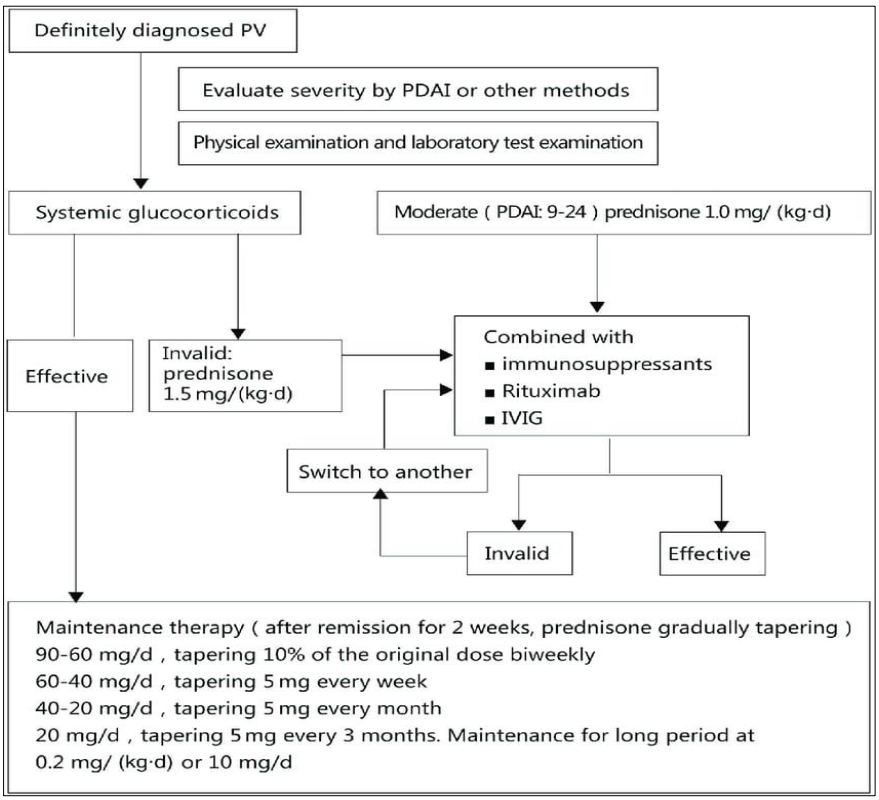


Figure 5: Diagnosis of pemphigus vulgaris [11]

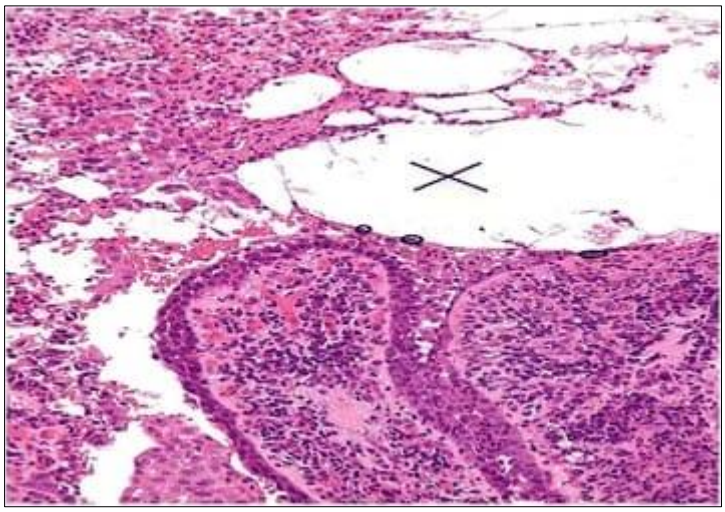


Figure 6: Pemphigus Vulgaris [11]

Treatment:

Without treatment, PV has a mortality rate ranging from 60 to 90%. Moreover, multiple life-threatening complications may occur, such as sepsis, fluid and electrolyte impaired thermoregulation, as well as cardiac and renal failure. Systemic corticosteroids and adjuvant therapies have reduced the mortality rate of PV patients to approximately 10% .The role of treatment in patients with PV is to suppress the immune system and to prevent the production of pathogens. The immunological response is due to the significant decrease of pathogens in the skin and serum of patients, which clinically corresponds to the cessation of new vesicle formation and the maintenance of remission. Given the rarity of this disease, there are few evidence-based controlled studies in literature regarding the safety and efficacy of the therapeutic interventions for PV.The British guidelines recommend the consideration of two stages in the management of PV: induction of remission and maintenance of remission. Thus, in the first stage, the treatment is represented by corticosteroids, less than adjuvant therapy, until 80% of the lesions heal and for 2 weeks no new lesions will appear, both cutaneous and mucosal. The remission maintenance phase is about gradual dose reduction in order to achieve effective pathology control. The goal of treatment is to keep the remission as long as possible [(14).] The mainstay of treatment involves the cessation of the causal agent and the use of immunosuppressants or immunomodulators to turn off the host autoimmune response. Pemphigus can be life-threatening and requires intensive and prompt use of systemic corticosteroids for induction at a dose of 1mg/kg body weight. Immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide are also used in severe disease. The use of an anti-CD-20 antibody, rituximab, has also shown to be a promising therapy for refractory pemphigus in a number of cases by targeting the aberrant B cells. Some cases also suggest an exacerbation of disease after the treatment with rituximab. Overall, there is a lack of well-controlled clinical studies on the proper treatment of drug-induced pemphigus, but the mainstay of the therapy continues to consist of a combination of corticosteroids and an immunosuppressive agent such as azathioprine.following an international consensus the 10 mg daily dose of prednisolone was estabiished [24].

PHARMACOLOGICAL THERAPY

- **Corticosteroids:**

Corticosteroids act rapidly in PV, effecting improvement in several days and impeding the emergence of new lesions after 2 to 3 weeks. Complete re-epithelization can take up to 2 months. After the condition is controlled, defined as the disruption of the emergence of new lesions and total re-epithelialization of existing lesions, the corticosteroid dose is slowly reduced. The rate of this decrease should decline toward the end, which can sometimes take years, due to the lack of uniform protocols for this practice. Certain groups recommend that starting from a specific daily dose (usually 40mg/day prednisone), the drug should be administered every other day, which would minimize the side effects. Similarly, there is no consensus on how to increase the dose in cases of recurrence. Generally, relapse is milder than the initial presentation of the disease and requires doses of prednisone that are equal to or lower than the initial dose for control. Corticosteroids can also be administered as pulse therapy for cases in which control with prednisone at dosages of over 1mg/kg/day is not achieved. To this end, methylprednisolone 1g/day IV and dexamethasone 300mg/day IV are used, both for 3 consecutive days. The advantage of pulse therapy is that it allows for a faster reduction in the prednisone dose, minimizing its side effects Although corticosteroids are effective in controlling PV in most patients, they have frequent and potentially severe side effects, the most significant of which are hypertension, diabetes mellitus, cutaneous and systemic infections, gastric ulcer, osteoporosis, femoral head necrosis, glaucoma, and cortisone cataract. These side effects are partly responsible for the morbidity and lethality of the disease, often due to the increase in the frequency of consultations, laboratory tests, and hospital admissions. All patients should receive gastric mucosal protectors and vitamin D supplementatioTo minimize the side effects, morbidity, and mortality of PV, contrary to what was advocated several decades ago, it is recommended that the daily dosage of prednisone does not exceed 1.5mg/kg/day-above this value, the likelihood of skin infection and evolution to septicemia (the main death cause in these patients) increases progressively. Thus, other drugs are recommended, in association with corticosteroids-termed adjuvant drugs (corticosteroid-sparing agents).

Adjuvant Drugs:

When the condition is not controlled solely with corticosteroids or when the patient has clinical contraindications to high-dose corticosteroids (e.g., hypertension, diabetes mellitus, glaucoma, osteoporosis-all of which are frequent in the age group in which the prevalence of PV peaks) other drugs, called adjuvants or corticosteroid-sparing agents, should be incorporated. Adjuvant drugs also prevent relapses in previously controlled patients.

- **Azathioprine (AZA)**:

Azathioprine is a cytotoxic drug that is used in most autoimmune diseases. It is an imidazole derivative of mercaptopurine, which antagonizes purine metabolism and inhibits the synthesis of DNA, RNA and proteins. It can also interfere with cellular metabolism and impede mitosis. AZA affects several aspects of the immune system. It reversibly reduces the number of monocytes and Langerhans cells and inhibits gamma globulin synthesis, T lymphocyte function, T helper-dependent B cell responses, and B cell suppressor function. The efficacy of AZA as a corticosteroid-sparing agent in autoimmune bullous diseases, particularly in PV is well documented and is the oldest

and most prescribed immunosuppressive medication in this context. The recommended dosage of AZA in PV is 100 to 200mg/ day (1 to 3mg/kg/day), orally, divided into 2 doses. Its therapeutic effect begins after 4 to 6 weeks, which restricts its use as monotherapy. Three months of use should elapse before replacing it with another adjuvant when there is no satisfactory clinical response. Its main side effects are leukopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity. Long-term immunosuppression can increase the risk of infections and neoplasms. Individuals with a genetic deficiency in thiopurine methyltransferase (TPMT) present with greater sensitivity to AZA-induced myelotoxicity. This medication is contraindicated in pregnant women and nursing mothers.

- **Rituximab:**

Chimeric anti-CD20 monoclonal antibody (which depletes normal and pathogenic B lymphocytes) has been used for cases of severe and refractory PV since 2006. Following the administration of rituximab, there is a rapid and sustained depletion of circulating and tissue B lymphocytes that persists for at least 6 to 12 months. Recent evidence demonstrates that it also affects T lymphocytes. In June 2018, the US FDA approved rituximab for PV. There are many prospective and retrospective studies that have proven its efficacy, leading to complete and sustained remission in most patients in 3 to 4 months. A recent systematic review that included 114 studies and 1085 patients concluded that rituximab is an excellent treatment for refractory cases. Rituximab should be administered IV as a slow infusion (4 to 6 hours). There are no standardized protocols for the use of rituximab in autoimmune bullous diseases, but studies have been published using the lymphoma protocol (375mg/m2, 1x/week for 4 weeks) and that for rheumatoid arthritis (1000mg with an interval of 2 weeks; can be repeated after 6 months). There seems to be no difference in percentage in remission or disease-free interval between these protocols. Rituximab can be used alone or in combination with IVIG, plasmapheresis, or immunoadsorption (the latter appears to prolong the response time with respect to rituximab alone). It can also be administered to patients who are already taking prednisone and immunosuppressants, and the dose reduction and suspension of the latter should be accelerated due to the increased risk of infection. Rituximab is generally well tolerated, and serious adverse effects are rare. Infusion reactions (which can be reduced with prior administration of analgesics, antihistamines, and corticosteroids) include anaphylaxis, fever, hypotension, chills, headache, nausea, pruritus, and skin rash. In addition, neutropenia, hypogammaglobulinemia, and infections, including sepsis, are rarely reported. Certain authors and expert groups recomend rituximab as a first-line treatment option for PV.

- **Mycophenolate Mofetil:**

MMF is a safe steroid-sparing agent. It is considered a first-line adjuvant immunosuppressant according to the EDF guidelines. The optimal dose is weight dependent with a dose of 2 g/d recommended for the average patient of 75 kg. Progressive dose increases by 500 mg/wk until the final dose of 2 g/d has been proposed to avoid gastrointestinal adverse events. Efficacy is debated. In a recent RCT, MMF (2 or 3 g/d) plus oral CSs was not found to be superior when compared with oral CSs and placebo in patients with mild or moderate PV. The primary end point was patients responding to treatment. Other investigators have also reported no clinical benefit using adjuvant MMF to steroids in patients with PV. MMF in combination with prednisolone seems to have a more prominent beneficial role in patients with relapses of PV or in cases of refractory PV.

- **Cyclophosphamide:**

Cyclophosphamide is an alkylating agent that selectively affects B lymphocytes and antibody production. It can be administered orally in PV (1 to 3mg/kg/day) or intravenously, with or without dexamethasone IV, in the form of pulse therapy. In such cases, dexamethasone is administered at 100mg/day IV for 3 days, with cyclophosphamide 500mg/day IV being administered on the first day. This pulse therapy is repeated every 2 to 4 weeks, between which an oral dose of cyclophosphamide 50mg/day and prednisone 1mg/kg/day is maintained. Treatment failure should be considered after 3 months of use at 2mg/kg/day. Its main toxic effects are infertility, predisposition to neoplasia, lymphopenia, and sepsis. Due to its greater toxicity, it can be considered as an adjuvant only in cases that are refractory to AZA and MMF.

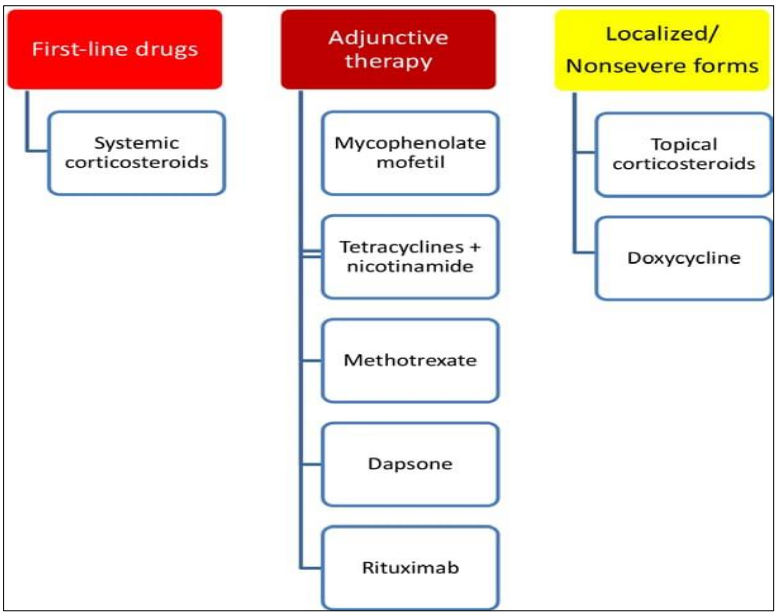


Figure 7: Pharmacological therapy for pemphigus vulgaris medication in pv [26].

Non Pharmacological Therapy:

- **Methotrexate:** Based on its anti-inflammatory activity and inhibition of cell proliferation through the suppression of dihydrofolate reductase, methotrexate can be added as an adjuvant in PV at 10 to 20mg/ week in cases of therapeutic failure to other adjuvants. The most frequent side effects are gastrointestinal intolerance, hematological toxicity, and infection.
- **Dapsone:** Drug with anti-inflammatory and anti-TNF activity that can be attempted as adjuvant medication in PV at 50 to 200mg/day orally, but there are conflicting reports in the literature. Its side effects are usually dose-dependent and reversible.
- **Cyclosporine:** Cyclosporine is a calcineurin inhibitor with potent immunosuppressive activity against B and T lymphocytes. It is effective as an adjuvant in the treatment of PV in rare cases at dosages of 3 to 5mg/kg/day, po or IV.
- **Intravenous immunoglobulin (IVIG):** Derived from a donor pool, the mode of action of IVIG in PV is complex, with several mechanisms acting synergistically (selectively removing pathogenic antibodies; altering the expression and function of Fc receptors; affecting the activation, differentiation, and effector functions of T and B cells; and interfering with the activation of cytokines and complement). Its advantage is its safety profile, with few side effects (headache, dyspnea, tachycardia, abdominal discomfort). IVIG is used in cases of PV that do not respond to other treatments or those that present with severe side effects, and it is effective in certain cases at a dosage of 0.4g/kg/day for 5 days, always as an adjunct to corticosteroid therapy once per month. It is expensive and takes 3 to 6 cycles on average. It can be used in pregnant women [25].

Management and Treatment:

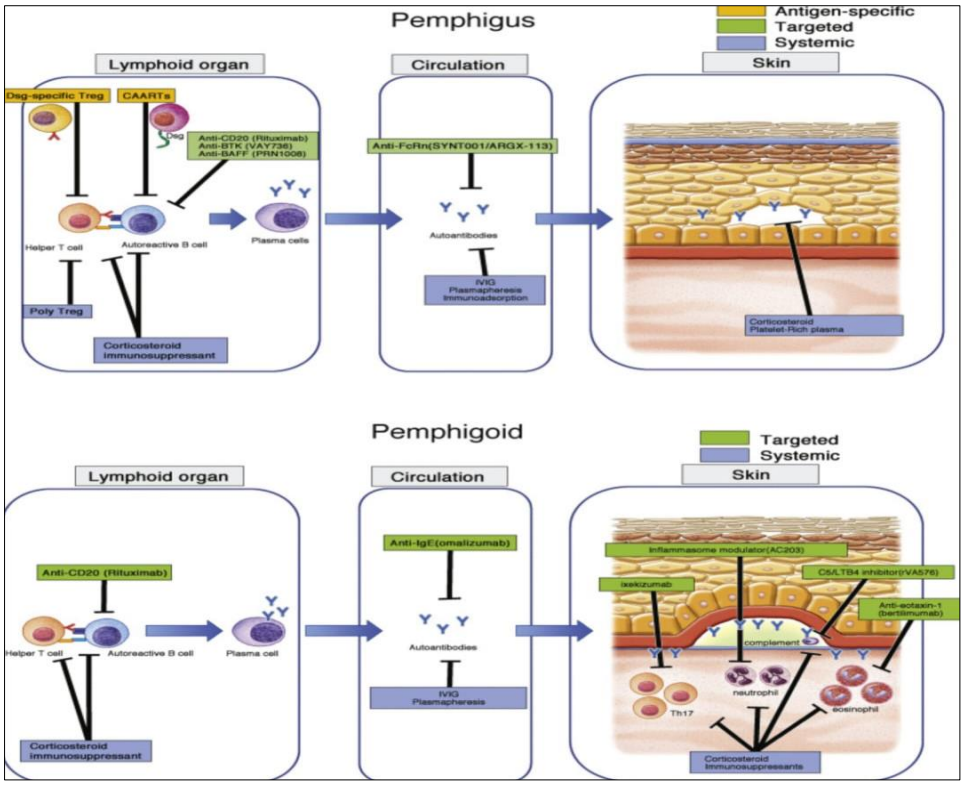
Treatment for pemphigus vulgaris focuses on managing symptoms and preventing complications like infections. Treatment is unique to each person and could include:

1. Taking medicines to treat infections
2. Stopping any medicines that cause symptoms.
3. Using medicines, creams or ointments to treat, soothe and heal sores.
4. Caring for sores and broken blisters as you would a burn or wound.mouth prevent you from eating.
5. Your healthcare provider might recommend taking medicines to reduce your symptoms, prevent flares of symptoms or treat infections.
6. Medicines could include topical (or) oral corticosteroids,Immune system suppressants (azathioprine, cyclosporine, mycophenolate, cyclophosphamide, methotrexate or rituximab) Antibiotics (or) antifungals [18].

Preventive Measures:

You can't prevent pemphigus vulgaris because the cause is unknown. Treatment is effective to reduce your symptoms.Living With How do I take care of myself.You can take care of yourself and manage your symptoms of pemphigus vulgaris at home by:

1. Eating a bland, smooth and liquid-based diet when you have active sores in your mouth.
2. Cleaning and caring for your blisters and sores like wounds or burns.
3. Protecting your skin from the sun's UV rays by wearing protective clothing and sunscreen.
4. Using gentle soaps or unscentedlotions on your skin [18].



Figur 8: Skin diseases of pemphigus vulgaris [22].

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